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Cocaine Versus Food Choice Procedure in Rats: Environmental Manipulations and Effects of Amphetamine

Morgane Thomsen, Andrew C. Barrett, S. Stevens Negus, and S. Barak Caine

McLean Hospital and Harvard Medical School

Abstract

We have adapted a nonhuman primate model of cocaine versus food choice to the rat species. To evaluate the procedure, we tested cocaine versus food choice under a variety of environmental manipulations as well as pharmacological pretreatments. Complete cocaine-choice dose-effect curves (0–1.0 mg/kg/infusion) were obtained for each condition under concurrent fixed ratio schedules of reinforcement. Percentage of responding emitted on the cocaine-reinforced lever was not affected significantly by removal of cocaine-associated visual or auditory cues, but it was decreased after removal of response-contingent or response-independent cocaine infusions. Cocaine choice was sensitive to the magnitude and fixed ratio requirement of both the cocaine and food reinforcers. We also tested the effects of acute (0.32, 0.56, 1.0, 1.8 mg/kg) and chronic (0.1, 0.32 mg/kg/hr) d-amphetamine treatment on cocaine choice. Acute and chronic d-amphetamine had opposite effects, with acute increasing and chronic decreasing cocaine choice, similar to observations in humans and in nonhuman primates. The results suggest feasibility and utility of the choice procedure in rats and support its comparability to similar procedures used in humans and monkeys.

Keywords

chained schedule; fixed ratio; concurrent; choice; alternative reinforcer; lever press; rat

Cocaine abuse continues to be a significant public health problem. There are currently no widely approved medications effective in reducing cocaine intake. The standard preclinical evaluation of a medication's potential to treat cocaine abuse is to assess its effect on cocaine self-administration. A weakness of this approach is that the primary dependent measure is the rate of responding, and test compounds may decrease rate of responding either by reducing the reinforcing effect of cocaine or by producing nonspecific effects that might include motor impairment or disrupted stimulus control (Woolverton, 1986; Caine & Koob, 1994; see for review Mello & Negus, 1996, Negus & Banks, 2011). This problem has traditionally been addressed by comparing treatment effects on cocaine self-administration with effects on responding maintained by an alternative reinforcer, such as food. Choice procedures provide an alternative strategy to preclinical evaluation of potential treatments for cocaine abuse. In choice procedures, the primary dependent measure is the allocation of responding, and treatment effects on behavioral allocation can be measured independently of effects on response rates. Rates of responding are recorded at the same time, giving a

Corresponding author: Morgane Thomsen Alcohol and Drug Abuse Research Center McLean Hospital, Mail Stop 214 115 Mill Street Belmont, MA 02478. mthomsen@mclean.harvard.edu Phone: 617 855 3285 – Fax: 617 855 3865. Address correspondence to M. Thomsen at: thomsen@mclean.harvard.edu..
Andrew Barrett is now at Synchrony Healthcare Group, 2 W. Market St., West Chester, PA 19382. S. Stevens Negus is now at Department of Pharmacology and Toxicology, Virginia Commonwealth University, 410 N 12th St, P.O. Box 980613, Richmond, VA 23298.

potential estimate of both nonspecific and undesirable effects. Choice procedures are now routinely used in clinical and preclinical human studies of novel medications (Donny, Bigelow, & Walsh, 2003; Foltin & Fischman, 1992; Haney & Spealman, 2008), as well as being used with increasing frequency for preclinical studies in nonhuman primates (Banks, Blough & Negus, 2011; Czoty & Nader, 2011; Woolverton & Balster, 1981).

Proposed advantages of choice procedures over single-reinforcer classic self-administration are several, and have been discussed in detail elsewhere (Ahmed, 2010; Negus & Banks, 2011). In brief, key arguments include the following: First, choice schedules measure response selection in addition to overall response rate, and thus may provide a measure of medication effects on cocaine's reinforcing efficacy independent of nonspecific effects (e.g., general rate suppression). Second, allocation of behavior to drug seeking and taking at the expense of nondrug-related behaviors is a direct parallel to a DSM-IV criterion for substance abuse. Indeed, Ahmed (2010) argues that the observed reinforcing effects of drugs may be artificially increased by measuring self-administration under conditions where the rat has essentially no behavioral alternatives but to take drug (Ahmed). Third, the use of choice procedures may simplify comparison between species, as they are increasingly preferred over single-response procedures in human studies. Finally, we found previously that the choice procedure in rats was amenable to systematic comparison of acute and chronic administration of candidate medications (Thomsen et al., 2008), and chronic treatment may be especially important for predicting the effects of a candidate medication in the clinic.

Although we and other groups have employed choice procedures in the rat species (Caprioli et al., 2009; Lenoir, Serre, Cantin, & Ahmed, 2007; Manzardo, Del Rio, Stein, & Belluzzi, 2001; Podlesnik, Jimenez-Gomez, & Woods, 2010; Schindler, Panlilio, & Thorndike, 2009; Thomsen et al., 2008; Ward, Morgan, & Roberts, 2005), the procedure has not yet gained wide popularity for rodent studies and has been used very little for candidate medication evaluation. In addition, systematic manipulations of experimental variables comparable to what has been shown in rhesus and cynomolgus monkeys have not yet been reported in rodents. The purpose of this study was to systematically evaluate, in male and female rats, our choice procedure based upon methods used in nonhuman primates (Negus, 2003). To our knowledge, such manipulations have not been explored in rats using multiple cocaine doses, although the effect of increasing the response requirement for a sweet liquid, and of varying sweetness intensity, have been evaluated in a single-dose procedure (Cantin et al., 2010). We first assessed the comparability of dose-effect functions of cocaine choice determined within-session and between-session, as the former, if validated, is more efficient and more amenable to evaluation of chronic treatments. We then examined the effect on cocaine choice of removing a) cocaine-associated visual cues, b) cocaine-associated auditory cues, c) response-independent ("priming") cocaine infusions, or d) response-contingent cocaine infusions, in order to evaluate the influence on choice behavior of these various stimuli. We also assessed the effect on cocaine choice of varying e) the magnitude of the food reinforcer, f) the fixed ratio (FR) response requirement for the food reinforcer, and g) the FR response requirement for the cocaine reinforcer, in order to verify that behavior under the present conditions is parametrically related to reinforcement contingencies. Finally, we evaluated the effect of acute and chronic treatment with d-amphetamine, an indirect monoamine agonist that has been found to reduce cocaine intake under some conditions in clinical and preclinical studies, including using a cocaine versus food choice assay in rhesus monkeys (*Macaca mulatta*) (Grabowski et al., 2001; Negus, 2003; Negus & Mello, 2003a,b; Rush, Stoops, & Hays, 2009).

Method

Subjects

Male and female Sprague-Dawley rats were purchased at ≈ 8 weeks of age (Charles River, Wilmington, MA) and acclimated to the laboratory for at least 1 week. Male rats were maintained at 400-500g body weight with once-daily feedings of ≈ 17 g standard rat chow (Rat Diet 5001; PMI Feeds, Inc., St. Louis, MO), and female rats were maintained at 320-400g with once-daily feeding of ≈ 14 g of rat chow. Bacon-flavored biscuits (5g, Bio-Serve, Frenchtown, NJ) were provided once or twice weekly, primarily for enrichment. Rats were housed individually with free access to water in a temperature-and humidity-controlled facility maintained on a 12-h light/dark cycle (lights on at 07:00). Behavioral testing was typically conducted between 11:00 and 13:00. Husbandry and testing complied with the guidelines of the National Institutes of Health Committee on Laboratory Animal Resources, and all protocols were approved by the Institutional Animal Care and Use Committee (McLean Hospital). Animal health was monitored daily by research technicians and as needed by consulting veterinarians.

Apparatus

Operant conditioning chambers and hardware from MED Associates Inc. (Georgia, VT) were used, and floor dimensions were 29.5 cm $\times$ 23.5 cm. Chambers of two heights, 20 or 28 cm, were used interchangeably (for convenience and availability). The chambers were placed in sound-attenuating cubicles equipped with a house light (model ENV-221M, MED Associates Inc.) and an exhaust fan. Each chamber contained three response levers situated 3.0 cm above the grid floor, two on one wall of the chamber ("reinforcer levers"), and a third centered on the opposite wall ("observer lever"). A steel cup between the two reinforcer levers, 2.0 cm above the floor, served as a reservoir for the delivery and consumption of liquid food. An array of three 8 mm LED lights (red, yellow, and green; ENV-222M), located above each of the reinforcer levers, could be illuminated to signify the availability of cocaine and food reinforcers. A single white 25 mm light (ENV-229M) was located above the observer lever. Two infusion pumps (3.3 rpm, model PHM-100, MED Associates Inc.) were mounted inside each cubicle, one delivering liquid food and the other i.v. cocaine, from 10 cc syringes through Tygon tubing. Cocaine was delivered using a single channel fluid swivel (MS-1, Lomir Biomedical, Malone, NY) mounted on a balance arm, allowing rats free movement; food was delivered into the steel cup.

Liquid Food Training

Lever-pressing was initially shaped in daily 2-hr training sessions in which liquid food (vanilla flavor Ensure® protein drink, Abbott Laboratories, Abbott, IL, diluted to 56% in water) reinforced responding under an FR 1 schedule of reinforcement. Simultaneous illumination of the red, yellow and green cue lights above the right reinforcer lever signaled that responding on that lever had scheduled consequences. Responses on the other levers were recorded but had no scheduled consequences, and the associated cue lights remained off. Completion of the response requirement turned off the cue-light array and delivered 75 μ l of liquid food over 4.2 s. Responding was reinforced under this schedule until rats earned 100 food reinforcers in a single 2-hr session, and 90% of total responses were emitted on the food-associated lever. Thereafter, the ratio requirement was increased gradually to FR 5, and food training continued until rats again earned 100 reinforcers in a single session.

When these criteria were met, a chained schedule of food reinforcement was introduced in which one response on the observer lever initiated an FR 5 timeout 20-s schedule on the right reinforcer lever. Daily 2-hr training sessions were initiated after the rat was placed in the chamber, by the delivery of one response-independent, automated delivery of liquid

food. Thereafter, the white cue light above the observer lever was illuminated, and one response on that lever turned off the cue light and simultaneously turned on the array of cue lights over the right reinforcer lever. Completion of the FR 5 response requirement on the right reinforcer lever turned off the cue-light array, produced a food reinforcer, and initiated a 20-s timeout (including the 4.2-s food infusion) period. Responses on other levers were recorded and reset the ratio requirement on the right reinforcer lever. This was frequent initially, but happened rarely under baseline conditions once rats met training criteria (resets were not quantified for the experimental manipulations data). After food delivery and expiration of the time out, a new chain was initiated by illumination of the white cue light above the observer lever. Rats trained under this schedule until they earned 100 food reinforcers in a single session.

Finally, sessions were modified to include five sequential 20-min components of food availability, with 2-min intercomponent timeout periods. In these sessions, the same chained schedule was implemented in which one response on the observer lever initiated an FR 5 timeout 20-s schedule on the right reinforcer lever. Each component began with a response-independent food delivery. A maximum of 15 food reinforcers could be earned in each component, and responding was reinforced under this schedule until rats earned 15 food reinforcers in all five components over three consecutive training sessions. After these criteria were met, rats were prepared with i.v. catheters.

Surgery

Rats were anesthetized by isoflurane/oxygen vapor and implanted with chronic indwelling i.v. catheters as described previously (Thomsen & Caine, 2005). Briefly, a catheter was inserted 3.2 cm (females) or 3.7 cm (males) into the right external jugular vein and anchored to the vein. The catheter ran s.c. to the base located at the midscapular region. All animals were allowed to recover for ≈ 7 days before being given access to i.v. cocaine. During this period, a prophylactic dose of ticarcillin (20 mg/kg) was delivered daily through the catheter. Thereafter, catheters were flushed daily with sterile saline containing heparin (3 USP U/0.1 ml). If blood could not be withdrawn through the catheter, then catheter patency was tested by administering a solution containing 25 mg/ml ketamine and 1.25 mg/ml midazolam (0.05-0.1 ml) through the catheter. Animals with patent catheters exhibited prominent signs of sedation within 3 s of infusion. Animals with faulty catheters were prepared with a new catheter in the left jugular vein, unless both veins were exhausted, in which case they were removed from the study. Only data collected with patent catheters were included.

Cocaine Self-Administration Training

Cocaine self-administration started 5-7 days after surgery with daily 2-hr sessions, under a chained schedule in which one response on the observer lever initiated an FR 1 timeout 20-s schedule on the left reinforcer lever. Sessions started with a response-independent cocaine infusion to fill the catheter (17 μ l) and to deliver one unit dose of cocaine (1.0 mg/kg). Thereafter, the white stimulus light over the observer lever was illuminated and one response on that lever turned off the cue light and simultaneously turned on the red, yellow, and green cue-light array over the left reinforcer lever. Completion of the response requirement on the left lever produced an i.v. infusion of 1.0 mg/kg cocaine and initiated a 20-s timeout period (including drug infusion time), during which the cue-light array was turned off and responses had no scheduled consequences. Rats were weighed before each session, and the infusion duration was adjusted to ensure accurate unit doses using 5.6 mg/ml cocaine (e.g., 1.0 mg/kg for a 320 g rat was delivered over 3.2 s in 56 μ l). In subsequent training sessions, the response requirement on the left reinforcer lever was gradually increased to FR 5, and training continued until cocaine self-administration behavior

stabilized, defined as three consecutive sessions with a minimum of 10 mg/kg of cocaine self-administered per 2-hr session and 90% of total responses on the drug-associated reinforcer lever. Responses on other levers were recorded and reset the ratio requirement on the drug-associated lever.

In the last cocaine-training phase, sessions were modified to include five sequential 20-min components of cocaine availability (1.0 mg/kg/infusion), with 2-min intercomponent timeout periods. The same FR 1 FR 5 chained schedule was used, each component beginning with a response-independent automated infusion. This schedule remained in effect until cocaine self-administration behavior stabilized, satisfying the following criteria: 10 mg/kg of cocaine self-administered per session, 1 reinforcer earned per component, and 90% of total responses on the drug-associated reinforcer lever. After these criteria were met, rats were given access to 0.32 mg/kg/infusion cocaine for at least 1 day (and until approximately ten reinforcers were earned per component) before choice training began, to ensure that the rats would emit sufficiently high rates of responding reinforced by cocaine.

Assessment of Cocaine versus Food Choice

Choice training was based on procedures described previously in rhesus monkeys (Negus, 2003). Daily sessions consisted of five 20-min components separated by 2-min intercomponent timeout periods. Responding on the right reinforcer lever resulted in delivery of 56% liquid food, and responding on the left reinforcer lever resulted in infusion of various unit doses of cocaine. One response on the observer lever turned off the associated cue light and initiated a concurrent FR 5 timeout 20-s FR 5 timeout 20-s schedule of reinforcement, with the left cue-light array flashing to indicate cocaine reinforcer availability and magnitude. Longer flashes and shorter interflash intervals were associated with higher cocaine doses. In all cases, flashing frequency was every 3 s, with the duration of illumination increasing from component 1, lights remaining off, to component 5, lights remaining on; in components 2, 3 and 4, illuminations was 0.1, 0.3, and 1.0 seconds, respectively (i.e., 2.9, 2.7, and 2.0 seconds interflash intervals). The right cue-light array remained illuminated to indicate liquid-food reinforcer availability and magnitude (56% in water). Each component was initiated by one response-independent automated delivery of each reinforcer (cocaine, then food) that would be available in the component, and the illumination of the observer lever's cue light to signify that responses had scheduled consequences. The different cocaine doses for each component were achieved by varying the infusion time, adjusted to each rat's bodyweight, and were delivered in ascending order: 0, 0.032, 0.10, 0.32, 1.0 mg/kg/infusion. A 1.8 mg/ml solution was used, and infusion volumes and durations were 0, 5.6, 18, 56, 180 μ l and 0, 0.32, 1, 3.2, 10 s for a 320 g rat. Responding on one reinforcer lever reset the ratio requirement on the other. Per component, 15 total reinforcers were available, and completion of the response requirement on the cocaine-associated lever during availability of the zero cocaine dose counted as one reinforcer even though no cocaine was delivered. If all 15 reinforcers were earned in less than 20 min, all stimulus lights were extinguished, and responding had no scheduled consequences for the remainder of the 20-min component. Choice training continued until behavior stabilized, defined as three consecutive sessions in which 5 reinforcers/component were earned in components 1-4 and 1 reinforcer was earned in component 5, and in which the dose of cocaine that produced > 80% cocaine choice on any given day was within one-half log unit of the 3-day mean.

Testing procedures—Once training was completed, testing sessions commenced to evaluate the role of environmental and pharmacological variables on choice between cocaine and food in five experiments. Rats were assigned randomly to experiments as they met criteria, and data from all rats that were tested in at least one experiment were included in

the baseline data. The variables manipulated were: 1) within-session versus between-session cocaine dose presentation, 2) removal of antecedent and reinforcing stimuli associated with cocaine choice, 3) magnitude of the food reinforcer, 4) FR value on the food- and cocaine-associated levers, and 5) acute and chronic treatment with amphetamine. The food reinforcer remained constant, at 56% food in water, for all but Experiment 3. For Experiments 1, 3, and 4, each experimental manipulation was implemented for 3 consecutive days, and data were averaged across the 3 days for data presentation and analysis (with the exception that data are shown for each day for Experiment 1 to show the degree of reliability). For Experiment 2, rats were tested on only one occasion to decrease the likelihood of behavioral extinction due to omission of cocaine-associated stimuli. Acute drug pretreatments during Experiment 5 were, by definition, also generally tested on only one occasion (in the rare cases where a dose was repeated, determinations were separated by baseline sessions). After each manipulation, baseline choice behavior was reestablished in each rat. Baseline choice behavior could be reestablished in one training session if: five reinforcers/component were earned in components 1-4 and one reinforcer was earned in component 5 and, and if the dose of cocaine that produced > 80% cocaine choice was within one-half log unit of the previously established baseline. Alternatively, a new baseline was established with criteria identical to those used for initial baseline (see above).

Experiment 1

We first examined choice when the same dose of cocaine was tested across the five components, but varied between sessions, to test the comparability of the shape and position of cocaine dose-effect curves determined between- and within-sessions. Response-independent priming deliveries of both reinforcers were given at the start of each component, and stimulus conditions above each lever corresponded to the magnitude of each reinforcer. Cocaine doses were presented for 3 consecutive days in a pseudorandom order counterbalanced across subjects.

Experiment 2

Both visual (cue lights) and pharmacological (response-independent cocaine “priming” infusions) cues associated with cocaine availability might have served as discriminative stimuli. In addition, both auditory stimuli (sound of the drug infusion pump) and pharmacological stimuli (response-contingent cocaine injections) were consequent stimuli following completion of the response requirement on the cocaine-associated lever. To assess the role of these stimuli on choice between cocaine and food, the second experiment examined the effects of omitting each stimulus, one at a time, from the experimental apparatus. Stimuli were omitted in a nonsystematic order between rats. During sessions designed to assess the contribution of the drug pump noise, the pump was placed outside the sound-attenuating cubicle.

Experiment 3

The magnitude of the food reinforcer was manipulated by making available concentrations of food from 0% (water) to 56% (Ensure diluted with water). Each concentration was available for the entire session. Stimulus (cue) conditions on the right, food-associated lever were varied corresponding with the food reinforcer: When water was available, none of the cue lights were illuminated; when 5.6%, 18%, and 56% food were available, one (red), two (red and yellow), or three (red, yellow, and green) cue lights were illuminated, respectively. Concentrations of food greater than 56% were not tested beyond pilot experiments, which indicated that choice behavior was similar for 56% and 100% food.

Experiment 4

The relative response requirements for food and cocaine were manipulated. In one manipulation, the FR on the cocaine-associated lever was held constant, and the FR on the food-associated lever was varied from FR 1 to FR 25. In another manipulation, the FR on the food-associated lever was held constant, and the FR on the cocaine-associated lever was varied from FR 1 to FR 45.

Experiment 5

The effects of acute and chronic pretreatment with the indirect monoamine agonist d-amphetamine were evaluated. In acute tests, d-amphetamine was administered i.p. 10 min before the session, at doses of 0.32, 0.56, 1.0 and 1.8 mg/kg. Chronic treatment was achieved with the use of osmotic minipumps (Alzet, model 2ML2) implanted s.c., delivering drug continuously at a rate of 5 μ l/hr for 7 days, during which time rats were tested daily. D-amphetamine concentrations were adjusted for each rat to deliver sterile water, 0.1 mg/kg/hr, or 0.32 mg/kg/hr (doses selected based on pilot studies). Most rats received more than one acute dose of amphetamine, with at least three sessions of baseline between acute doses. However, due to attrition, not all doses were tested in all rats. In an effort to avoid confounding effects due to tolerance, different rats were used for the acute and chronic administrations, and only 2 rats were tested with both chronic amphetamine doses (> weeks apart).

Data Analysis

The primary dependent variables for each response period were: (1) percent cocaine choice, calculated as (number of ratios completed on the cocaine-associated lever $\div$ total number of ratios completed) $\times$ 100, (2) response rate, calculated as the total number of responses $\div$ total time responses had scheduled consequences, (3) total number of reinforcers earned (i.e., total number of ratios completed), (4) number of cocaine injections earned, and (5) number of food reinforcers earned. The latter two measures are reported for the baseline and Experiment 1 data only, for brevity. The A_{50} value of the cocaine-choice dose-effect function was defined as the dose of cocaine that produced 50% cocaine choice in each rat, and was determined by interpolation from two adjacent points spanning 50% cocaine choice (log-linear). During some manipulations, rats allocated all behavior to the cocaine-associated lever during availability of the lowest unit dose of cocaine (0.03 mg/kg). Under these conditions, the A_{50} value was estimated as 0.03 mg/kg. In other manipulations, rats allocated all behavior to the food-associated lever across all five components, and the A_{50} value was estimated as 1.0 mg/kg. Group means and 95% confidence intervals were calculated from the individual A_{50} values. A_{50} values were considered statistically different from control conditions if the 95% confidence intervals did not overlap.

Repeated measures ANOVA was used to analyze the effects of cocaine dose on cocaine choice, response rates, and total reinforcers earned, as well as cocaine injections earned and food reinforcers earned (the latter for the baseline data only). Repeated measures ANOVA was also used to analyze the effect of component for the between-session dose-effect determination in Experiment 1. In a few cases, rats were missing percent cocaine choice for one or two components (i.e., cocaine doses) because no reinforcers were earned; in those cases the whole dose-effect function of that rat was omitted from analysis because repeated measures ANOVA cannot be performed with missing values (this accounts for discrepancies in the reported degrees of freedom). Standard linear model ANOVA was used to analyze effects of sex, manipulations, and for the baseline data only, of test day. While repeated measures statistics could have been employed in a few of the latter comparisons, most manipulations were not performed in all subjects, and we therefore chose to maintain the same analysis method across experiments to avoid biased significance levels. Significant

effects of cocaine dose were scrutinized post hoc by Dunnett's multiple comparisons test versus the no-injection component (zero dose). Significant effects of manipulation (or test day for the baseline data) were scrutinized post hoc by Bonferroni posttest versus baseline (or between days 1, 2 and 3 for the baseline data). With the exception of scrutinizing the baseline data for effects of test day, all other analyses were performed on data averaged across the triplicate determinations. For chronic d-amphetamine, data from days 5, 6, and 7 of drug administration were averaged in each rat. Significance level was set at $p < .05$.

Drugs

Cocaine hydrochloride was provided by the National Institute on Drug Abuse, National Institutes of Health (Bethesda, MD) and was dissolved in saline; d-amphetamine sulfate was purchased from Sigma-Aldrich (St. Louis, MO) and was dissolved in sterile water. Doses reflect the weight of the salts.

Results

Baseline Cocaine Choice and Experiment 1: Within- versus Between-session Dose Presentation

Figure 1, left panels, shows baseline behavior of 26 rats, in which the cocaine choice curve was determined within session. Percent cocaine choice increased with cocaine dose ($F_{4,100} = 442$, $p < .0001$); unit doses of 0.1, 0.32 and 1.0 mg/kg maintained higher % cocaine choice than in the no-infusion condition ($p < .01$). Individually, all but 4 rats responded exclusively on the food-associated lever in the first component (zero cocaine), and all but 3 responded exclusively on the food-associated lever in the second component (0.03 mg/kg/infusion). At 0.1 mg/kg/infusion cocaine, 15 of 26 rats responded only on the food-associated lever, the other 11 responded on both levers, and none responded on the cocaine-associated lever exclusively. At 0.32 mg/kg/infusion cocaine, all but 3 rats emitted over 90% of responses on the cocaine-associated lever (64%, 67% and 89%), and 17 of 26 rats chose cocaine exclusively. All rats pressed the cocaine-associated lever exclusively at the highest dose.

Response rate was related to cocaine dose ($F_{4,100} = 51$, $p < .0001$), and was significantly decreased at the highest two doses, when cocaine was chosen almost exclusively ($p < .01$), while the two lower doses were associated with rates higher than the no-cocaine condition ($p < .05$). Total number of reinforcers earned was close to the maximum number available up to the highest cocaine dose, at which it was decreased to typically 3-4 reinforcers (main effect [$F_{4,100} = 174$, $p < .0001$]). The bottom panels of Figure 1 show the dose-effect curves of cocaine injections earned per component, which had the inverted U-shape typical of FR schedules of cocaine reinforcement, as well as food reinforcers earned per component. Both cocaine injections ($F_{4,100} = 136$, $p < .0001$) and food reinforcers ($F_{4,100} = 319$, $p < .0001$) were related to component/cocaine dose, with all but the lowest cocaine dose reaching significance relative to the no-cocaine condition ($p < .01$). There were no significant differences in choice or estimated potency (A_{50}) across the three testing days (see lines 4-6 in Table 1). We detected no significant effect of sex on the choice curves, nor did inspection of the individual data suggest any differences.

Figure 1, center panels, shows the cocaine dose-effect functions assessed by between-session determinations (i.e., the same dose was available in all five components) in the 9 rats completing Experiment 1). As with baseline conditions, each dose was tested for three sessions, and the determinations showed good repeatability in individual rats, and yielding closely matched potencies for cocaine choice (see Table 1). A few rats departed from this stable pattern, as follows. At 0.10, 1 rat switched from taking (almost) exclusively food on days 1 and 2, to taking exclusively cocaine on day 3, and 2 rats chose food or cocaine on

alternate days in one or two individual components, while maintaining the overall reinforcer distribution relatively constant over days. At 0.32 mg/kg/infusion, 1 rat responded very little on day 1 but responded avidly on the cocaine-associated lever on days 2 and 3, while another rat switched gradually from all-cocaine to all-food over the three days. A 3rd rat switched from all-cocaine on days 2 and 3 to choosing food exclusively in the first three components of day 3, but then earned exclusively cocaine reinforcers in the last two components.

All five measures shown (% cocaine choice, response rate, total reinforcers earned, cocaine reinforcers earned, food reinforcers earned) were related to cocaine dose (all $p < .0001$) in patterns similar to the baseline data, with 0.32 and 1.0 mg/kg/infusion cocaine reaching significance versus. no-cocaine for all measures ($p < .01$). The data did not suggest any effect of sex or day in the between-session group, and these factors were not statistically significant. More importantly, dose-effect functions for cocaine choice were comparable between the two methods. Indeed, individual data showed the same patterns as the baseline conditions, with exclusive food choice in the first two components, exclusive cocaine choice in the last component, and 5 of 9 rats responding on both levers in components 3 and 4. ANOVA revealed no significant effect of between- versus within-session determination on cocaine choice, and calculated potencies were comparable (Table 1). Some measures did differ between the two methods, mainly numbers of cocaine reinforcers earned (effect of within vs. between method [$F_{1,132} = 9.3, p < .01$], cocaine dose by method interaction [$F_{4,132} = 7.2, p < .0001$]). This difference was driven by a lower peak of the cocaine dose-effect function for the ratio of cocaine to food reinforcers in the between-sessions condition, that is, when 0.32 mg/kg/infusion cocaine was available (compare lower left and center panels in Figure 1; $p < .001$). This effect was typical of the rats tested, rather than due to a few “outliers”. Numbers of food reinforcers earned were comparable between the two methods, and total reinforcers earned reflected the difference in cocaine reinforcers earned when 0.32 mg/kg/infusion cocaine was available (cocaine dose by method interaction [$F_{4,132} = 3.3, p < .05$]; post hoc $p < .01$). Rates of responding were generally comparable, but were somewhat higher in the between-session method when no cocaine was available (cocaine dose by method interaction [$F_{4,132} = 3.3, p < .05$]; post hoc $p < .01$). Rates were also less stable across the three days, with 5 of 9 rats showing a marked tendency to increase response rates on the last or last two days relative to the first day that a dosing regimen was introduced.

Figure 1, right panels, shows the same data as the center panels, but graphed for each cocaine unit dose as a function of component in the session, averaged over the triplicate test. All five measures shown were again related to cocaine dose (all $p < .0001$). Scrutiny of Figure 1, bottom right panel, reveals that cocaine intake was stable through the session, while food intake tended to decrease moderately as a function of component for all cocaine doses. All but 2 of 9 rats showed this tendency. This observation is supported by the ANOVAs, which showed no effect of component on cocaine reinforcers, but a significant effect of component on food reinforcers ($F_{4,160} = 9.0, p < .0001$), with no cocaine dose by component interactions. Cocaine reinforcers being fairly constant, this “descending drift” in food reinforcers resulted in a similar effect of component on total reinforcers earned ($F_{4,160} = 20, p < .0001$), and in a corresponding “ascending drift” of the percent cocaine choice as a function of component ($F_{4,160} = 3.3, p < .05$), with a significant cocaine dose by component interaction ($F_{16,160} = 2.3, p < .01$). Effects on response rate were less orderly, but also showed some “descending” or shallow inverted U patterns as a function of component ($F_{4,160} = 6.9, p < .0001$), with a significant cocaine dose by component interaction ($F_{16,160} = 1.8, p < .05$).

Experiment 2: Removal of Cocaine-associated Cues or Cocaine Infusions

To determine the role of cocaine-associated antecedent (cue lights and response-independent infusions) and consequent stimuli (sound of drug pump and response-contingent infusions) in cocaine choice, these were removed, one by one, from the test environment. Figure 2 shows the data obtained. For all these and the remaining data sets, each measure was significantly related to cocaine dose similarly to what was reported for baseline data; these analyses will not be detailed for brevity. Individual data did not suggest an effect of sex, and there were no significant effects of sex in any of the manipulations.

Compared to baseline conditions, in which all stimuli were intact, removal of cocaine-associated visual or auditory cues (left half of Figure 2) produced small, nonsignificant decreases in the cocaine choice curve and the potency of cocaine. At 0.32 mg/kg/infusion cocaine, removing visual cues produced a decrease in cocaine choice in 4 of 11 rats, and an increase in 1; similar effects were seen at 0.10 mg/kg/infusion cocaine. After removal of the visual cues the A_{50} decreased in 2 rats, increased in 5. Removing auditory cues decreased cocaine choice in 2 of the 9 rats exposed to this manipulation at 0.1 mg/kg/infusion and in 3 of 9 rats at 0.32 mg/kg/infusion, and the A_{50} increased in 3 rats. Table 2 shows mean A_{50} values for these and other parametric manipulations, which indicate that removal of exteroceptive stimuli (antecedent or consequent) altered the cocaine choice dose-effect function by less than 1.7-fold (not significant).

In contrast to these effects, removal of response-independent “priming” cocaine infusions and response-contingent cocaine infusions (right two columns in Figure 2) produced rightward and downward shifts in the cocaine choice dose-effect function. There was a significant effect on cocaine choice of both response-independent cocaine infusion removal ($F_{1,80} = 9.9, p < .01$) and of response-contingent infusion removal ($F_{1,25} = 49, p < .0001$), as well as manipulation by cocaine dose interactions ($[F_{4,80} = 19, p < .0001]$ and $[F_{4,25} = 12, p < .0001]$, respectively). The mean A_{50} value for cocaine choice was increased by 4.5- and 5.6-fold, respectively ($p < .01$ and $p < .001$; Table 2). Removal of response-independent cocaine infusions decreased cocaine choice to zero in 8 of 11 rats at 0.32 mg/kg/infusion and in 6 of 11 rats at 1.0 mg/kg/infusion, typically going from 100% cocaine. The A_{50} increased in 9 of 11 rats. Removal of response-contingent cocaine infusions decreased cocaine choice in all 6 rats, at both 0.32 and 1.0 mg/kg/infusion, but only eliminated cocaine choice in 2 of 6 rats at 0.32 mg/kg/infusion, and in none at 1.0 mg/kg/infusion. The A_{50} increased in all 6 rats. Thus, although the average level of attenuation of cocaine choice was comparable between these two manipulations, the pattern of behavior differed markedly. The peak 40% cocaine choice during removal of response-independent cocaine infusions reflected the average between 6 rats that emitted 0% cocaine choice and 4 rats that emitted 100% cocaine choice (1 rat failed to respond altogether). In contrast, the peak 47% cocaine choice during removal of response-contingent cocaine infusions reflected similar patterns of behavior across rats: Responding was initially directed toward the cocaine-associated lever, with a subsequent reallocation of responding toward the food-associated lever (range: 7%-77% cocaine choice). During both of these manipulations, the typical decreases in response rates and total number of reinforcers earned during availability of 0.32 and 1.0 mg/kg/injection cocaine were more or less attenuated compared to baseline control conditions. The latter effects were accompanied by significant “priming infusion” by cocaine dose interactions on rate ($F_{4,80} = 6.1, p < .001$) and total reinforcers earned ($F_{4,80} = 3.2, p < .05$), a significant effect of reinforcer removal on total reinforcers ($F_{1,40} = 15, p < .01$), and a significant cocaine dose by response-contingent infusion interaction ($F_{4,80} = 6.1, p < .001$). These effects were most likely a consequence of behavioral reallocation to food, which maintained higher rates of responding than cocaine.

Experiment 3: Varying the Food Reinforcer Magnitude

Figure 3 shows the effects of decreasing the food reinforcer magnitude, achieved here by decreasing the concentration of liquid food in water from the 56% baseline. Decreasing the food concentration produced systematic leftward and upward shifts in the cocaine choice dose-effect function, with a significant effect of food concentration ($F_{3,116} = 6.8, p < .01$) and a significant cocaine dose by food concentration interaction ($F_{12,116} = 4.4, p < .0001$). Of 7 rats tested, 2 showed increased cocaine choice at 18% food, 2 more showed increases at 5.6%, and all rats did so at 0% food. Two-thirds of increases represented complete reallocation of behavior, that is, 100% cocaine choice, while one third reflected partial increases (50% - 95% cocaine choice). Cocaine choice was significantly increased at 5.6% and 0% (water) food concentrations (see Figure 3 for post-hoc significances). The 5.6% and 0% concentrations also produced significant 4.0- and 6.7-fold leftward shifts in calculated potency of cocaine (see Table 2). Note that decreasing the food concentration also increased cocaine choice during the first component, when no cocaine was available and none of the stimulus lights above the cocaine lever were illuminated.

Response rates and number of reinforcers earned decreased with decreased food concentration, with significant effects of food concentration ($[F_{3,128} = 11, p < .0001]$; $[F_{3,128} = 4.6, p < .01]$) and cocaine by food interactions ($[F_{12,128} = 7.3, p < .0001]$; $[F_{3,128} = 6.8, p < .0001]$). Rates in the first three components were decreased at all food concentrations relative to baseline, while total numbers of reinforcers earned were decreased only at the two lower concentrations (see Figure 3). This result was most likely a consequence of a reallocation of behavior from food, which maintained relatively high rates of behavior, to cocaine, which maintained lower rates of behavior. When 0% food (water) was available, responding was allocated almost exclusively to the cocaine-associated lever during all five components. Under these conditions, the total reinforcers earned reflected the inverted U shape of the cocaine dose-effect function.

Experiment 4: Varying the Response Requirement for Food and Cocaine

Figure 4, left panels, shows the effects of manipulating the FR response requirement on the food-associated lever (FR_{food}) while holding the FR requirement on the cocaine-associated lever constant at FR 5. Varying FR_{food} produced systematic shifts in the cocaine choice dose-effect function, with a significant effect of FR_{food} ($F_{3,100} = 9.1, p < .001$) and a cocaine dose by FR_{food} interaction ($F_{12,100} = 6.6, p < .0001$). Decreasing FR_{food} to 1 produced a rightward shift, with a significant decrease in cocaine choice when 0.32 mg/kg/infusion cocaine was available ($p < .05$). Specifically, at this dose 2 of 7 rats reallocated their behavior to all food choice (the same 2 rats on days 1 and 2, 1 new rat on day 3). Increasing FR_{food} to 15 and 25 produced leftward and upward shifts in the cocaine choice dose-effect function, with significantly increased cocaine choice when 0.032 and 0.1 mg/kg/infusion cocaine was available ($p < .01$ to $p < .001$). $FR_{\text{food}} = 15$ effected full reallocation toward cocaine choice in 4 of 8 rats, remaining consistent over the three test days. At $FR_{\text{food}} = 25$, the behavior of all 5 rats was affected in components 1-3; 1 stopped responding altogether in components 1-3, while the other 4 reallocated behavior to cocaine (3 did so from day 1, 1 did not show a change until day 2). $FR_{\text{food}} = 25$ also yielded a significant 5.0-fold leftward shift in cocaine's potency (Table 2).

Response rates were somewhat decreased for all FR_{food} manipulations ($p = .06$), but the effect, seen in most rats on day 1, tended to dissipate over days 2 and 3. Numbers of reinforcers earned were unaffected by decreased FR_{food} but decreased with increased FR_{food} (main effect $[F_{3,104} = 6.6, p < .01]$, cocaine by FR_{food} interaction $[F_{12,104} = 3.4, p < .001]$). This effect was evident, with varying intensity, in all tested rats over all three test days, and was most likely a consequence of a reallocation of behavior from food, which maintained

relatively high rates of behavior, to cocaine, which maintained lower rates of behavior. Thus for the high FR_{food} values, as observed for low food reinforcer magnitudes (Experiment 3), the total reinforcers earned reflected the inverted U shape of the cocaine dose-effect function.

Figure 4, right panels, shows the effects of manipulating the FR response requirement on the cocaine-associated lever (FR_{cocaine}) while holding the FR requirement on the food-associated lever constant at FR 5. Varying FR_{cocaine} also produced systematic shifts in the cocaine choice dose-effect function, with a significant effect of FR_{cocaine} ($F_{3,92} = 9.1, p < .001$) and a cocaine dose by FR_{cocaine} interaction ($F_{12,92} = 6.6, p < .0001$). Decreasing FR_{cocaine} to 1 produced a leftward shift, with a significant increase in cocaine choice when 0.10 mg/kg/infusion cocaine was available ($p < .05$). This effect was not stable over days in the individual rats, with 1 or 2 of the 6 rats showing an increase on a given day. Increasing FR_{cocaine} to 25 and 45 produced rightward and downward shifts in the cocaine choice dose-effect function, with significantly decreased cocaine choice when 0.32 and/or 1.0 mg/kg/infusion cocaine was available ($p < .001$, see Figure 4). At $FR_{\text{cocaine}} = 25$, 4 of 7 rats reallocated behavior from the cocaine-associated lever to the food-associated lever, consistent over test days. At $FR_{\text{cocaine}} = 45$, the effect grew over days, with 3 of 5 rats reallocating behavior to the food-associated lever when 0.32 mg/kg/infusion cocaine was available on day 1, then 4 rats, then all 5. The same trend was apparent at the highest cocaine dose, going from 2 to 3 rats reallocating behavior over test days. An FR_{cocaine} of 15 was also tested and produced results similar to $FR_{\text{cocaine}} = 25$ with 3 of 6 rats reallocating behavior to the food-associated lever, consistent over test days (data not shown). The highest FR_{cocaine} also yielded a significant 3.6-fold rightward shift in the dose-effect function (Table 2). In all cases, the rats showing an effect reallocated behavior fully (from 0% to 100% cocaine choice or from 100% to 0% cocaine choice).

There was a trend for increased response rates during availability of 0.32 and 1.0 mg/kg/infusion cocaine for $FR_{\text{cocaine}} = 45$, when responding was allocated more to the food-associated lever, but effects on response rates and total reinforcers earned were not statistically significant or otherwise notable.

Experiment 5: Acute and Chronic Treatment with d-amphetamine

Figure 5, left panels, shows the effects of acute pretreatment with d-amphetamine on cocaine choice. Increasing doses of d-amphetamine produced dose-dependent leftward and upward shifts in the cocaine choice dose-effect function, with a significant effect of amphetamine ($F_{3,148} = 11, p < .0001$) and a significant cocaine by amphetamine interaction ($F_{12,148} = 9.1, p < .0001$). Cocaine choice was significantly increased by 0.56 and 1.0 mg/kg amphetamine when the two lowest cocaine doses were available, and also when no cocaine was available ($p < .05$ to $p < .001$, see Figure 5). Doses of 0.56 mg/kg and 1.0 mg/kg also produced significant 2.9- and 3.6-fold leftward shifts, respectively, in the potency of cocaine (Table 3). The 1.8 mg/kg amphetamine dose produced such marked decrements in response rates that most rats were missing percentages of choice at this dose, which was therefore excluded from the ANOVA on choice. Indeed, rates of responding and total numbers of reinforcers earned were both significantly decreased as a function of amphetamine dose ($[F_{4,184} = 15, p < .0001]$, $[F_{4,184} = 28, p < .0001]$), with a cocaine by amphetamine interaction ($[F_{16,184} = 7.9, p < .0001]$, $[F_{16,184} = 7.6, p < .0001]$). Effects were significant for 1.0 and 1.8 mg/kg amphetamine, the highest dose resulting in practically flattened curves (see Figure 5 for post-hoc statistical details).

Because the duration of treatment may be a critical factor for determining the effects of candidate medications, we also tested chronic infusion of d-amphetamine, shown in Figure 5, right panels. After 24 hr of continuous d-amphetamine infusion, the cocaine choice dose-

effect function was shifted leftward and upward in a manner that resembled acute pretreatment with d-amphetamine (data not shown). In contrast to those effects, 5-7 days of continuous d-amphetamine infusion shifted the cocaine choice dose-effect function rightward and downward in a dose-dependent manner, supported by a significant effect of amphetamine treatment ($F_{2,60} = 13, p < .001$) and a cocaine dose by amphetamine dose interaction ($F_{8,60} = 7.8, p < .0001$). Both amphetamine doses produced significant decreases in cocaine choice when 0.32 mg/kg/infusion cocaine was available ($p < .001$ vs. chronic vehicle treatment), and produced significant rightward shifts in the calculated potency of cocaine (Table 3). Response rates and total numbers of reinforcers earned were increased during days 5-7 of chronic infusion with d-amphetamine, supported by a cocaine dose by amphetamine dose interaction on the rate factor ($F_{8,60} = 1.4, p < .01$), reaching significance at the highest amphetamine dose (see Figure 5). Numbers of reinforcers earned were related to amphetamine dose ($F_{2,60} = 4.6, p < .05$), with a significant cocaine by amphetamine interaction ($F_{8,60} = 8.1, p < .0001$), and were increased at both amphetamine doses relative to vehicle (see Figure 5).

The rightward shift in cocaine choice persisted a few days after removal of the minipump, typically returning gradually to baseline within a week (data not shown). We did not see evidence of a “rebound” leftward shift. Two rats were also implanted with minipumps delivering 0.56 mg/kg/hr d-amphetamine, but this dose was discontinued after it resulted in marked stereotyped grooming in one rat, and proved lethal within 2 days of treatment in both rats tested.

Discussion

This study employed a cocaine versus food choice procedure in male and female rats, similar to procedures previously reported in rhesus monkeys (Negus, 2003), and related to human studies of novel medication effects on choice between cocaine and an alternative reinforcer, typically money or vouchers (Donny et al., 2003; Martinez et al., 2007). The purpose of this study was to validate our choice procedure by showing that it produced repeatable data and was sensitive to parametric manipulations known to modify cocaine choice in nonhuman primates (Negus, 2003). We compared cocaine choice dose-effect functions determined within-session and between-session. We examined the effect of removing cocaine-associated visual or auditory cues, and of removing response-independent or response-contingent cocaine infusions. We assessed the effect of varying the magnitude of the food reinforcer, and the response requirement for food or cocaine. Finally, we evaluated acute and chronic treatment with d-amphetamine.

Baseline Cocaine Choice and Experiment 1: Within- versus Between-session Dose Presentation

Holding the food reinforcer constant, allocation of behavior to the cocaine-reinforced lever increased as a function of cocaine dose, as previously observed in cynomolgus monkeys (*Macaca fascicularis*) and rhesus monkeys (Czoty, McCabe, & Nader, 2005; Negus, 2003; Paronis, Gasior, & Bergman, 2002). The baseline data obtained in the present study were also comparable to what we reported previously in rats (Thomsen et al., 2008). Rates of responding decreased at the higher cocaine doses, for which cocaine was chosen almost exclusively. In this respect, the procedure was similar to classic, single-reinforcer FR schedules of reinforcement, in that high doses of cocaine were self-administered reliably at relatively low rates, and with low variability (Barrett, Miller, Dohrmann, & Caine, 2004). Using a similar drug versus food, concurrent FR schedule of reinforcement in cynomolgus and rhesus monkeys, rates of responding on the drug-reinforced manipulandum were found relatively constant across doses, for both cocaine and 3,4-methylenedioxymethamphetamine

(MDMA, “ecstasy”), despite robust dose-dependent changes in drug versus food choice (Banks, Gould, Czoty, & Nader, 2008). However, total response rates did decrease significantly with higher drug doses in that study as well, in agreement with the present results.

We found the cocaine-dose choice curve to be stable in each rat—in fact more so than under a single-reinforcer, multiple-component procedure of cocaine self-administration used in our laboratory, in which a moderate rightward shift was often observed after several months of testing—in that low to moderate doses of cocaine ceased to maintain responding in many rats (unpublished observations). Good stability of choice procedures has also been reported in rhesus monkeys, in which even extended access to cocaine, and withdrawal from extended access, failed to significantly alter cocaine versus food choice (Banks & Negus, 2010; Negus, 2003). This stability of the choice curve is an important feature in making it suitable for testing candidate medications during and after repeated or chronic treatment.

No sex differences were found in any of our assessments of cocaine choice. Although group sizes were not sufficient to detect moderate effects statistically, scrutiny of the individual data did not suggest sex was a notable determinant of the recorded behaviors. This is consistent with studies in rats from our laboratory in which neither sex nor gonadal hormones affected cocaine dose-effect curves significantly (Caine et al., 2004). Sex differences in cocaine self-administration behavior have been observed in rats under different experimental conditions, such as extended access (Lynch & Taylor, 2004). While clinical studies have found evidence for gender differences in the subjective and physiological effects of cocaine, differences were often modest, and we are not aware of any clinical studies that have examined gender differences in cocaine choice (Evans, Haney, Marian, & Foltin, 1999; Lukas et al., 1996; Sofuoglu, Dudish-Poulsen, Nelson, Pentel, & Hatsukami, 1999).

The first experiment examined choice when the same dose of cocaine was tested across the five components (between-session, random order) rather than within-session in ascending order, to test the comparability of the shape and position of the dose-effect curve between procedures. The main finding of this experiment was that the choice dose-effect functions were comparable regardless of the method of dose presentation. The only noticeable difference was a somewhat lower cocaine intake at the peak unit dose of 0.32 mg/kg when the same dose was available throughout the session, for reasons that are not clear to us. Cocaine intake was stable through the session, so effects of self-administered cocaine on rate of responding or reinforcing value of cocaine later into the session do not offer a clear explanation for the lower cocaine intake. The lack of effect of the method of dose presentation on cocaine choice is in agreement with findings in rhesus monkeys, in which between-session, and within-session ascending, descending, and mixed order dose presentation all produced comparable choice dose-effect functions and potencies (Negus, 2003), and cocaine dose available in the previous component had little effect on cocaine choice (Paronis et al., 2002).

Although there were moderate but significant effects of component, that is, session time, on several measures in the between-session determinations, these all appeared driven by a moderate decrease in food reinforcers earned as the session progressed, while cocaine intake remained constant. This effect may be attributable to satiety, although rats typically earned and consumed much higher volumes of the same liquid food reinforcer (even undiluted) within a comparable session duration in single-reinforcer FR schedules of food reinforcement in our laboratory (e.g., Barrett et al., 2004). Anorectic effects of cocaine likely contributed to the observed pattern, but since the same trend was apparent, though modest, even when no cocaine was available, it may not be the only factor. It is possible that some

conditioned effects of cocaine in the later components carried over from the baseline/training condition in the form of decreased food intake. It is worth noting that similar trends of percent cocaine choice increasing during the session were observed in rhesus monkeys when intermediate cocaine doses were available throughout the session, the pattern only differing from the present findings in that the monkeys tended to switch from food to cocaine, while the rats maintained cocaine intake constant while decreasing food choices (Negus, 2003).

Experiment 2: Removal of Cocaine-associated Cues or Cocaine Infusions

The second experiment examined the effect of removing cocaine-associated exteroceptive stimuli (cues), and of removing interoceptive cocaine stimuli by withholding response-independent or response-contingent cocaine infusions. Removal of cocaine-associated visual or auditory cues produced only small, statistically nonsignificant rightward shifts in cocaine choice. Note that this minimal control of visual or auditory cues over the operant behavior may not generalize to other species or reinforcers (e.g., nicotine), where exteroceptive cues may have a more profound impact (Caggiula et al., 2001). In contrast to the exteroceptive stimuli, removal of either response-independent ("priming") or response-contingent cocaine infusions resulted in pronounced decreases in cocaine choice. Although both manipulations reduced cocaine choice by about 50-60% as a group, the patterns of behavior differed. During removal of response-independent cocaine infusions, some rats reallocated behavior completely from cocaine to food at cocaine doses that engendered all cocaine choice under baseline conditions, while some rats were unaffected by the manipulation. Thus some rats appeared to rely heavily on the "priming" infusion to allocate behavior for each component, while others appeared to ignore it. This suggests rats used various stimuli in allocating behavior between components; for example, time elapsed since the beginning of the session might also serve as a cue to cocaine dose availability. In contrast, removal of response-contingent cocaine infusions had more uniform effects across subjects: Responding was initially directed toward the cocaine-associated lever, with a subsequent reallocation of responding toward the food-associated lever, similar to patterns of extinction as observed under single-reinforcer schedules of reinforcement. Allocation of behavior towards food was accompanied, in both cases, by higher response rates similar to those emitted during no-cocaine or low-dose cocaine components under baseline conditions.

Experiment 3: Varying the Food Reinforcer Magnitude

In the third experiment, we examined the effect of varying the alternative reinforcer magnitude. Decreasing the concentration of liquid food in water produced concentration-dependent leftward and upward shifts in the choice curve, and replacing food with water resulted in allocation of behavior almost exclusively to the cocaine-associated lever, similar to observation in rhesus monkeys when food pellets were withheld (Negus, 2003). Similarly, in another cocaine versus food choice procedure in rhesus monkeys, cocaine choice was higher when the alternative reinforcer was one food pellet relative to four or more pellets (Nader & Woolverton, 1991; 1992). Even when no cocaine was available (first component), we found that responding was allocated predominantly to the cocaine-associated lever when no liquid food was presented, though at very low rates and earning typically only one to three reinforcers. Pilot experiments indicated that increasing the food concentration to 100% did not affect choice behavior noticeably, and we did not test further food reinforcers that may have produced rightward shifts in the choice curve similar to what was reported in rhesus monkeys (Negus, 2003). Our findings are also similar to results obtained in cocaine-dependent human subjects, where cocaine choice increased as a function of decreased alternative, monetary, reinforcer value (Donny, Bigelow, & Walsh, 2004). It is worth noting that food concentration was held constant through the session in the present investigation, and that varying the food concentration within-session may have had different effects. Thus,

cocaine choice was only related to the alternative reinforcer value in the human study when money was presented by descending value (Donny et al., 2004), while subjects chose cocaine fairly independently of the monetary reinforcers when the latter were presented in ascending order (Donny et al., 2003). In other words, when subjects started out choosing money, they typically switched to cocaine at some dose versus dollar value, but when subjects started out choosing cocaine, they typically did not switch. This suggests that cocaine choice is affected by previous cocaine intake or intoxication.

Although we did vary the magnitudes of both reinforcers, the present paper is limited to choice between intravenous cocaine and a palatable food. Studies in both humans and laboratory animals indicate that the nature of the alternative reinforcer can affect cocaine choice. For example, money was chosen over cocaine more than food or merchandise vouchers of a comparable value in humans (Hart, Haney, Foltin, & Fischman, 2000; Stoops, Lile, & Rush, 2010), and highly sweet saccharin or sucrose solutions were chosen over cocaine by most rats (Lenoir et al., 2007; Cantin et al., 2010). It should be noted that methodological differences between the latter studies and the present experiments may also have contributed to this apparent liquid food versus “intense sweetness” discrepancy (e.g., the presence or absence of a forced sampling phase at the beginning of the session), and it would be interesting to test sucrose/saccharin solutions under the present conditions for comparison.

Experiment 4: Varying the Response Requirement for Food and Cocaine

The fourth experiment examined the effect of varying the FR response requirement on either the cocaine-associated lever or the food-associated lever. These manipulations produced orderly shifts in cocaine choice towards the lower-requirement reinforcer. These findings are in line with studies in humans, cynomolgus monkeys, rhesus monkeys, and rats, where increasing the response requirement for one reinforcer generally shifted the allocation of behavior towards the lower-requirement choice under a variety of conditions (Cantin et al. 2010; Czoty et al., 2005; Johanson, 1976; Nader & Woolverton, 1992; Negus, 2003; Stoops, Lile, Glaser, Hays, & Rush, 2012; Woolverton, English, & Weed, 1997). In the present study, baseline conditions had identical, FR 5, response requirements for both reinforcers. This mirrors some previous studies (Czoty et al., 2005; Nader & Woolverton, 1992; Paronis et al., 2002), while others used unbalanced response requirements under baseline conditions (Negus, 2003), but both types of procedures were similarly affected by differential changes in response requirements.

Experiment 5: Acute and Chronic Treatment with d-amphetamine

The last experiment examined the effects of acute and chronic d-amphetamine administration on cocaine choice, using male rats. Acute pretreatment with d-amphetamine increased cocaine choice in a dose-dependent manner, producing leftward shifts in the cocaine choice curve. This is in agreement with previous findings using a single lever self-administration procedure in rats in our laboratory (Barrett et al., 2004). Similarly in humans, a priming dose of cocaine increased cocaine versus money choice, and acute d-amphetamine treatment increased subject ratings for cocaine effects, even though self-administration was not significantly affected in the latter study (Donny et al., 2004; Stoops, Vansickel, Lile, & Rush, 2007). This leftward shift of the choice curve may thus represent increased reinforcing effects of the low cocaine doses, conceivably by combining the psychostimulant effects of amphetamine and cocaine. The similar discriminative stimuli of cocaine and d-amphetamine possibly also played a role in this leftward shift of the cocaine choice curve, an interpretation supported by the fact that amphetamine-treated rats emitted appreciable responding on the cocaine-associated lever during the first component, during which no cocaine was available. Pretreatment with cocaine similarly engendered responding on the

cocaine-associated lever in rhesus monkeys, when saline versus food was available (Gasior, Paronis, & Bergman, 2004; Paronis et al., 2002). Thus, just as removal of the interoceptive cocaine-cue decreased cocaine choice (in Experiment 2), the introduction of a cocaine-like interoceptive stimulus may have engendered responding on the cocaine-reinforced lever at low cocaine unit doses by mimicking a cue signaling availability of higher cocaine unit doses. Finally, amphetamine treatment may have diminished the reinforcing efficacy of food (e.g., anorectic effects; Foltin & Evans, 1999).

In contrast to its acute effects, chronic d-amphetamine decreased cocaine choice in the present experiment, comparable to effects previously observed in rhesus monkeys (Negus, 2003). These data are also compatible with reports of reduced cocaine use during chronic d-amphetamine treatment in human studies (Charnaud & Griffiths, 1998; Grabowski et al., 2001; Greenwald, Lundahl, & Steinmiller, 2010; Shearer, Wodak, van Beek, Mattick, & Lewis, 2003), and of decreased cocaine self-administration in rats or rhesus monkeys using single-reinforcers procedures (Chiodo, Läck, & Roberts, 2008; Czoty, Martelle, & Nader, 2010; Czoty, Gould, Martelle, & Nader, 2011; Negus & Mello, 2003a,b). While Negus (2003) showed complete reallocation of behavior to food at the highest tested amphetamine dose, we only observed a surmountable shift in the choice curve, similar to effects reported previously in rats using single-reinforcer procedures (Chiodo et al., 2008; Chiodo & Roberts, 2009). We attempted testing a higher amphetamine dose, 0.56 mg/kg/hr, but this dosing regimen proved lethal in the first few rats tested. Therefore it seems unlikely that we would have been able to achieve complete reallocation of behavior to obtaining food without deleterious effects. Whether this difference is a function of the species or other factors remains to be determined, although different monoamine releasers failed to effect a complete reallocation of behavior towards food in a cocaine versus food procedure in rhesus monkeys (Banks et al., 2011).

Converse to the postulated role of overlapping discriminative stimulus effects of amphetamine and cocaine in the acute treatment, it is likely that chronic amphetamine produced cross-tolerance to the discriminative stimulus of cocaine. This interpretation is consistent with the similar effects of removing response-independent or response-contingent cocaine infusions and of chronic amphetamine treatment in the present investigation (compare Figures 2 and 5), and by previous studies showing that continuous administration of 0.03-0.27 mg/kg/hr d-amphetamine for 7 days produced rightward and downward shifts in the discriminative stimulus effect of cocaine in rats (Peltier, Li, Lytle, Taylor, & Emmett-Oglesby, 1996). Chiodo and co-workers suggested pharmacological tolerance alone may not explain amphetamine's effects, because amphetamine administration produced sustained decreases in cocaine intake only in rats allowed access to cocaine during treatment, but had no effect in rats that did not self-administer cocaine during amphetamine treatment (Chiodo et al., 2008). Interestingly, access to self-administered cocaine during amphetamine treatment was not necessary to observe subsequent attenuation of cocaine self-administration in rhesus monkeys (Czoty et al., 2010; Czoty et al., 2011). Finally, repeated amphetamine administrations before access to self-administered cocaine was initiated increased subsequent cocaine intake in rats, further highlighting the importance of the treatment regimen and timing (Ferrario & Robinson, 2007; Suto et al., 2002; Valadez & Schenk, 1994). Taken together these studies suggest multiple factors, including pharmacological and behavioral tolerance, play a role in the effects of amphetamine treatment.

In summary, rats allocated behavior to the food or cocaine lever in a dose-dependent fashion, increasing cocaine choice with cocaine dose. We found the cocaine choice dose-effect curve to be stable in each rat, and comparable whether cocaine dose was tested within-session (the baseline condition) or between sessions. Because the choice procedure

produced stable baseline behavior, it is well suited for the evaluation of chronic treatments, an important feature for the preclinical evaluation of potential treatments for drug abuse. Removal of cocaine-associated exteroceptive cues had little effect on cocaine choice, but removal of response-independent or response-contingent cocaine markedly decreased cocaine choice. Manipulations of food reinforcer magnitude and response requirement for food or cocaine all yielded orderly, predicted results: Increased food rewards decreased cocaine choice, increased cost decreased choice for that reinforcer. Finally, acute pretreatment with d-amphetamine produced dose-related leftward shifts in cocaine choice, while chronic administration of d-amphetamine produced dose-related rightward shifts in cocaine choice. Thus in our rat choice procedure, manipulations of the experimental parameters as well as a well-studied pharmacological manipulation yielded results comparable to findings previously reported in nonhuman primates and humans. The advantages offered by choice procedures have made them increasingly popular in human studies; this set of experiments shows that choice assays can also be applied to advantage in rats.

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Fig. 1.

Dose-effect determinations for cocaine versus food choice (baseline, experiment 1). Abscissae: unit dose cocaine (mg/kg/infusion). Ordinates: top panels, percent cocaine choice (i.e., percent cocaine infusions out of total reinforcers earned); middle panels, responses per second (total rate including observer, cocaine- and food-reinforced levers); bottom panels, total number of reinforcers earned per 20-minute component. Left panels show cocaine dose-effect functions for baseline within-session assessment, center panels show cocaine dose-effect functions for between-session assessment. Right panels show the same data as center panels, but detailed by component for each cocaine dose (doses are in mg/kg/infusion). Food reinforcers in the bottom right panel are shown in grey for clarity. In both types of determination, each rat was tested for 3 consecutive days, and data are shown for each day to show the degree of stability/repeatability of the behavior (left and center panels). Data are group means $\pm$ SEM. Left panels, $N = 26$ (12 females, 14 males); center and right panels, $N = 9$ (5 females, 4 males). See also Table 1.

Fig. 2.

Effects of removing exteroceptive stimuli (visual, auditory) and interoceptive stimuli (cocaine response-independent and response-contingent injections) on cocaine versus food choice (Experiment 2). Axes are as in Figure 1. Filled symbols are baseline data, open symbols show data during removal of cues. Data are group means $\pm$ SEM, averaged over three determinations for each rat. $N = 11, 9, 11, 6$, respectively, from left to right (see Table 2 for numbers of males and females). ** $p < .01$, *** $p < .001$ versus baseline.

Fig. 3.

Effects of varying the liquid food concentration on cocaine versus food choice (Experiment 3). Axes as in Figure 1. Filled symbols are baseline data, open symbols show data for varying the food concentration from 56%. Data are group means $\pm$ SEM, averaged over three determinations for each rat. $N = 7$ rats (4 females, 3 males). See also Table 2. $*p < .05$, $**p < .01$, $***p < .001$ versus 56% Ensure baseline.

Fig. 4.

Effects of varying the fixed ratio on the food-reinforced lever or the cocaine-reinforced lever on cocaine versus food choice (Experiment 4). Axes are as in Figure 1. Filled symbols are baseline data (FR 5 FR 5), open symbols show data for varying the fixed ratio for one or the other lever. Data are group means $\pm$ SEM, averaged over three determinations for each rat. N = 5-10 male rats. See also Table 2. * $p < .05$, ** $p < .01$, *** $p < .001$ versus FR 5 baseline.

Fig. 5.

Effects of acute and chronic treatment with d-amphetamine on cocaine versus food choice (Experiment 5). Axes are as in Figure 1. Filled symbols are baseline data (vehicle administration), open symbols show data for d-amphetamine treatments. Data are group means $\pm$ SEM. Acute treatment (left panels) are, per definition, group means of single determinations, while the chronic treatment data (right panels) were averaged over days 5, 6 and 7 of treatment for each rat. $N = 9-13$ male rats. See also Table 3. $*p < .05$, $**p < .01$, $***p < .001$ versus vehicle.

Table 1

Cocaine choice A_{50} values in mg/kg/infusion for within- and between-session dose-effect determinations in female and male rats.

Drug	A_{50} (95% CI) [mg/kg/infusion]	<i>N</i>
Within-session dose-effect		
All rats mean	0.15 (0.14 – 0.18)	26
Females mean	0.15 (0.15 – 0.19)	12
Males mean	0.16 (0.14 – 0.18)	14
All rats day 1	0.15 (0.12 – 0.18)	26
All rats day 2	0.17 (0.14 – 0.18)	26
All rats day 3	0.14 (0.12 – 0.21)	26
Between-session dose-effect		
All rats mean	0.20 (0.16 – 0.26)	9
Females mean	0.23 (0.15 – 0.36)	5
Males mean	0.17 (0.16 – 0.19)	4
All rats day 1	0.19 (0.15 – 0.23)	9
All rats day 2	0.21 (0.17 – 0.27)	9
All rats day 3	0.21 (0.13 – 0.34)	9

Note. Values are group means, with 95% confidence intervals in parentheses, calculated from the individual A_{50} values for each rat. *N* indicates group size.

Table 2

Cocaine choice A_{50} values in mg/kg/infusion following manipulation of cocaine-associated exteroceptive and interoceptive cues, food concentration, and FR values for food and cocaine.

Manipulation	A_{50} ($\pm 95\%$ CI) [mg/kg/infusion]	N (f+m)	Ratio
Removing exteroceptive cues			
Baseline	0.15 (0.14 – 0.18)	26 (12+14)	
Visual Cues	0.23 (0.15 – 0.37)	11 (7+4)	1.53
Auditory Cues	0.25 (0.17 – 0.37)	9 (4+5)	1.67
Removing interoceptive cues			
Baseline	0.15 (0.14 – 0.18)	26 (12+14)	
Resp. independent cocaine	0.67 (0.44 – 1.04) ^b	11 (7+4)	4.47
Resp. contingent cocaine	0.84 (0.65 – 1.08) ^b	6 (3+3)	5.60
Change in food concentration			
Baseline (56% Ensure)	0.20 (0.15 – 0.35)	7 (4+3)	
17.8% Ensure	0.14 (0.06 – 0.32)	7 (4+3)	0.70
5.6% Ensure	0.05 (0.03 – 0.09) ^a	7 (4+3)	0.25
0% Ensure (water)	0.03 (0.03 – 0.03) ^a	7 (4+3)	0.15
Change in the FR for food			
FR _{food} =1	0.30 (0.21 – 0.43)	7 (3+4)	1.50
Baseline (FR _{food} =5)	0.20 (0.15 – 0.26)	10 (4+6)	
FR _{food} =15	0.09 (0.05 – 0.16)	8 (3+5)	0.45
FR _{food} =25	0.04 (0.02 – 0.06) ^a	5 (1+4)	0.20
Change in the FR for cocaine			
FR _{cocaine} =1	0.13 (0.09 – 0.20)	6 (3+3)	0.76
Baseline (FR _{cocaine} =5)	0.17 (0.12 – 0.23)	9 (2+7)	
FR _{cocaine} =25	0.30 (0.18 – 0.50)	6 (2+4)	2.30
FR _{cocaine} =45	0.61 (0.38 – 0.97) ^b	5 (2+3)	3.59

Note. Values are group means $\pm$ 95% confidence intervals, calculated from the individual A_{50} values for each rat. Ratio refers to the fold shift produced by each dose of pretreatment drug. Group sizes (N) are indicated as sexes combined followed by numbers of female and male rats in parentheses (f + m).

^a significant leftward shift as determined by nonoverlapping 95% confidence intervals

^b significant rightward shift as determined by nonoverlapping 95% confidence intervals

Table 3Cocaine choice A_{50} values in mg/kg following acute and chronic pretreatment with d-amphetamine

Drug	A_{50} ($\pm 95\%$ CI) [mg/kg/infusion]	<i>N</i>	Ratio
d-Amphetamine (acute)			
Vehicle	0.18 (0.15-0.23)	13	
0.32 mg/kg i.p.	0.13 (0.10-0.18)	10	0.72
0.56 mg/kg i.p.	0.06 (0.04-0.11) ^a	8	0.35
1.0 mg/kg i.p.	0.05 (0.03-0.08) ^a	11	0.28
1.8 mg/kg i.p.	NC	9	NC
d-Amphetamine (chronic)			
Vehicle	0.16 (0.12-0.21)	6	
0.1 mg/kg/hr s.c.	0.32 (0.23-0.43) ^b	6	2.02
0.32 mg/kg/hr s.c.	0.53 (0.37-0.77) ^b	6	3.39

Note. Values are group means and 95% confidence intervals, calculated from the A_{50} values for each rat. Dose ratio refers to the fold shift produced by each dose of pretreatment drug. *N* indicates group size; all male rats were used for this experiment.

^a significant leftward as determined by nonoverlapping 95% confidence intervals

^b rightward shift as determined by nonoverlapping 95% confidence intervals NC could not be calculated