Published in final edited form as:

Exp Clin Psychopharmacol. 2014 August ; 22(4): 364–372. doi:10.1037/a0037019.

Drug Specificity in Drug vs. Food Choice in Male Rats

Brendan J. Tunstall,

American University Department of Psychology

Anthony L. Riley, and

American University Department of Psychology

David N. Kearns

American University Department of Psychology

Abstract

Although different classes of drug differ in their mechanisms of reinforcement and effects on behavior, little research has focused on differences in self-administration behaviors maintained by these drugs. Persistent drug choice despite available reinforcement alternatives has been proposed to model behavior relevant to addiction. The present study used a within-subjects procedure, where male rats (Long-Evans, $N = 16$) were given a choice between cocaine (1.0 mg/kg/inf) and food (a single 45-mg grain pellet) or between heroin (0.02 mg/kg/inf) and food in separate phases (drug order counterbalanced). All rats were initially trained to self-administer each drug, and the doses used were based on previous studies showing that small subsets of rats tend to prefer drug over food reinforcement. The goal of the present study was to determine whether rats that prefer cocaine would also prefer heroin. Choice sessions consisted of two forced-choice trials with each reinforcer, followed by 14 free-choice trials (all trials separated by 10 minute inter-trial interval). Replicating previous results, small subsets of rats preferred either cocaine (5 of the 16 rats) or heroin (2 of the 16 rats) to the food alternative. Although one of the 16 rats demonstrated a preference for both cocaine and heroin to the food alternative, there was no relationship between degree of cocaine and heroin preference in individual rats. The substance-specific pattern of drug preference observed suggests that at least in this animal model, the tendencies to prefer cocaine or heroin in preference to a non-drug alternative are distinct behavioral phenomena.

Keywords

Addiction; Choice; Cocaine self-administration; Heroin self-administration; Rat

Correspondence concerning this article should be addressed to Brendan J. Tunstall, Psychology Department, American University, 4400 Massachusetts Ave NW, Washington, DC, 20016. Phone: +1 (202) 885-1725. FAX: +1 (202) 885-1023. bt5712a@student.american.edu.

Brendan J. Tunstall, MA. Department of Psychology, American University; Anthony L. Riley, PhD. Department of Psychology, American University; David N. Kearns, PhD. Department of Psychology, American University.

All authors were responsible for the study concept and design. BT acquired and analyzed animal data. All authors were responsible for interpretation of findings. BT and DK drafted the manuscript. All authors critically reviewed content and approved final version for publication.

All authors wish to state that they have no conflict of interest which may inappropriately impact or influence the research or the interpretation of the findings.

If addiction is drug-specific (i.e., individuals are especially likely to become addicted to a particular drug but not others), then treatment efforts might be most effective if tailored to specific drug addictions. Although population studies suggest that poly-drug use/abuse is common across different classes of abused drugs (e.g., Kendler, Jacobson, Prescott, & Neale, 2003), it is difficult to ascertain whether the co-occurrence of substance use/abuse with drugs from different classes (e.g., cocaine and heroin) reflects the development of co-morbid, distinct conditions or multiple symptoms of a single condition (for a review of heroin and cocaine co-use, see Leri, Bruneau, & Stewart, 2003). Furthermore, it is difficult to answer the question about the drug specificity of addiction in humans because a number of non-pharmacological variables (e.g., availability) likely co-vary across drugs and fluctuate over time. This makes animal models especially useful here, where drug history can be controlled and extraneous variables can be held constant across drugs.

Previous studies with animals have found that psychostimulants (e.g., cocaine) and opiates (e.g., heroin) differ in many important aspects with regards to drug-taking behavior (Bozarth & Wise, 1985; for a review, see Badiani, Belin, Epstein, Calu, & Shaham, 2011). Furthermore, it has previously been demonstrated that the reinforcing effects of self-administered cocaine and heroin are mediated by dissociable neurobiological substrates (Ettenberg, Pettit, Bloom, & Koob, 1982). While this may seem indicative of drug-specificity in addiction-like behavior, there is a growing appreciation that drug-taking behavior per se does not necessarily model addiction (Ahmed, 2010, 2012; Deroche-Gamonet, Belin, & Piazza, 2004). As is the case in humans (Wagner & Anthony, 2002), only a subset of rats that self-administer drugs like cocaine and heroin go on to display addiction-like behavior (e.g., Cantin et al., 2010; Deroche-Gamonet, et al., 2004; Lenoir, Guillem, Koob, & Ahmed, 2012; Lenoir, Serre, Cantin, & Ahmed, 2007; Perry, Westenbroek, & Becker, 2013). In accord with this notion, there is a growing field of research with a focus on understanding individual differences in drug self-administration behaviors (e.g., Beckmann, Marusich, Gipson, & Bardo, 2011; Belin, Mar, Dalley, Robbins, & Everitt, 2008; Dalley, et al., 2007; Deroche-Gamonet, et al., 2004; Flagel, Akil, & Robinson, 2009; Saunders, & Robinson, 2011). Recent work has demonstrated that individual rats demonstrating a propensity for choosing cocaine over a concurrently available alternative reinforcer are also distinct from their counterparts in other measures of addiction-like behavior (Perry et al., 2013). Many have argued that drug vs. non-drug choice procedures may serve as a more representative model of human drug abuse when compared to single-schedule drug self-administration (e.g., Ahmed, 2010, 2012; Kerstetter et al., 2012; Thomsen, Barrett, Negus, & Caine, 2013; Vanderschuren & Ahmed, 2013).

There is a long and rich literature on the use of concurrent schedules in assessing relative reinforcement strength via examination of the allocation of behavior between reinforcement alternatives. One of the first such studies was performed by Spragg (1940), in a paper titled 'Morphine Addiction in Chimpanzees'. Since intravenously self-administered drug was first used in drug vs. non-drug choice studies (i.e., Aigner & Balster, 1978), a great deal of work has been performed using this method and it has been well established that many factors determine drug choice behavior in animals. For example, the schedule and economy type, delay and magnitude of reinforcer delivery and a host of pharmacological, environmental and biological variables have all been demonstrated as determinants of drug choice (e.g.,

Nader & Woolverton, 1991, 1992; Thomsen et al., 2013; Woolverton, Myerson, & Green, 2007; for a systematic review of preclinical studies on determinants of drug choice, see Banks and Negus, 2012). While choice behavior is a complex phenomenon, much research and theorizing suggests that choice procedures will be essential in order for drug-abuse researchers working at the pre-clinical level to completely model behavior relevant to drug addiction (e.g., Ahmed, 2010; Haney & Spealman, 2008; Heyman, 2009; Hernstein, 1992; Vocci, 2007).

The present study used a choice procedure to identify rats displaying cocaine or heroin self-administration despite the concurrent availability of a food alternative. This study used a within-subjects design where rats self-administered cocaine and heroin in separate phases to determine whether (and to what degree) the subset of rats that chose one drug over food also chose the other drug over food. The doses of cocaine and heroin used here were based on previous studies showing that, under the conditions to be used here, only a small percentage of rats choose the drug over the non-drug reinforcer (for cocaine, see Kerstetter et al., 2012; Lenoir et al., 2007; Perry et al., 2013; Tunstall & Kearns, 2013; for heroin, see Lenoir, Cantin, Vanhille, Serre, & Ahmed, 2013). The goal of the present study was to determine whether choice of one drug under these conditions would be predictive of choice of the other drug. Identification of a subset of rats displaying heroin over food choice but not cocaine over food choice, and vice versa, would have important implications, as this would suggest that certain individuals may be especially susceptible to developing patterns of drug self-administration maintained by one class of drug but not others.

Methods

Subjects

Sixteen adult male Long-Evans rats completed the experiment. Rats were individually housed in plastic cages (21 × 19 × 20 cm) with wood-chip bedding and metal wire tops. They were maintained at 85% of their free-feeding weights (approximately 300–400 g) throughout the experiment by feeding them approximately 15–20 g of rat chow following training sessions. Rats had unlimited access to water in their home cages. The colony room where the rats were housed had a 12-h light:dark cycle with lights on at 08:00 h. Training sessions were conducted 5–7 days per week during the light phase of the light:dark cycle. Throughout the experiment, rats were treated in accordance with the Guide for the Care and Use of Laboratory Animals (National Academy of Sciences, 2011) and all procedures were approved by American University's Institutional Animal Care and Use Committee (IACUC).

Apparatus

Training took place in 10 Coulbourn Instruments (Whitehall Township, PA) modular test cages (30 × 25.5 × 29 cm) enclosed in sound attenuation chests (Coulbourn Instruments). Each apparatus was equipped with two non-retractable levers (3.4 × 1.7 cm) positioned approximately 6 cm above the grid floor and equidistant from the food receptacle located in the centre of the front wall of the chamber. A shielded 100-mA light bulb mounted to the ceiling at the front of the chamber was used as a houselight to signal the start and end of

trials. Two 100-mA cue lights were also mounted to the front wall, located approximately 10 cm above the floor and directly above each lever. These cue lights were used to signal that a lever was active on a particular trial.

To equate infusion volume over drugs, cocaine and heroin (both generously provided by the National Institute on Drug Abuse) were prepared in saline at concentrations of 5.12 mg/ml for cocaine and 0.1024 mg/ml for heroin. Both drug solutions were infused at a rate of 1.06 ml/min by 10-ml syringes driven by Med-Associates (St. Albans, VT) syringe pumps located outside of the sound attenuation chests. Tygon tubing extended from the 10-ml syringes to a 22-gauge rodent single-channel fluid swivel and tether apparatus (Instech Laboratories, Plymouth Meeting, PA) that descended through the ceiling of the chamber. Drug solutions were delivered to the subject through Tygon tubing that passed through the metal spring of the tether apparatus. This metal spring was attached to a plastic screw cemented to the rat's head to reduce tension on the catheter. A white-noise generator was used in the self-administration room to mask background noise. All self-administration testing equipment and data acquisition were controlled by a desktop personal computer running Med-Associates software (MED-PC for Windows).

Procedure

Phase 1: Food-pellet-reinforced Operant Response Acquisition—Rats were trained to lever press for 45-mg food pellets on a fixed-ratio (FR) 1 schedule of reinforcement. Sessions began with the illumination of the houselight and with illumination of the stimulus light above the food lever (either the right or left lever, counterbalanced across subjects). Each lever press was followed by delivery of a 45-mg food pellet and initiation of a 10-s time-out (TO) period during which both the houselight and stimulus light were extinguished. TO responses were recorded, but had no consequences. Rats were trained in sessions lasting 2 h or until 50 pellets were earned. Rats were trained until they completed a minimum of three sessions in which 50 food pellets were earned.

Surgery—Following food training, rats were surgically prepared with chronic indwelling jugular vein catheters, using a modification of the procedure originally developed by Weeks (1962). In brief, under ketamine (60 mg/kg) and xylazine (10 mg/kg) anesthesia, approximately 3 cm of Silastic tubing (0.044mm i.d., 0.814mm o.d.) was inserted into the right jugular vein. This Silastic tubing was connected to 8 cm of vinyl tubing (Dural Plastics; 0.5mm i.d., 1.0mm o.d.) that was passed under the skin around the shoulder and exited the back at the level of the shoulder blades. The vinyl tubing was threaded through a section of Tygon tubing (10 mm long, 4 mm diameter) that served as a subcutaneous anchor. Six stainless steel jeweler's screws were implanted in the skull, to which a 20-mm plastic screw was cemented with dental acrylic. Catheters were flushed daily with 0.1 ml of a saline solution containing 1.25 U/ml heparin and 0.08 mg/ml gentamycin.

Phase 2: Drug 1 Self-administration Acquisition—After 5–7 days of recovery from surgery, self-administration training began with Drug 1. Cocaine (1.0 mg/kg/inf) and heroin (0.02 mg/kg/inf) were counterbalanced across rats in their roles as Drug 1 or Drug 2. Sessions began with illumination of the houselight and stimulus light located above the drug

lever (the lever not previously associated with food). Rats were trained to lever press for drug infusions on a FR 1 schedule. Each reinforcement was followed by a 10-s TO period, during which the houselight and stimulus light were extinguished and the drug lever was inactive (TO responses were recorded but had no consequence). The 1.0 mg/kg/inf dose of cocaine used throughout this experiment was the same as that used in previous studies that compared the essential reinforcing value of cocaine and a 45-mg food pellet (Christensen, Silberberg, Hursh, Huntsberry, & Riley, 2008a; Christensen, Silberberg, Hursh, Roma, & Riley, 2008b; Christensen, Kohut, Handler, Silberberg, & Riley, 2009) as well as that used in previous work from this lab using the choice paradigm (Tunstall & Kearns, 2013). Although the reinforcing strength of cocaine generally appears weak when compared to that of food, the choice procedure may be especially useful in this regard as it appears sensitive enough to detect individual subjects prone to drug choice and to detect situations where drug-taking/-seeking behavior may predominate over food-taking/-seeking behavior (e.g., Tunstall and Kearns, 2013). The 0.02 mg/kg/inf dose of heroin used throughout this experiment was chosen to support rates of self-administration that would be comparable to those expected with cocaine. This decision was informed by previous work that established dose-response curves for heroin self-administration in rats and which has demonstrated that this dose and lower ones serve as reinforcers (e.g., Martin et al., 2000; Martin, Smith, & Dworkin, 1998; Martin, Walker, Sizemore, Smith, & Dworkin, 1996). The doses of both cocaine and heroin used here were expected to produce small subsets of rats that preferred the drug over the food reinforcer based on previous studies using similar choice procedures (for cocaine, see Kerstetter et al., 2012; Lenoir et al., 2007; Perry et al., 2013; Tunstall & Kearns, 2013; for heroin, see Lenoir et al., 2013).

Rats were trained in sessions lasting 3 hours or until 50 infusions were earned. Self-administration training continued until a minimum of 10 sessions was completed and stable rates of responding were observed (defined as number of infusions self-administered on the last 2 days being within 30% of the average of those 2 days).

Phase 3: Choice between Drug 1 and Food—In this phase, for the first time, both the food lever and the Drug 1 lever were active in the same session (signaled by the appropriate stimulus lights). Each choice session began with four forced-choice trials in which either the food lever or Drug 1 lever was active. There were two trials of each type, with the order of presentation randomized within blocks of two. A lever press resulted in delivery of the designated reinforcer (either food pellet or Drug 1 infusion), and commencement of a 10-minute inter-trial interval (ITI) during which the houselight and all stimulus lights were extinguished. This 10-min ITI was implemented after every trial in order to minimize any potential interaction between the effects of one reinforcer with the other (e.g., cocaine's anorectic properties on the motivation for food). Following the completion of forced-choice trials, 14 free-choice trials were presented. Each free choice trial began with the simultaneous illumination of the houselight and the cue lights above both levers. Again, 10-min ITIs separated trials and sessions lasted approximately 3 hours. Rats were run for a minimum of five sessions. Initially, we intended upon a stability criterion for all rats of no more than 20% change in the percentage of trials on which the drug was chosen across the final 2 days. However, this criterion needed to be relaxed for three rats demonstrating

variability in choosing between cocaine and food. These three rats were held to a criterion of no more than 50% change in percentage of trials on which the drug was chosen over the final 3 days. Importantly, none of these rats reversed their absolute food/drug preference over these days (i.e., if a rat preferred drug, it chose drug on the majority of trials on all three sessions).

Phase 4: Drug 2 Self-administration Acquisition—After a 5-day washout period during which rats were maintained in their home cages, self-administration training began with Drug 2 (i.e., the drug not received in previous phases). Sessions proceeded as described in Phase 2 with the exception that the position of the drug and food levers was switched for half of the rats. This was done to control for potential lever biases formed in training Phases 1–3. Again, self-administration training continued until a minimum of 10 sessions was completed and stable rates of responding were observed (infusions self-administered on last 2 days within 30% of their average).

Phase 5: Choice between Drug 2 and Food—This phase proceeded as described in Phase 3 with the exception that Drug 2 was the reinforcer available for responding on the drug lever. Rats were run for a minimum of five sessions and until they met the same choice criterion described above.

Statistical Analyses

For all statistical tests, significance was set at $\alpha = 0.05$. A 2×10 repeated measures ANOVA (Drug $\times$ Session) was used to compare self-administration with each drug across self-administration sessions (i.e., Phases 2 and 4). Similarly, a 2×5 repeated measures ANOVA (Drug $\times$ Session) was performed on drug choice percentage to compare drug choice with each drug across drug vs. food choice sessions. The relationship of individuals' cocaine preference and heroin preference was analyzed with a Pearson correlation coefficient as well as with a partial correlation controlling for Order.

Results

Food-pellet-reinforced Operant Response Training

Rats required a mean of 3.6 ($SEM = 0.3$) sessions to meet the food lever-pressing criterion. Over the last three sessions, every subject earned 50 food pellets per session.

Drug 1 Self-administration Acquisition

All rats met the criterion for stable self-administration with the minimum of 10 sessions, except for one rat (Drug 1 was heroin for this rat) that required 13 sessions ($M = 10.2$, $SEM = 0.2$). Figure 1 (left panel) shows the mean number of infusions taken during the last 10 self-administration sessions prior to each rat reaching criterion. Over the last two sessions, subjects trained with cocaine ($n = 9$) self-administered an average of 37.2 ($SEM = 2.7$) infusions per session. Subjects trained with heroin ($n = 7$) self-administered an average of 23.7 ($SEM = 4.2$) infusions per session. A 2×10 repeated measures ANOVA (Drug $\times$ Session) was used to compare self-administration with each drug. A significant effect of Session ($F [9, 126] = 2.35$, $p = 0.018$), but no Drug $\times$ Session interaction ($F [9, 126] = 1.00$,

$p = 0.44$), was observed, as rats acquired the self-administration response with both drugs. A significant effect of Drug was also observed ($F [1, 14] = 10.96, p = 0.005$), as rats self-administered more cocaine infusions than heroin infusions across sessions. While response rates were generally lower for heroin self-administration in this phase, compared to cocaine self-administration rates, the significant increase in the number of heroin infusions self-administered across sessions is indicative of the acquisition of heroin self-administration (i.e., heroin served as a reinforcer).

Choice between Drug 1 and Food

One rat required nine complete choice sessions to reach criterion for stable choice (Drug 1 was cocaine for this rat), all other rats required five complete sessions. On average, rats chose cocaine 53% of the time during the final two sessions. Considering individual subjects, five out of the nine rats (56%) trained with cocaine as Drug 1 chose cocaine more frequently than food (see Figure 2, left panel). On average, rats chose heroin on 5% of trials during the final two sessions. Considering individual subjects, none of the seven rats trained with heroin as Drug 1 chose heroin more frequently than food (see Figure 2, left panel). In this phase, no rat demonstrated a change in heroin vs. food preference greater than 15% across the last 2 days of choice and all except three rats did not demonstrate a change in cocaine vs. food choice greater than 15% across the last 2 days of choice. A 2×5 repeated measures ANOVA (Drug $\times$ Session) was performed on drug choice percentage. (One rat did not complete more than four trials on three sessions when choosing between heroin and food. These incomplete sessions, although representative of that rat's preference, were discarded from analysis and re-run on the following days to ensure preference was captured in a similar manner for all rats. As a result, with the exception of one rat completing 13 out of 14 free-choice trials on one session, all data presented and analyzed are based on sessions where all rats completed all trials available in each session). No main effect of Session ($F [4, 56] = 0.22, p = 0.92$) or Drug $\times$ Session interaction ($F [4, 56] = 2.02, p = 0.11$) was observed, as rats generally demonstrated their preference between the alternatives as early as Session 1 and maintained this preference across sessions. However, there was a significant effect of Drug ($F [1, 14] = 14.98, p = 0.002$) as rats chose cocaine over food more frequently than heroin over food across sessions.

Drug 2 Self-administration Acquisition

All rats met the criterion for stable self-administration with the minimum of 10 sessions, except for one rat (Drug 2 was cocaine for this rat) which required 12 sessions ($M = 10.1, SEM = 0.1$). The right panel of Figure 1 shows the mean number of infusions taken during the last 10 self-administration sessions prior to each rat reaching criterion. Over the last two sessions, subjects trained with cocaine ($n = 7$) administered an average of 33.3 ($SEM = 2.2$) infusions per session. Subjects trained with heroin ($n = 9$) administered an average of 33.8 ($SEM = 4.4$) infusions per session. A 2×10 repeated measures ANOVA (Drug $\times$ Session) was used to compare self-administration with each drug. A significant effect of Session ($F [9, 126] = 2.00, p = 0.045$) was observed, as rats' self-administration stabilized, but no significant effect of Drug ($F [1, 14] = 0.04, p = 0.84$) or Drug $\times$ Session interaction ($F [9, 126] = 0.31, p = 0.97$) was observed.

Choice between Drug 2 and Food

All rats required five complete sessions to reach criterion for stable choice. On average, rats trained with cocaine as Drug 2 chose cocaine on 16% of trials during the final two sessions. Considering individual subjects, none of the seven rats trained with cocaine as Drug 2 chose cocaine more frequently than food during the final two sessions (one rat chose cocaine on 50% of trials; see Figure 2, right panel). On average, rats trained with heroin as Drug 2 chose heroin on 21% of trials. Of the nine rats trained with heroin as Drug 2, two (22%) chose heroin more frequently than food (see Figure 2, right panel). In this phase, no rat demonstrated a change in drug vs. food preference with either cocaine or heroin greater than 15% across the last 2 days of choice. A 2×5 repeated measures ANOVA (Drug $\times$ Session) was performed on drug choice percentage (One rat did not complete more than four trials in one session, while choosing between cocaine and food. Although this incomplete session was representative in terms of that rat's preference, the incomplete session was discarded from analysis and re-run on the following day to ensure preference was captured in a similar manner for all rats. As a result, all data presented and analyzed are based on sessions where all rats completed all trials available in each session). Significant main effects of Session ($F [4, 56] = 4.07, p = 0.006$) and a Drug $\times$ Session interaction ($F [4, 56] = 2.90, p = 0.030$) were observed, as rats tended toward their stable preference between the alternatives, but there was no significant effect of Drug ($F [1, 14] = 0.003, p = 0.958$).

Within-subject Comparison of Cocaine vs. Food and Heroin vs. Food Choice

The cocaine vs. food and heroin vs. food preferences obtained for the 16 animals assessed are shown in Figure 3. This allows for the relationship between cocaine and heroin preference to be visualized. To assess the commonality of cocaine and heroin preference statistically, a Pearson correlation coefficient was calculated to correlate individuals' cocaine and heroin preferences. This test found no evidence of a significant relationship between the two measures, ($r [14] = 0.23, p = 0.391$). As there was an apparent effect of drug history on choice behavior (i.e., a main effect of Drug during Drug 1 vs. food choice but not during Drug 2 vs. food choice), a partial correlation was conducted controlling for the order of drug presentation, in case drug history was acting as a suppressing variable on the correlation between cocaine and heroin preference (Warner, 2007). This test found no evidence of a significant relationship between cocaine and heroin preference ($r [13] = 0.07, p = 0.796$).

Discussion

The goal of the present investigation was to determine, under conditions known to produce small subsets of cocaine preferrers and heroin preferrers, whether preference for one drug was predictive of preference for the other drug. The results generally suggest that, with the doses and procedural conditions used here, preference for one drug was not predictive of preference for the other drug (see Figure 3).

It is important to note that in the present study, a single dose of cocaine and heroin was used in screening for cocaine and heroin preferrers. It is possible that different doses of drug could generate different rates of drug choice. There is an apparent discrepancy in the drug

vs. food choice literature in this regard. Some studies have reported choice between sucrose/saccharin vs. cocaine or heroin is stable across a wide range of doses in rats (e.g., 0.015 mg/kg/inf – 0.06 mg/kg/inf heroin, in Lenoir et al., 2013; 1.0 mg/kg/inf – 6.0 mg/kg/inf cocaine, in Lenoir et al., 2007). However, these studies stand in contrast to a large body of work which has demonstrated that dose manipulations have an effect on drug-choice in both rats (e.g., Kerstetter et al., 2012; Thomsen et al., 2013) and in non-human primates (see for review, Banks and Negus, 2012). We note an important difference in methodology which is likely the cause of this discrepancy. In work published by Ahmed and colleagues assessing the effect of heroin or cocaine dose on drug v. food choice, the ITI was systematically altered to account for the increasing potency and duration of the effect of the drug with increases in dose (Lenoir et al., 2013; Lenoir et al., 2007), while other studies have manipulated dose while the ITI is held constant (see for review, Banks and Negus, 2012). It has been suggested that at least in rats, the state of drug intoxication is likely an important factor mediating drug vs. food preference, as using a shorter (20 s) rather than longer (10 min) ITI can generate higher preference for drug over food with a single dose of drug (Kerstetter et al., 2012). Also, an acute pre-treatment of d-amphetamine serves to increase preference for cocaine over food (see Thomsen et al., 2013; for a discussion of this issue, see Perry et al., 2013). It should be noted, however, that studies in non-human primates have shown that drug preference can be produced with very long (up to 3 hr) ITIs (Findley et al., 1972; Griffiths, 1981; Nader & Woolverton, 1992).

The present study used doses of cocaine and heroin which were known to generate small subsets of animals demonstrating preference for each drug over a non-drug alternative. The present study implemented a 10-min ITI between all choice trials, to minimize the impact of drug intoxication on preference. In addition to this, the doses used in the present study generated a baseline intake (an average on last two sessions of greater than 20 inf over 3 hr, see Figure 1) which was higher than the maximum number of infusions available to the rat during choice sessions (i.e., 16 inf over 3 hr). This suggests that rats' preference for either drug would not be limited by drug satiety during choice sessions.

The generally low rates of heroin preference in the 16 rats assessed may have limited the ability of the present experiment to detect a relationship between drug preferences across drugs due to a floor effect. However, considering only the subjects that showed a preference for cocaine or for heroin, the large difference observed in individual preference across drugs in all but one animal, supports a conclusion of drug-specific preference. Only one rat preferred both cocaine (75%) and heroin (89%) over food, while one rat preferred heroin (75%) but not cocaine (28%) over food, and four rats preferred cocaine ($M = 81\%$, $SEM = 4.5$) but not heroin ($M = 4\%$, $SEM = 2$). While this analysis involves a relatively small number of subjects, in only one out of six instances was preference for both drugs observed, given preference for either one of the drugs. Thus, the present results suggest drug-specific factors may govern an individual's propensity for choosing drug reinforcement over non-drug reinforcement.

In the present study, aggregate rates of self-administration in the absence of a food alternative (i.e., Phases 2 and 4) were predictive of rates of drug self-administration responding during drug vs. food sessions (i.e., Phases 3 and 5). Interestingly, an effect of

drug order was also apparent. While a significant main effect of Drug was observed in self-administration with Drug 1 (rats self-administered more infusions of cocaine than heroin), this effect of Drug was not observed with Drug 2 self-administration (see Figure 1). Similarly, while a significant main effect of Drug was observed in the choice phase with Drug 1 (rats chose infusions of cocaine over food more frequently than rats chose heroin over food), this effect of drug was not observed with Drug 2 (see Figure 2). This order effect appears to have impacted aggregate choice behavior, as average heroin choice was slightly lower when heroin was first as compared to second (5% vs. 21%), and cocaine preference was higher when cocaine was first as compared to second (53% vs. 16%). It seems that a self-administration history with the weaker drug reinforcer used (heroin, 0.02 mg/kg/inf) attenuated responding for a potentially stronger reinforcer (cocaine, 1.0 mg/kg/inf) and vice versa. As the goal of the present study was to assess individual differences in drug preference and the drug-specificity of drug choice, it should be noted that the conclusion that individuals demonstrate drug-specific drug choice may be conservative under these conditions. An order effect that renders Drug 2 preference more similar to Drug 1 preference would be expected to artificially strengthen the association between Drug 1 and Drug 2 preference relative to food. Despite this, no significant correlation was observed with a standard Pearson r coefficient, and when Order was partialled out, an even smaller r value was found ($r = 0.07$ vs. $r = 0.23$). While not the focus of the present study, it seems drug self-administration history could influence drug choice behavior. This warrants further study, as such a function could be an important factor for understanding human drug use, where multiple drugs are often co-abused (e.g., Kendler, et al., 2003).

It has long been known that self-administration of cocaine and heroin are mediated by separate neurobiological substrates (Ettenberg et al., 1982) and that with continuous access, very different patterns of self-administration appear when behavior is maintained by each of these drugs (Bozarth & Wise, 1985). More recently, it has been noted that while extended access to cocaine self-administration does not generate a higher frequency of cocaine preference among rats in the choice procedure (Lenoir et al., 2007), extended access to heroin self-administration does increase frequency of heroin choice. The mechanism for this appears to be dependence and withdrawal processes resulting from self-administration of opiates (Griffiths, Wurster, & Brady, 1975; Lenoir et al., 2013; Negus, 2006; Spragg, 1940). While these studies are suggestive of distinct processes underlying cocaine and heroin taking behavior, not until recently have animal studies examined individual differences in drug-taking behavior and demonstrated that for each drug there are distinct traits which predispose individuals to develop addiction-like behaviors. For example, while escalation of cocaine self-administration is predicted by impulsivity (Anker, Perry, Gliddon, & Carroll, 2009) and anxiety (Dilleen et al., 2012), the escalation of heroin self-administration is not (for impulsivity, see McNamara, Dalley, Robbins, Everitt, & Belin, 2010; Schippers, Binnekade, Schoffelmeer, Pattij, & De Vries, 2012; for anxiety, see; Dilleen et al., 2012). Furthermore, escalation of heroin intake does not appear to influence the escalation of cocaine intake, and vice versa (Lenoir et al. 2012). The result of the present study, suggesting a distinction between propensity to choose cocaine (1.0 mg/kg/inf) and heroin (0.02mg/kg/inf) over food, fits with this emerging body of work. The present results are also consistent with a pilot drug-substitution study involving a small subset ($n = 5$) of rats, four

of which preferred heroin (approximately 0.045 mg/kg/inf) over a non-drug alternative (20-s access to water sweetened with 0.2% saccharin). When those rats had cocaine (approximately 0.75 mg/kg/inf) substituted as the drug reinforcer, they all rapidly switched their preference from the drug to the non-drug alternative (see Fig 6d. Lenoir et al., 2013).

Future work examining the extent to which different drug-reinforced behaviors are drug-specific may be instrumental in changing the current approach to the treatment of drug addiction. This is especially true if distinct processes underlie addictive behaviors maintained by commonly abused drugs from other classes (e.g., alcohol and cannabis; for further discussion of this idea, see Badiani, 2013). For example, recent work by Peters, Pattij, and De Vries (2013) has identified very different roles of the ventromedial prefrontal cortex in cocaine vs. heroin addiction. Further work with pre-clinical models of drug abuse will likely be informative here, as it provides an opportunity to hold constant (or systematically manipulate) factors such as drug self-administration history. Differential diagnoses based on meaningful differences occurring in the patterns of addictive behavior maintained by different classes of drug would likely lead to improved treatment outcomes if it were possible to tailor treatment toward the specific maladaptive processes observed in an individual. For example, treatment which corrects an individual's high impulsivity or anxiety may be effective for psychostimulant, but not opiate, abuse.

Acknowledgments

This research was supported by Award Number R01DA008651 from the National Institute on Drug Abuse. The National Institute on Drug Abuse had no role other than financial support, and as such the content is solely the responsibility of the authors.

All authors wish to thank the reviewers for their extensive reviews and constructive criticism of an earlier version of this manuscript.

References

- Ahmed SH. Validation crisis in animal models of drug addiction: Beyond non- disordered drug use toward drug addiction. *Neuroscience & Biobehavioral Reviews*. 2010; 35:172–184. [PubMed: 20417231]
- Ahmed SH. The science of making drug addicted animals. *Neuroscience*. 2012; 211:107–125. [PubMed: 21864653]
- Anker JJ, Perry JL, Gliddon LA, Carroll ME. Impulsivity predicts the escalation of cocaine self-administration in rats. *Pharmacology Biochemistry and Behavior*. 2009; 93:343–348.
- Badiani A. Substance-specific environmental influences on drug use and drug preference in animals and humans. *Current opinion in neurobiology*. 2013; 23:588–596. [PubMed: 23622777]
- Badiani A, Belin D, Epstein D, Calu D, Shaham Y. Opiate versus psychostimulant addiction: the differences do matter. *Nature Reviews Neuroscience*. 2011; 12:685–700.
- Banks ML, Negus SS. Preclinical determinants of drug choice under concurrent schedules of drug self-administration. *Advances in pharmacological sciences*. 2012; 2012:Article ID 281768, 17.10.1155/2012/281768
- Beckmann JS, Marusich JA, Gipson CD, Bardo MT. Novelty seeking, incentive salience and acquisition of cocaine self-administration in the rat. *Behavioral Brain Research*. 2011; 216:159–165.
- Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ. High impulsivity predicts the switch to compulsive cocaine-taking. *Science*. 2008; 320:1652–1355.
- Bozarth MA, Wise RA. Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat. *The Journal of the American Medical Association*. 1985; 254:81–83.

- Cantin L, Lenoir M, Augier E, Vanhille N, Dubreucq S, Serre F, Vouillac C, Ahmed SH. Cocaine is low on the value ladder of rats: Possible evidence for resilience to addiction. *PLoS ONE*. 2010; 5(7):e11592.10.1371/journal.pone.0011592 [PubMed: 20676364]
- Caprioli D, Celentano M, Dubla A, Lucantonio F, Nencini P, Badiani A. Ambience and drug choice: cocaine-and heroin-taking as a function of environmental context in humans and rats. *Biological Psychiatry*. 2009; 65:893–899. [PubMed: 19217078]
- Christensen CJ, Kohut SJ, Handler S, Silberberg A, Riley AL. Demand for food and cocaine in Fischer and Lewis rats. *Behavioral Neuroscience*. 2009; 123:165–171. [PubMed: 19170441]
- Christensen CJ, Silberberg A, Hursh SR, Huntsberry ME, Riley AL. Essential value of cocaine and food in rats: tests of the exponential model of demand. *Psychopharmacology*. 2008a; 198:221–229. [PubMed: 18351323]
- Christensen CJ, Silberberg A, Hursh SR, Roma PG, Riley AL. Demand for cocaine and food over time. *Pharmacology Biochemistry and Behavior*. 2008b; 91:209–216.
- Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Lääne K, Robbins TW. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science*. 2007; 315:1267–1270. [PubMed: 17332411]
- Deroche-Gamonet V, Belin D, Piazza PV. Evidence for addiction-like behavior in the rat. *Science*. 2004; 305:1014–1017. [PubMed: 15310906]
- Dilleen R, Pelloux Y, Mar AC, Molander A, Robbins TW, Everitt BJ, Dalley WJ, Belin D. High anxiety is a predisposing endophenotype for loss of control over cocaine, but not heroin, self-administration in rats. *Psychopharmacology*. 2012; 222:89–97. [PubMed: 22245944]
- Ettenberg A, Pettit HO, Bloom FE, Koob GF. Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems. *Psychopharmacology*. 1982; 78:204–209. [PubMed: 6296898]
- Findley JD, Robinson WW, Peregrino L. Addiction to secobarbital and chlordiazepoxide in the rhesus monkey by means of a self-infusion preference procedure. *Psychopharmacologia*. 1972; 26:93–114. [PubMed: 4672449]
- Flagel SB, Akil H, Robinson TE. Individual differences in the attribution of incentive salience to reward-related cues: implications for addiction. *Neuropharmacology*. 2009; 56(S1):139–48. [PubMed: 18619474]
- Griffiths RR, Wurster RM, Brady JV. Discrete-trial choice procedure: effects of naloxone and methadone on choice between food and heroin. *Pharmacological reviews*. 1975; 27:357–365. [PubMed: 817307]
- Griffiths RR, Wurster RM, Brady JV. Choice between food and heroin: effects of morphine, naloxone, and secobarbital. *Journal of the experimental analysis of behavior*. 1981; 35:335–351. [PubMed: 7241034]
- Haney M, Spealman R. Controversies in translational research: drug self-administration. *Psychopharmacology*. 2008; 199:403–419. [PubMed: 18283437]
- Herrnstein, RJ.; Prelec, D. A Theory of addiction. In: Loewenstein, G.; Elster, J., editors. *Choice over time*. New York: Russell Sage; 1992. p. 331–360.
- Heyman, GM. *Addiction: A disorder of choice*. Cambridge, MA: Harvard University Press; 2009.
- Kendler KS, Jacobson KC, Prescott CA, Neale MC. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *American Journal of Psychiatry*. 2003; 160:687–695. [PubMed: 12668357]
- Kerstetter KA, Ballis MA, Duffin-Lutgen S, Carr AE, Behrens AM, Kippin TE. Sex differences in selecting between food and cocaine reinforcement are mediated by estrogen. *Neuropsychopharmacology*. 2012; 37:2605–2614. [PubMed: 22871910]
- Lenoir M, Cantin L, Vanhille N, Serre F, Ahmed SH. Extended heroin access increases heroin choices over a potent nondrug alternative. *Neuropsychopharmacology*. 2013; 38:1209–1220. [PubMed: 23322185]
- Lenoir M, Guillem K, Koob GF, Ahmed SH. Drug specificity in extended access cocaine and heroin self-administration. *Addiction Biology*. 2012; 17:964–976. [PubMed: 21995515]

- Lenoir M, Serre F, Cantin L, Ahmed SH. Intense sweetness surpasses cocaine reward. *PLoS ONE*. 2007; 2(8):e698.10.1371/journal.pone.0000698 [PubMed: 17668074]
- Leri F, Bruneau J, Stewart J. Understanding polydrug use: review of heroin and cocaine co-use. *Addiction*. 2003; 98:7–22. [PubMed: 12492751]
- Martin TJ, Kim SA, Cannon DG, Sizemore GM, Bian D, Porreca F, Smith JE. Antagonism of δ 2-opioid receptors by naltrindole-5'-isothiocyanate attenuates heroin self-administration but not antinociception in rats. *Journal of Pharmacology and Experimental Therapeutics*. 2000; 294:975–982. [PubMed: 10945849]
- Martin TJ, Smith JE, Dworkin SI. Training dose and session time as contextual determinants of heroin self-administration in rats. *Pharmacology Biochemistry and Behavior*. 1998; 60:415–421.
- Martin TJ, Walker LE, Sizemore GM, Smith JE, Dworkin SI. Within-session determination of dose-response curves for heroin self-administration in rats: comparison with between-session determination and effects of naltrexone. *Drug and Alcohol Dependence*. 1996; 41:93–100. [PubMed: 8809497]
- McNamara R, Dalley JW, Robbins TW, Everitt BJ, Belin D. Trait-like impulsivity does not predict escalation of heroin self-administration in the rat. *Psychopharmacology*. 2010; 212:453–464. [PubMed: 20689939]
- Nader MA, Wolterton WL. Effects of increasing the magnitude of an alternative reinforcer on drug choice in a discrete-trials choice procedure. *Psychopharmacology (Berl)*. 1991; 105:169–174. [PubMed: 1796123]
- Nader MA, Wolterton WL. Effects of increasing response requirement on choice between cocaine and food in rhesus monkeys. *Psychopharmacology (Berl)*. 1992; 108:295–300. [PubMed: 1523280]
- National Academy of Sciences. *Guide for the Care and Use of Laboratory Animals*. National Academy Press; Washington, DC: 2011.
- Negus SS. Choice between heroin and food in nondependent and heroin-dependent rhesus monkeys: effects of naloxone, buprenorphine, and methadone. *Journal of Pharmacology and Experimental Therapeutics*. 2006; 317:711–723. [PubMed: 16456085]
- Perry AN, Westenbroek C, Becker JB. The Development of a Preference for Cocaine over Food Identifies Individual Rats with Addiction-Like Behaviors. *PLoS ONE*. 2013; 8(11):e79465.10.1371/journal.pone.0079465 [PubMed: 24260227]
- Peters J, Pattij T, De Vries TJ. Targeting cocaine versus heroin memories: divergent roles within ventromedial prefrontal cortex. *Trends in Pharmacological Sciences*. 2013; 34:689–695. [PubMed: 24182624]
- Saunders BT, Robinson TE. Individual variation in the motivational properties of cocaine. *Neuropsychopharmacology*. 2011; 36:1668–1676. [PubMed: 21471956]
- Schippers MC, Binnekade R, Schoffelmeer AN, Pattij T, De Vries TJ. Unidirectional relationship between heroin self-administration and impulsive decision-making in rats. *Psychopharmacology*. 2012; 219:443–452. [PubMed: 21887498]
- Spragg SDS. *Morphine Addiction in Chimpanzees*. Comparative Psychology Monographs. 1940; 15:1–132.
- Thomsen M, Barrett AC, Negus SS, Caine SB. Cocaine-food choice in rats: environmental manipulations and effects of amphetamine. *Journal of the Experimental Analysis of Behavior*. 2013; 99:211–233. [PubMed: 23319458]
- Tunstall BJ, Kearns DN. Reinstatement in a cocaine versus food choice situation: reversal of preference between drug and non-drug rewards. *Addiction Biology*. 2013 Epub ahead of print. 10.1111/adb.12054
- Vanderschuren LJ, Ahmed SH. Animal studies of addictive behavior. *Cold Spring Harbor Perspectives in Medicine*. 2013; 3(4):a011932.10.1101/cshperspect.a011932 [PubMed: 23249442]
- Vocci FJ. Can replacement therapy work in the treatment of cocaine dependence? And what are we replacing anyway? *Addiction*. 2007; 102:1888–1889. [PubMed: 18031424]
- Wagner FA, Anthony JC. Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. *American Journal of Epidemiology*. 2002; 155:918–925. [PubMed: 11994231]

- Ward SJ, Morgan D, Roberts DC. Comparison of the reinforcing effects of cocaine and cocaine/heroin combinations under progressive ratio and choice schedules in rats. *Neuropsychopharmacology*. 2005; 30:286–295. [PubMed: 15578009]
- Warner, RM. *Applied Statistics: From Bivariate Through Multivariate Techniques*. Thousand Oaks, CA: SAGE; 2007. Adding a Third Variable; p. 378-422.
- Weeks JR. Experimental morphine addiction: Method for automatic intravenous injections in unrestrained rats. *Science*. 1962; 138:143–144. [PubMed: 14005543]
- Woolverton WL, Myerson J, Green L. Delay discounting of cocaine by rhesus monkeys. *Experimental and Clinical Psychopharmacology*. 2007; 15:238–244. [PubMed: 17563210]

Figure 1. Cocaine and Heroin Self-administration

Mean number ($\pm$ SEM) of infusions self-administered over the last 10 self-administration sessions with Drug 1 and Drug 2. Sessions lasted 3 hours or until 50 infusions were earned. Rats were run for a minimum of 10 self-administration sessions and until the number of infusions consumed on the last 2 days was within 30% of the average of those 2 days. One rat required 13 sessions when heroin was Drug 1. One rat required 12 sessions when cocaine was Drug 2.

Figure 2. Cocaine and Heroin Preference

Mean percentage ($\pm$ SEM) of free choice trials (14 per session) on which drug was chosen in preference to food, over the last five choice sessions with Drug 1 and Drug 2. One rat completed 13 of 14 free choice trials on one session, otherwise, all rats completed all trials on all sessions (i.e., 0% = 0/14 trials, 50% = 7/14 trials, 100% = 14/14 trials). Rats were run for a minimum of five sessions and until there was no change greater than 20% in the percentage of trials on which the drug was chosen, across the final two sessions (for three rats choosing between cocaine and food, this was relaxed to a change no greater than 50% over three sessions). One rat required nine sessions when cocaine was Drug 1. Individual preferences are also shown (average of last two choice sessions).

Figure 3. Individual Subjects' Preference across Drugs

Individual subjects' preference for both cocaine and heroin relative to food. Each point in the scatterplot represents the percentage of free choice trials (14 per session; one rat completed 13 of 14 trials on one session, all others completed 14 of 14 on all sessions) on which an individual chose each drug in the presence of a food alternative (averaged over the last two choice sessions). Also presented is a regression line with 95% confidence limits ($R^2 = 0.05$, $p = 0.39$)