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Distinct relationships between risky decision making and cocaine self-administration under short- and long-access conditions

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Abstract

Substance use is strongly associated with impaired decision making, with cocaine use particularly linked to elevated risky and impulsive choice. It is not clear, however, whether such maladaptive decision making is a consequence of cocaine use or instead precedes and predisposes individuals to cocaine use. The current study was designed to specifically address the latter possibility with respect to risky choice in both male and female rats. Rats were first trained in a "Risky Decision-making Task" (RDT), in which they made discrete choices between a small, "safe" food reward and a large, "risky" food reward accompanied by increasing probabilities of mild footshock punishment. After reaching stable performance, rats underwent jugular catheter surgery followed by either short-access cocaine self-administration sessions (2 h, 0.5 mg/kg/infusion) for 5 days or long-access cocaine self-administration sessions (6 h, 0.5 mg/kg/infusion) for 14 days. Under short-access conditions, there was no relationship between risk preference and changes in cocaine intake over time, but greater risk aversion in females predicted greater overall cocaine intake. Under long-access conditions, heightened risk taking predicted greater escalation of cocaine intake over the course of self-administration, supporting the notion that pre-existing risk-taking behavior predicts cocaine intake. Collectively, results from these experiments have implications for understanding and identifying pre-existing vulnerabilities to substance use, which may lead to strategies to prevent development of substance use disorders.

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Ethical statement

All procedures were conducted in accordance with the University of Florida Institutional Animal Care and Use Committee and adhered to the National Institute of Health guidelines (Guide for the Care and Use of Laboratory Animals, 8th edition).

Declaration of Competing Interest

The authors declare no conflicts of interest.

Keywords

Cocaine; Self-administration; Risk taking; Choice

1. Introduction

Cocaine use is associated with altered cognitive function, such as impaired decision making (Gowin et al., 2018). Indeed, individuals with a history of cocaine use report engaging in riskier behavior and display increased levels of impulsivity and risk taking in laboratory decision-making tasks (Bornovalova et al., 2005; Lejuez et al., 2005; Leland and Paulus, 2005; Crowley et al., 2010; Gowin et al., 2017). These deficits in decision making may not only reduce quality of life, but also contribute to continued substance use and promote relapse after abstinence. This represents a significant challenge in developing treatments for cocaine use, particularly because it is difficult to disentangle whether impaired decision making precedes or results from chronic cocaine use. Animal models provide a tractable means by which to determine whether specific cognitive factors, such as dysfunctional decision making, contribute to the development of cocaine use or are consequences of the drug itself. For example, animal models of impulsive choice and impulsive action have been invaluable in dissociating a cause-and-effect relationship between impulsivity and cocaine use. Previous work has shown that in rats self-administering cocaine, higher levels of both forms of impulsivity predict greater cocaine intake (Dalley et al., 2007; Broos et al., 2012) and greater escalation of cocaine intake (Perry et al., 2008; Anker et al., 2009). Using the same animal models, others have also shown that cocaine self-administration can cause long-lasting increases in impulsive choice and impulsive action (Winstanley et al., 2009; Mendez et al., 2010; Mitchell et al., 2014b). Hence, these animal models demonstrate that higher levels of impulsivity predict vulnerability to cocaine use, but also that cocaine use itself increases impulsivity, which could contribute to continued use.

Cocaine use, however, is associated not only with greater impulsivity but also with other forms of maladaptive decision making, such as risk taking (Gowin et al., 2018). The relationship between risk-based decision making and cocaine use has not been as effectively parsed as it has been with impulsivity. Recently, Ferland and Winstanley (2017) used a rodent gambling task based on the Iowa Gambling Task to assess relationships between baseline risk preference and cocaine-seeking, and found that exaggerated preference for risky, or disadvantageous, options predicted greater cocaine-seeking during a test of relapse/reinstatement. Interestingly, risky choice in this task was also exacerbated by cocaine self-administration, but only in rats that preferred risky options at baseline, indicating that individual differences in risk preference may predict not only cocaine-seeking behavior, but also sensitivity to cocaine's impact on risky decision making (Ferland and Winstanley, 2017). In a similar vein, prior work from our laboratory using a decision-making task involving risk of explicit punishment showed that risk-seeking rats, or those that predominantly preferred larger, riskier rewards, self-administered more cocaine than risk-averse rats, or those that predominantly preferred smaller, safer rewards, under short-access conditions (Mitchell et al., 2014a). Hence, these initial studies suggest that, as with

impulsivity, elevated risk preference may contribute to vulnerability to development of cocaine use.

The goal of the current study was to extend our previous work on relationships between pre-existing risk preference and cocaine self-administration. Specifically, we assessed whether risk preference was associated with changes in cocaine intake under short-access or long-access cocaine self-administration conditions. We further evaluated these associations in both male and female rats. This is an important distinction from prior work and, given well-established sex differences in both risk taking and substance use (Lynch, 2006; Becker and Hu, 2008; van den Bos et al., 2013; Orsini et al., 2016; Orsini and Setlow, 2017), is paramount for fully understanding how decision-making endophenotypes might predispose individuals to cocaine use. Risk preference was assessed using a "Risky decision-making task" (RDT), in which rats choose between a small, safe food reward and a large food reward accompanied by variable probabilities of punishment (Simon et al., 2009). In previous work with this model, we showed that risk-seeking males self-administer more cocaine than their risk-averse counterparts under short-access conditions (Mitchell et al., 2014a). We expected that, at least in males, a similar relationship would be evident between risk preference and changes in cocaine intake under long-access self-administration conditions.

2. Materials and methods

2.1. Subjects

Male (n = 31) and female (n = 26) Long-Evans rats (55 days old upon arrival; Charles River Laboratories, Raleigh, NC) were individually housed in ventilated cages with Sani-chip bedding (P.J. Murphy Forest Products) and kept on a 12-h reverse light/dark cycle (lights off at 0800) for the duration of the experiment. Rats were given free access to water and food (soy-free; Envigo Teklad Irradiated Global 19% Protein Extruded Rodent Diet, #2919), except as noted below. Prior to behavioral training and testing in the decision-making task, rats were handled 3 times a week to acclimate them to the researchers, after which they were food restricted to 85% of their free-feeding weight. Over the course of the experiment, these target weights were adjusted upward by 5 g per week to account for growth. During training and testing in the decision-making task, rats were fed based on their target weight in order to maintain them at these weights. During cocaine self-administration, however, rats were limited to 30 g of food per day (and water ad libitum), irrespective of target weights, to minimize the impact of motivational differences on self-administration behavior due to natural variations in food intake and weight gain. Behavioral procedures occurred between 0900 and 1800, six to seven days a week. All procedures were conducted in accordance with the University of Florida Institutional Animal Care and Use Committee and adhered to NIH guidelines.

2.2. General experimental design

Rats were given one week to habituate to the environment and the researchers prior to initiation of experiments. Each experiment used two separate cohorts of rats. Experiment 1 (n = 16 male; n = 14 female) was designed to assess the relationship between baseline risk

preference and cocaine intake during acquisition of cocaine self-administration (hereupon referred to as short-access self-administration). Rats were trained in the Risky Decision-making Task (RDT) until stable behavioral performance emerged. Rats then underwent jugular catheter surgery and after a week of recovery, began cocaine self-administration for 2 h/day for 5 days at 0.5 mg/kg/infusion.

Experiment 2 (n = 15 male; n = 12 females) was designed to assess the relationship between baseline risk preference and escalation of cocaine intake across two weeks of long-access cocaine self-administration. Experimental procedures were identical to those of Experiment 1 except that cocaine self-administration sessions were 6 h in duration and occurred daily for 14 days.

2.3. Apparatus

For the RDT, rats were trained and tested in twelve identical computer-controlled operant chambers (30.5 × 25.4 × 30.5 cm; Coulbourn Instruments) housed in sound-attenuating cabinets. Each chamber was equipped with a centrally located recessed food trough bounded by a retractable lever on each side. Food troughs were outfitted with a photobeam to detect nosepokes and a 1.12-W lamp to illuminate the trough, and were connected to food hoppers from which 45 mg soy-free food pellets (Test Diet, AIN-76A, 5UTL) were dispensed into the troughs. Each chamber contained a stainless steel grid floor connected to a shock generator, which controlled delivery of scrambled foot-shocks. To monitor locomotor activity, an activity monitor was placed on the center of each chamber's ceiling and used infrared detectors to measure relative changes (in *x, y,* and *z* planes) in infrared energy. Finally, a 1.12-W house light was fixed to the back of each sound-attenuating cabinet. Each operant chamber was connected to a computer running Graphic State 4.0 software (Coulbourn Instruments), which controlled task events and collected behavioral data concurrently.

Cocaine self-administration was conducted in twelve identical computer controlled operant chambers (30.5 × 25.4 × 30.5 cm; Coulbourn Instruments) housed in sound-attenuating cabinets and located in a different room from those used for the RDT. Each self-administration chamber was outfitted with a liquid dipper trough located on the center of the front wall into which the sucrose solution reward was delivered. Nosepoke holes were located to the left and right of the trough and contained lights that could illuminate the holes. Cocaine was delivered intravenously (IV) via 20 ml syringes mounted on infusion pumps that were connected to a tether system (Instech Laboratories) consisting of fluid-filled PE50 tubing that ran from the syringe, through a swivel located above the operant chamber to a venous access port implanted in the rats' backs. Each operant chamber was interfaced with a computer running Graphic State 4.0 software (Coulbourn Instruments), which controlled task events and collected behavioral data concurrently.

2.4. Risky Decision-making Task (RDT) procedures

Training in the RDT proceeded as in our previous work (Simon et al., 2011; Shimp et al., 2015; Orsini et al., 2016; Blaes et al., 2018; Deng et al., 2018; Orsini et al., 2018). Prior to training in the RDT, rats were shaped to perform the basic components of the task. Rats were

first shaped to obtain food rewards from the food trough and were then trained to lever press for the food rewards. Finally, rats were shaped to nosepoke in the food trough to initiate extension of both levers, which when pressed, resulted in the food rewards. Once shaping was complete, rats began daily training sessions in the RDT until stable behavior emerged. Each session lasted 60 min and consisted of five blocks of 18 trials (8 forced choice and 10 free choice). Each 40 s trial began with illumination of the house light and food trough light. A nosepoke into the food trough extinguished both lights and triggered extension of either one lever (forced choice trial) or both levers (free choice trial). If a rat failed to nosepoke within 10 s, lights were extinguished and the trial was scored as an omission. Irrespective of trial type, a press on one lever resulted in a small, “safe” food reward (1 pellet) and a press on the other, “risky” lever resulted in a large food reward (2 pellets) that was accompanied by the possibility of a 1 s scrambled footshock. Shock delivery depended upon a predetermined probability that was specific to each of the five blocks of trials, with the probability starting at 0% in the first block and increasing by 25% in each subsequent block across the session (0%, 25%, 50%, 75%, 100%). Irrespective of footshock, however, the large food reward was always delivered. The identities of the small, safe lever and the large, risky lever were counterbalanced across the left/right position of the levers but remained the same for each rat for the entirety of the RDT. We showed previously that at the same shock intensity, males choose the large, risky reward to a greater extent than females (Orsini et al., 2016). In light of this difference, males and females were maintained at different footshock intensities during the RDT in order to maximize the range of individual differences in risk taking within each sex. In the first eight trials of a block, each lever was randomly presented four times, allowing rats to learn the shock contingencies for that block before proceeding to the free choice trials. The probability of footshock on each forced choice trial depended on the other forced choice trials in that block. For example, in the 25% block, a lever press in one and only one of the four forced choice trials yielded a footshock. Similarly, in the 75% block, a lever press in three and only three of the four forced choice trials yielded a footshock. During the free choice trials, rats were allowed to choose between the two levers. In contrast to the forced choice trials, the probability of footshock in free choice trials was independent of the other free choice trials in that block. In other words, the shock probability for each free choice trial was identical within a block, irrespective of whether shocks had been delivered in previous trials in that block. Once pressed, levers were retracted, the house light and food trough lights were illuminated, and food was delivered. If rats failed to press a lever within 10 s, however, levers were retracted and the trial was scored as an omission. Lights were extinguished once food was collected or after 10 s, whichever occurred first.

2.5. Jugular catheter surgery

After stable performance in the RDT was achieved, rats were allowed free access to food and water for one week prior to surgery. On the day of surgery, rats were anesthetized with isoflurane gas (1–5% in O_2) and Metacam (1 mg/kg), buprenorphine (0.05 mg/kg) and sterile saline (10 ml) were subcutaneously administered. Hair on the rat’s back and chest was clipped and the skin disinfected with chlorohexidine. Using aseptic surgical techniques, a small incision was made in the skin above the jugular vein and fat was dissected away to access the vein. The top of the jugular vein was ligated and a catheter (Instech Laboratories) was inserted through a small incision in the middle of the vein and fed into the length of the

vein. Once the catheter was inserted, it was sutured into place. The other end of the catheter was passed subcutaneously over the right shoulder and through a small incision in the skin over the scapulae. This end of the catheter was attached to a port (Instech Laboratories), which, after clearing away the fascia of the back skin, was placed underneath the skin and sutured into the surrounding muscle (to minimize movement of the implant during recovery). The skin around the port was sutured and cleaned with sterile saline. Finally, a protective aluminum cap was placed on the port to minimize contact with debris in the home cage. Rats were given 7 days to recover from surgery, during which catheters were flushed daily with an antibiotic solution (0.1 ml cefazolin, 30 mg/kg) and locked with a heparinized glycerol solution (40 U/ml heparin in 50:50 glycerol:0.9% sterile saline). Rats continued to receive i.v. antibiotics throughout the course of self-administration, given at the end of each self-administration session, to prevent infection and the accumulation of fibroids that could occlude the catheter. Catheters were tested for patency once a week with an i.v. infusion of 0.1 ml propofol, which causes rapid, but transient, loss of muscle tone.

2.6. Self-administration procedures

Rats first learned to procure 40 μl of a 20% sucrose solution reward from the liquid dipper trough, after which they were trained to nosepoke in the “active”, illuminated hole to activate delivery of the same sucrose reward. Rats were required to reach a criterion of 50 nosepokes in the “active” hole in 30 min (which took approximately three sessions) before proceeding to cocaine self-administration. During self-administration, nosepokes into the “active” hole were reinforced on a fixed ratio 1 (FR1) schedule with an infusion of cocaine HCl (0.5 mg/kg/infusion, dissolved in 0.9% sterile saline; Drug Supply Program, NIDA) in a volume of 0.16 ml over 6 s. After each infusion, there was a 20 s timeout period in which nosepokes into the “active” hole had no effect. Nosepokes into the “inactive” hole were recorded but had no programmed consequences. For Experiment 1, self-administration sessions lasted for 2 h/day for 5 days (short-access condition). For Experiment 2, self-administration sessions lasted for 6 h/day for 14 days (long-access condition).

2.7. Statistical analyses

For the RDT, data were collected using Graphic State 4.0 software and analyzed with customized Graphic State 4.0 templates. These templates extracted the number of lever presses and nosepokes during free and forced choice trials, locomotor activity, percentage of trial omissions, and latencies to nosepoke and lever press. Data from the Graphic State 4.0 templates were analyzed using SPSS 25. The primary dependent variable was the choice of the large, risky reward (otherwise referred to as risky choice or risk taking), defined as the percentage of free choice trials on which rats chose the large, risky reward (excluding omissions). To determine whether behavioral performance was stable, risky choice from the last three consecutive days was analyzed with a two-way repeated measures analysis of variance (ANOVA), with day and trial block as within-subject variables. Behavior was considered stable if there was a main effect of trial block, but neither a main effect of day nor an interaction between day and trial block. Once stable, the final data from the RDT to be used for correlational analyses with self-administration variables were the mean choice of the large, risky reward across trials blocks 2–5 (the trial blocks in which the risk of punishment was present) for the three days of stable performance.

In addition to choice performance, analyses were conducted on other behavioral variables associated with the RDT. A repeated measures ANOVA was used to analyze the latencies to press levers in the forced choice trials, with lever identity (small, safe lever vs. large, risky lever) and trial block as within-subjects variables. Locomotor activity during the intertrial intervals (ITIs) was averaged across the five blocks of trials and across the three sessions of stable behavior; locomotor activity during shock delivery (1 s) was calculated similarly, with the exception that only the blocks involving shock delivery were included (blocks 2–5). Finally, omissions were defined as the percentage of omitted free choice trials out of the maximum number of free choice trials (Orsini et al., 2018) in a session. Locomotor activity during the ITIs and shock delivery as well as the percentage of omissions were compared between sexes using unpaired *t*-tests and are reported in Table 1.

During self-administration sessions, the number of active and inactive nosepokes, the latency to nosepoke, and the quantity of cocaine intake (mg/kg) were collected and analyzed. A repeated measures ANOVA was used to confirm preference for the active over the inactive nosepoke, with both self-administration session (day) and nosepoke identity as within-subject variables. Similarly, a one-way repeated measures ANOVA was conducted to determine whether latency to nosepoke for cocaine or mean cocaine intake changed across days. Spearman's correlations were used to evaluate relationships between risk preference and cocaine intake under short-access (Experiment 1) and long-access (Experiment 2) conditions. Note that analyses were initially conducted among all rats, followed by identical analyses conducted in each sex separately. For all analyses, a p-value less than or equal to 0.05 was considered statistically significant.

3. Results

3.1. Experiment 1

3.1.1. Risky decision making—Stable performance was obtained after 25–30 sessions [day, $F(2, 58) = 0.34$, $p = 0.72$, η_P^2; trial block, $F(4, 116) = 42.37$, $p < 0.01$, η_P^2; day × trial block, $F(8, 232) = 0.90$, $p = 0.52$, η_P^2]. Performance in the RDT did not differ between males and females [sex, $F(1, 28) < 0.01$, $p = 1.0$, η_P^2; trial block, $F(4, 112) = 41.26$, $p < 0.01$, η_P^2; sex × trial block, $F(4, 112) = 0.46$, $p = 0.77$, η_P^2.]; this was unsurprising, however, as different shock intensities were used in the two sexes to maximize the range of choice variability in each sex (see Methods). The distribution of choices in the RDT in both sexes is presented in Fig. 1A. Analyses of latencies to press levers in forced choice trials revealed that, as in our previous work (Shimp et al., 2015; Orsini et al., 2016; Blaes et al., 2018), as risk of punishment increased across the session, there was an increase in the latency to press the large, risky lever relative to the small, safe lever [lever identity, $F(1, 28) = 19.29$, $p < 0.01$, η_P^2; trial block, $F(4, 112) = 24.29$, $p < 0.01$, η_P^2; lever identity × trial block, $F(4, 112) = 23.82$, $p < 0.01$; η_P^2]. As with choice behavior, this pattern did not differ between males and females [sex, $F(1, 27) = 0.94$, $p = 0.34$, η_P^2; lever identity × sex, $F(1, 27) < 0.01$, $p = 0.96$, η_P^2; lever identity × trial block × sex, $F(4, 108) = 0.52$, $p = 0.72$, η_P^2]. Mean locomotor activity and percentage of omissions in the RDT are presented for males and females in Table 1. Consistent with previous work (Orsini et al., 2016), females omitted significantly more free choice trials than males [$t(28) = -3.07$, $p < 0.01$] and males

exhibited higher levels of locomotor activity during the intertrial interval than females [$t(26) = 2.79$, p = 0.01]. There were no sex differences in locomotor activity during the delivery of footshock [$t(24) = 1.63$, p = 0.12].

3.1.2. Cocaine self-administration—Under short-access conditions, there was a significant change in cocaine intake across days 1–5 [Fig. 1B; $F(4, 116) = 4.76$, p < 0.01, η_P^2]; this effect, however, was mainly driven by a sharp decrease in intake between days 1 and 2. Indeed, the main effect of day on intake was eliminated when an identical analysis was conducted only on days 2 through 5 [$F(3, 87) = 1.70$, p = 0.17, η_P^2]. This pattern of behavior, whereby cocaine intake is initially high but sharply declines, is not uncommon and likely due to a carryover of nosepoking for sucrose to day 1 of cocaine self-administration. As initial cocaine intake can be aversive (Ettenberg et al., 1999; Knackstedt et al., 2002; Ettenberg, 2004; Jhou et al., 2013; Ettenberg et al., 2015), cocaine intake then declines on day 2. Notwithstanding, rats clearly preferred the active over the inactive nosepoke across all 5 days of self-administration [Fig. 1C; nosepoke, $F(1, 28) = 133.96$, p < 0.01, η_P^2; nosepoke × day, $F(4, 112) = 3.01$, p = 0.02, η_P^2]. There were no changes in the latency to nosepoke for cocaine infusions across days 1 through 5 [$F(4, 112) = 1.46$, p = 0.22, η_P^2] or days 2 through 5 [$F(3, 84) = 0.70$, p = 0.55, η_P^2], suggesting that even if initial cocaine intake on day 1 was aversive, it was not sufficiently aversive to increase latencies to self-administer additional cocaine on day 2 or thereafter. Comparisons between sexes revealed that neither changes in cocaine intake [sex, $F(1, 28) = 0.86$, η_P^2; sex × day, $F(4, 84) = 2.33$, p = 0.08, η_P^2] nor nosepoke preference [sex, $F(1, 27) = 0.02$, p = 0.88, η_P^2; nosepoke × sex, $F(1,27) = 0.36$, p = 0.55, η_P^2; nosepoke × day × sex, $F(4, 108) = 1.01$, p = 0.36, η_P^2] nor latency to nosepoke for cocaine [sex, $F(1, 27) = 0.15$, p = 0.70, η_P^2; sex × day, $F(3,81) = 0.34$, p = 0.80, η_P^2] differed between males and females.

3.1.3. Relationships between risky choice and cocaine intake under short-access conditions—Spearman's correlational analyses were conducted to determine whether mean risky choice was associated with cocaine intake under short-access self-administration conditions (Fig. 2). There were no significant associations between risky choice and mean cocaine intake across the last 4 days of self-administration ($r = -0.13$, p = 0.49) nor were there significant associations between risky choice and changes in cocaine intake, measured as the difference in intake across days ($r = -0.07$ p = 0.73). Note that only days 2 through 5 were used for these analyses to avoid the confounding effect that high levels of nosepoking on day 1 may have on these measures. Finally, there were no significant correlations between risky choice and latency to self-administer cocaine for any of the self-administration sessions ($ps > 0.05$).

When the correlational analyses were conducted for males and females separately, there were no significant relationships between risky choice and measures of cocaine intake in males (mean intake, $r = 0.07$, p = 0.81, Fig. 3; difference in cocaine intake, $r = -0.27$, p = 0.31). Although there were also no associations in females between risky choice and differences in cocaine intake across days ($r = 0.19$, p = 0.52), there was a significant correlation between risky choice and mean cocaine intake ($r = -0.53$, p = 0.05, Fig. 3), such that greater risk aversion was associated with higher levels of cocaine intake. There were,

however, no significant relationships between risky choice and latencies to self-administer cocaine in either males or females (*p*s >0.05). Collectively, these results indicate that individual risk preference in males is not predictive of cocaine intake or changes in cocaine intake under short-access conditions, but that greater risk aversion in females may be predictive of higher levels of cocaine intake under such conditions.

3.2. Experiment 2

3.2.1. Risky decision making—Stable performance in the RDT emerged after 35–40 sessions [day, $F(2, 52) = 1.03$, p = 0.36, η_P^2; trial block, $F(4, 104) = 30.16$, p < 0.01, η_P^2; day × trial block, $F(8, 208) = 1.32$, p = 0.24, η_P^2]. As expected, there were no sex differences in choice of the large, risky reward [sex, $F(1, 25) = 0.09$, p = 0.76, η_P^2; sex × trial block, $F(4, 100) = 0.17$, p = 0.96, η_P^2]. The distribution of choices during stable behavior in the RDT is presented in Fig. 4A. A repeated measures ANOVA revealed that, in contrast to latencies to lever press for the small, safe reward, the latencies to press the large, risky lever increased as the risk of punishment increased [lever identity, $F(1, 24) = 8.85$, p < 0.01, η_P^2; trial block, $F(4,96) = 11.34$, p < 0.01, η_P^2; lever identity × trial block, $F(4,96) = 14.02$, p < 0.01; η_P^2]. This pattern of behavior did not differ between males and females [sex, $F(1, 23) = 0.95$, η_P^2; sex × lever identity, $F(1, 23) = 0.57$, p = 0.46, η_P^2; sex × lever identity × trial block, $F(4, 92) = 0.18$, p = 0.95, η_P^2]. Mean locomotor activity and percentage of omissions during the RDT are presented in Table 1. There were no sex differences in omissions during free choice trials [$t(25) = -0.13$, p = 0.90] or locomotor activity during either the intertrial intervals [$t(25) = 0.26$, p = 0.80] or shock delivery [$t(24) = -0.47$, p = 0.64].

3.2.2. Cocaine self-administration—During long-access cocaine self-administration, rats gradually escalated their cocaine intake across sessions [$F(12, 300) = 4.48$, p < 0.01, η_P^2]. Similar to Experiment 1, data from day 1 of self-administration were excluded to avoid the potential confound of carryover from nosepoking for sucrose. To determine the point at which rats began to escalate their intake, a Bonferroni's multiple comparisons post hoc test was conducted, comparing intake on day 2 to intake on each subsequent day. This analysis revealed that significant escalation of cocaine self-administration began on day 6 compared to day 2 [$t(26) = 3.40$, p = 0.02] and significantly increased across days 6 through 14 [$F(8, 200) = 1.99$, p = 0.05, η_P^2; Fig. 4B]. In contrast, there was no change in cocaine intake between days 2 and 5 [$F(3, 78) = 0.88$, p = 0.45, η_P^2], confirming that rats escalated their intake specifically across days 6 through 14. Rats demonstrated a strong preference for the active over the inactive nosepoke, irrespective of whether nosepokes across days 2 through 14 [Fig. 4C; nosepoke, $F(1,23) = 187.94$, p < 0.01, η_P^2; nosepoke × day, $F(12, 276) = 3.82$, p < 0.01, η_P^2] or days 6 through 14 [nosepoke, $F(1, 23) = 217.78$, p < 0.01, η_P^2; nosepoke × day, $F(8, 184) = 1.19$, p = 0.31, η_P^2] were analyzed. In addition, latencies to self-administer cocaine did not change significantly across days 2 through 14 [$F(12, 228) = 1.26$, p = 0.24, η_P^2] or days 6 through 14 [$F(8, 160) = 0.77$, p = 0.63, η_P^2]. Comparison between sexes showed that males and females escalated their cocaine intake (days 6 through 14) to the same extent [day, $F(8, 192) = 1.95$, p = 0.05, η_P^2; sex, $F(1, 24) = 0.18$, p = 0.68, η_P^2; day × sex. $F(8, 192) = 0.80$, p = 0.60, η_P^2] and that there were no sex differences in nosepoke preference across days 2 through 14 [sex, $F(1, 22) = 1.66$, p = 0.21, η_P^2; nosepoke × sex, F

(1,22) = 0.63, p = 0.44, η_P^2; nosepoke × sex × day, $F(12, 264) = 0.87$, p = 0.58, η_P^2] or days 6 through 14 [sex, $F(1,22) = 1.61$, p = 0.22, η_P^2; nosepoke × sex, $F(1, 22) = 1.09$, p = 0.31, η_P^2; nosepoke × sex × day, $F(8, 176) = 1.07$, p = 0.38, η_P^2]. There were also no sex differences in latencies to self-administer cocaine across days 2 through 14 [sex, $F(1, 18) = 0.36$, p = 0.55, η_P^2; sex × day, $F(12, 216) = 0.65$, p = 0.80, η_P^2] or days 6 through 14 [sex, $F(1, 19) = 0.43$, p = 0.52, η_P^2; sex × day, $F(8, 152) = 0.70$, p = 0.69, η_P^2].

3.2.3. Relationship between risky choice and escalation of cocaine intake under long-access conditions—

The relationship between mean risky choice and cocaine intake was analyzed using Spearman's correlational analyses (Fig. 5). The measure of escalation used for this analysis was the difference in cocaine intake between days 6 and 14, the period in which escalation occurred during self-administration (see above). This analysis revealed a significant correlation between risky choice and escalation ($r = 0.42$, p = 0.03) such that greater risky choice predicted greater escalation of cocaine intake. There was not, however, a significant relationship between risky choice and mean cocaine intake during escalation ($r = 0.02$, p = 0.93). Similar to Experiment 1, there were also no significant correlations between risky choice and latencies to self-administer cocaine for any of the self-administration sessions ($ps > 0.05$).

When correlational analyses were split by sex, there was no longer a significant relationship between risky choice and escalation of cocaine intake ($r = 0.33$, p = 0.23, Fig. 6), nor a significant relationship between risky choice and mean cocaine intake during escalation ($r = 0.10$, p = 0.71) in males. Similarly, there was not a significant relationship between risky choice and mean cocaine intake ($r = -0.27$, p = 0.40) in females, although there was a near-significant correlation between risky choice and escalation of intake ($r = 0.55$, p = 0.06, Fig. 6). Finally, there were no significant correlations between risky choice and latencies to self-administer cocaine in either males or females ($ps > 0.05$). Taken together, these results suggest that preference for riskier choices may be predictive of greater increases in cocaine self-administration under long-access conditions, but that this effect does not differ between sexes.

4. Discussion

The main objective of this study was to examine relationships between baseline risk preference and cocaine intake in male and female rats, with the hypothesis being that, at least in males, risky choice precedes and predicts greater increases in cocaine intake over time. Surprisingly, there was no such relationship in either males or females between risky choice and changes in cocaine intake under short-access cocaine self-administration conditions, although baseline female risk preference did predict overall cocaine intake. Under long-access conditions, however, risky choice was associated with greater increases in cocaine intake across the two weeks of self-administration in both males and females. These unexpected results demonstrate the existence of a distinct relationship between pre-existing differences in risk taking and cocaine intake during the initial acquisition of cocaine-seeking behavior in females.

Previous work has shown that individual differences in impulsivity predict differences in the initial acquisition of cocaine self-administration. For example, male and female rats that display higher levels of impulsive choice or action acquire cocaine self-administration at a faster rate than those that display lower levels of impulsive choice or action (Perry et al., 2005; Dalley et al., 2007). Further, our lab previously showed that male rats characterized as risk-seeking self-administer more cocaine than risk-averse male rats during acquisition of cocaine self-administration, using the same short-access conditions employed in the current study (Mitchell et al., 2014a). Hence, it was surprising that in the present study, risky choice in males was not related to changes in cocaine intake or mean cocaine intake under short-access conditions. One possible explanation for this discrepancy concerns the age at which individual differences in risky choice were assessed. While rats in the current study were trained and tested in the RDT as adults, those in the study by Mitchell et al. (2014a) were trained and tested in the RDT as adolescents. It is conceivable, therefore, that adolescence is a period in which individual differences in risky choice have stronger predictive power regarding the extent to which an individual is prone to substance use. This is consistent with the fact that adolescents who exhibit greater sensation-seeking and risk taking also exhibit higher concurrent rates of substance use (Spear, 2000; Crowley et al., 2010; Klein et al., 2012; Richard et al., 2019).

It was also surprising that greater risk aversion in females was associated with greater cocaine intake under the short-access conditions. There is precedence for relationships between choice preference and subsequent acquisition of cocaine self-administration in females; for instance, higher levels of impulsive choice predict more rapid acquisition of cocaine self-administration in female rats (Perry et al., 2005; Perry et al., 2008). To date, however, the relationship between pre-existing risk preference and acquisition of cocaine self-administration has not been examined. Hence, these data provide novel evidence that individual differences in risk-taking propensity can predict subsequent acquisition of cocaine use in females, although the direction of the relationship seems counterintuitive. One possible explanation for this finding is that individual differences in risk preference may be related to differences in sensitivity to cocaine's reinforcing effects, with risk aversion being associated with enhanced sensitivity to the rewarding effects of cocaine. This hypothesis is difficult to test, however, as cocaine-induced locomotor activity, one commonly used proxy of cocaine's efficacy (Robinson and Becker, 1986), was not recorded during self-administration sessions. Despite this lack of empirical support, others have demonstrated that individual differences in other aspects of behavior, such as sensitivity to food cues, predict the locomotor-activating effects of cocaine, psychomotor sensitization to cocaine, and cocaine-induced ultrasonic vocalizations (Flagel et al., 2008; Tripi et al., 2017). Further, a recent study reported that individual differences in risk taking in the RDT predict sensitivity to nicotine's effect on locomotion upon first exposure (Gabriel et al., 2019), a measure shown to reliably forecast the development of nicotine dependence. This explanation is speculative, however, and additional experiments are needed to explore this unique relationship in females.

In contrast to Experiment 1, the results of Experiment 2 revealed that greater risk taking predicts greater escalation of cocaine intake under long-access cocaine self-administration conditions. This significant relationship is reminiscent of recent work showing that risk-

preferring male rats displayed heightened cocaine-seeking behavior after self-administration (Ferland and Winstanley, 2017). It is also consistent with previous work showing that high-impulsive females escalate cocaine intake at a greater rate than low-impulsive females under long-access cocaine self-administration conditions (Anker et al., 2009). Although females tend to escalate drug intake more rapidly than males (Lynch, 2006; Becker and Hu, 2008; Carroll and Anker, 2010; Bobzean et al., 2014), the current data suggest that the predictive power of risk preference for escalation of cocaine intake does not differ between sexes.

In previous work we found robust sex differences in the RDT, with females being more risk averse than males (Orsini et al., 2016). In the current study there were no sex differences in RDT performance in either Experiment 1 or 2; however, this is a direct result of the experimental design, which was structured to exploit individual differences in risk preference rather than to detect group sex differences. Because shock intensities have a significant impact on risky choice in the RDT (Shimp et al., 2015), Orsini et al. (2016) kept shock intensities identical across both males and females to specifically address sex differences in risky choice. In the current study, shocks were adjusted separately for each sex to maximize the range of individual differences in risk preference, which was a critical component of the study. The absence of sex differences in cocaine self-administration, however, was somewhat unexpected. Prior studies have shown that females self-administer more cocaine, acquire self-administration more quickly, and escalate their intake more rapidly than males (Lynch and Carroll, 1999; Hu et al., 2004; Roth and Carroll, 2004; Jackson et al., 2006; Cummings et al., 2011). Aside from marginal differences in cocaine dose and self-administration parameters, the primary difference between this study and those prior is the rat strain used [Long-Evans rats in the current study vs. Wistar or Sprague Dawley rats in prior work (Hu et al., 2004, Roth and Carroll, 2004, Cummings et al., 2011)]. Ostensibly, this difference may not seem to be a valid explanation for the discrepancy between studies except for the fact that drug self-administration behavior does differ across strains (Kosten et al., 1997; Brower et al., 2002; Deiana et al., 2007; Kosten et al., 2007; Freeman et al., 2009; Marusich et al., 2011). Further, sex differences in drug self-administration can also vary across strains. For example, in contrast to Sprague-Dawley rats, female Long-Evans rats acquire cannabinoid self-administration faster and respond more during maintenance of cannabinoid self-administration relative to males (Deiana et al., 2007; Fattore et al., 2007). Consequently, sex differences in cocaine self-administration may not manifest as robustly in Long-Evans compared to other strains. Importantly, this does not detract from or confound the results of the current study insofar as the main objective was to determine whether pre-existing levels of risk preference predict cocaine self-administration behavior, and not whether sex differences in such a relationship exist.

The relationships between risk preference and escalation of intake prompt the question as to the neurobiological mechanisms underlying these relationships. For example, Dalley et al. (2007) showed that greater impulsive action is associated with lower levels of D2/3 dopamine receptors in the nucleus accumbens (NAc) and that this behavioral phenotype predicts greater escalation of cocaine self-administration. Previous work from our lab has also shown that risk taking is inversely associated with D2 dopamine receptor (D2R) mRNA in the NAc in male rats, with greater risky choice associated with lower levels of D2R mRNA in the NAc (Mitchell et al., 2014a). Further, lower D2R availability in the NAc of

nonhuman primates predicts greater cocaine intake during self-administration (Morgan et al., 2002; Nader et al., 2006). Collectively, this raises the possibility that low levels of D2Rs in the NAc are related to a distinct endophenotype, which includes elevated risk taking and impulsivity, and that this pre-existing state confers vulnerability to the development of substance use disorders. Consistent with this hypothesis, a recent study found that greater risk taking in the RDT is associated with heightened impulsive action (Gabriel et al., 2019). It is important to note, however, that much of this evidence is derived from male subjects and thus may not translate directly to females. Additional studies are therefore warranted to determine whether a similar relationship between risk preference and NAc D2R expression exists in females, and how this may relate to substance use.

4.1. Limitations and future directions

The main objective of the current study was to evaluate the relationship between baseline risk preferences and changes in cocaine intake under two different self-administration conditions, both of which used a FR1 schedule of reinforcement. While this design allowed for a 1:1 measure of responding and cocaine delivery, it precluded the ability to assess relationships between risk preference and the motivation to take cocaine. Support for such an association comes from recent work by Ferland and Winstanley (2017), which showed that male rats that chose risky/disadvantageous options in a rat gambling task at baseline showed greater cocaine-seeking during reinstatement than rats that exhibited more optimal choice behavior. It is interesting to note, though, that performance in the Risky Decision-making Task does not correlate with food-seeking under a progressive ratio schedule of reinforcement in male rats (Simon et al., 2011). Given this dissociation, it is conceivable that the relationship between pre-existing risk preference and subsequent changes in cocaine intake may be unrelated to the motivation to take cocaine. Notwithstanding, future studies will employ self-administration schedules that more directly assess motivation for cocaine-seeking.

An additional limitation to the current study's experimental design is that self-administration occurred in a context in which there was no choice other than to take cocaine. It is clear from prior work that there are important behavioral differences in drug-seeking behavior, and consequently drug intake, depending on whether or not subjects have the opportunity to choose between drug and another, non-drug alternative (Ahmed, 2018). Further, these differences in self-administration behavior under choice conditions vary across males and females: while males preferentially choose food over cocaine, females prefer cocaine over the non-drug alternative (Lenoir et al., 2007; Kerstetter et al., 2012; Perry et al., 2013; Bagley et al., 2017). It would therefore be intriguing to examine whether baseline risk preference predicts drug-seeking behavior when subjects are given alternative choices to cocaine. One could hypothesize that greater preference for risky options at baseline may predict exaggerated choice of cocaine over a non-drug alternative under chronic, long-access conditions. If correct, this would suggest that greater escalation of cocaine intake in risk-preferring rats may be a manifestation of a broader maladaptive decision making phenotype. Such relationships will be examined in future experiments.

In humans, cocaine use is itself a risky behavior, with possible adverse consequences including loss of family, finances, and even life. Self-administration of cocaine in this study, however, involved arguably no risk to the rats. One might therefore expect that there would not be a relationship between pre-existing risky choice under drug-naïve conditions and drug-seeking using this self-administration regimen. There is evidence, however, that cocaine users display exaggerated risky choices in aspects of life that do not specifically involve the pursuit or consumption of cocaine. For example, cocaine use is associated with an increase in risky driving behavior such as failure to use protective devices (Pulido et al., 2011), and greater rates of unprotected sex (Lejuez et al., 2005). Additionally, in a laboratory gambling task wherein subjects make choices between rewards that are large but "risky" (accompanied by large losses) vs. small but "safe" (accompanied by small losses), cocaine users make riskier choices (Bechara et al., 2001). In rodents, others have shown in male rats that individual differences in risk preference are positively associated with cocaine-seeking behavior after self-administration using a regimen similar to that used in the current study (Ferland and Winstanley, 2017). Taken together, it is conceivable that a tendency to engage in risky behavior may be one behavioral characteristic that can predispose an individual to future initiation and development of cocaine use, even beyond any additive propensity provided by the risky nature of illicit substance use.

Finally, a potential explanation for the different relationships observed in Experiment 1 and Experiment 2 is that the positive association between risk preference and escalation of cocaine intake in Experiment 2 is due to the greater number of self-administration sessions under long access conditions (14 d vs. 5 d in the short access conditions). Because the objective of the current study was to assess relationships between risk taking and drug intake during different phases of drug use (initiation vs. more chronic use), the choice of the number of sessions for each experiment was intentional. Nevertheless, although some studies suggest that short-access self-administration across numerous sessions (e.g., 20 days) is insufficient to achieve robust escalation (Ahmed and Koob, 1998; Ahmed and Koob, 1999), others show that escalation of cocaine intake can occur even with 1 h sessions (Beckmann et al., 2012; Mandt et al., 2015). Based on these findings, it is conceivable that, if rats self-administered cocaine for 2 h a day for 14 d, similar relationships between risk preference and escalation of intake would emerge. This would indicate that the positive association between risk taking and cocaine intake hinges on whether there are changes in intake over time. In the current study, there was no change in cocaine intake under short-access conditions; the only relationship under short access conditions was a negative correlation between risk preference and mean cocaine intake. Under long-access conditions, however, there was an escalation of cocaine intake, and baseline risk preference predicted the magnitude of this escalation. Hence, in determining whether risky choice predicts cocaine intake, the number of sessions or even the duration of the sessions themselves may not be as important as whether there are changes in drug intake.

5. Conclusion

In summary, the current data shed new light on behavioral features that may predispose individuals to the development of substance use. Importantly, they suggest that this relationship may be more pronounced in females during the early, initiation phases of

substance use, further advocating for the study of decision making and drug-related behavior in both sexes. Beyond the initial development and escalation of cocaine use, relationships between risk preference and other phases of substance use should also be considered; for example, it is easy to imagine that individual differences in risk preference predict vulnerability to relapse after protracted abstinence. Indeed, such a relationship exists between impulsive choice and reinstatement of cocaine-seeking, with high-impulsive females exhibiting greater reinstatement than low impulsive females and all males (Perry et al., 2008). Understanding such associations will ultimately facilitate the development of preventative measures to reduce the incidence of substance use and its detrimental impacts on health and well-being.

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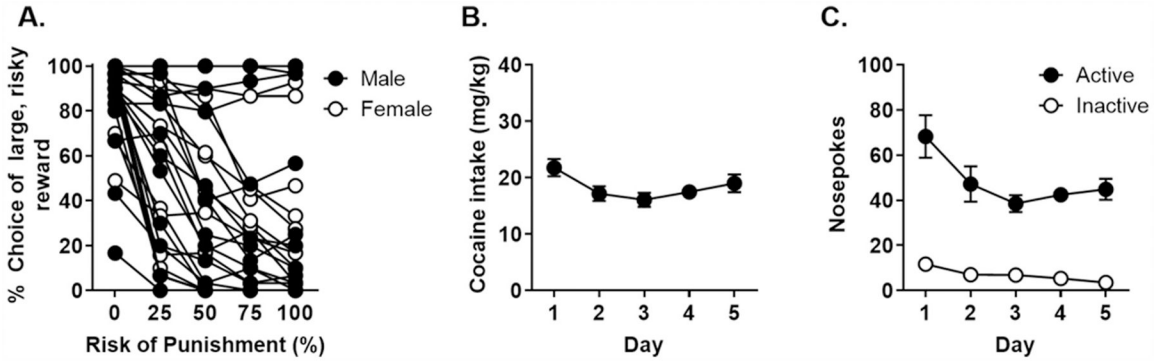

Fig. 1.

Performance in the Risky Decision-making Task and short-access cocaine self-administration. A. Distribution of individual values of choice performance in the Risky Decision-making Task in males and females. Each line represents data from a single rat. B. Cocaine intake across 5 days of short-access cocaine self-administration. Because there were no sex differences in cocaine intake, data from males and females are combined and presented as a group. C. Nosepoke behavior in the active and inactive hole across 5 days of short-access cocaine self-administration. Rats, irrespective of sex, preferred the active over the inactive nosepoke. For B and C, data are represented as the mean ± standard error of the mean.

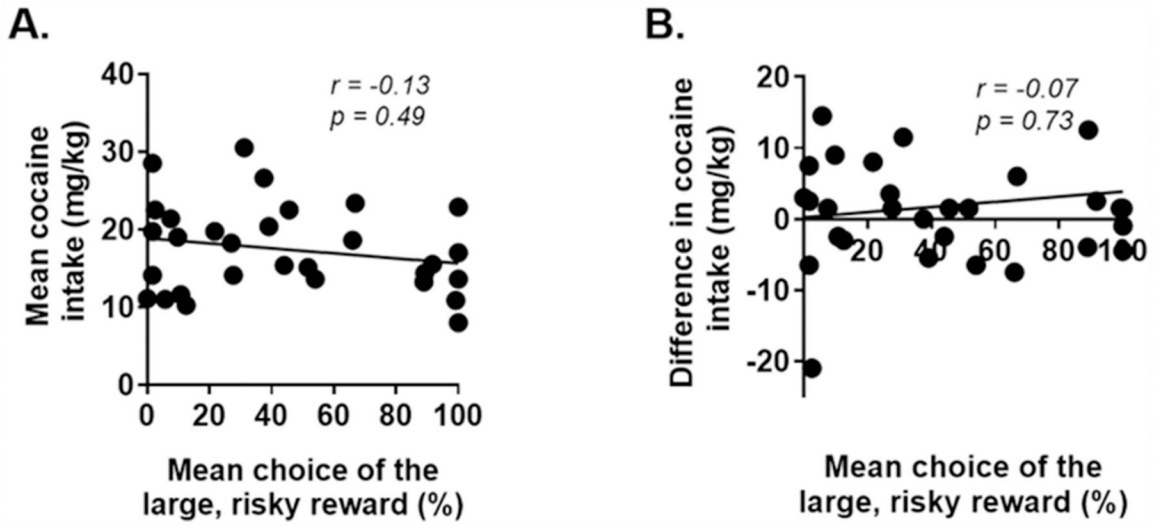

Fig. 2.

Relationships between risk preference and cocaine intake under short-access conditions. There were no significant relationships between risk preference and cocaine intake. A. Relationship between risk preference and mean cocaine intake. B. Relationship between risk preference and the difference in cocaine intake across days 2 through day 5.

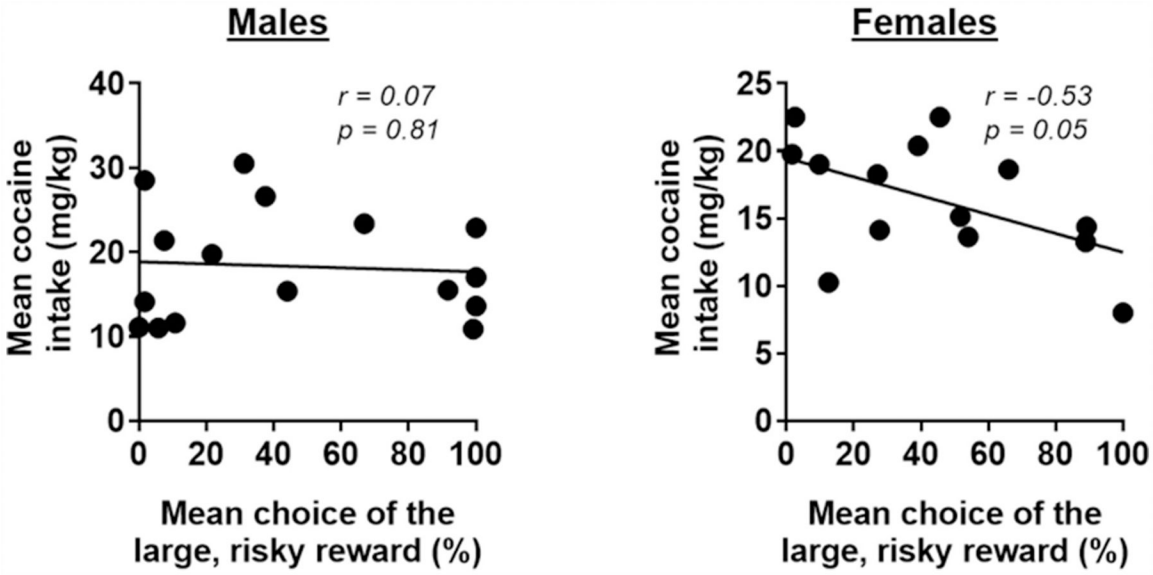

Fig. 3.

Relationships between risk preference and mean cocaine intake in males and females. While there was no association between risk preference and mean cocaine intake in males, greater risk aversion in females predicted greater cocaine intake.

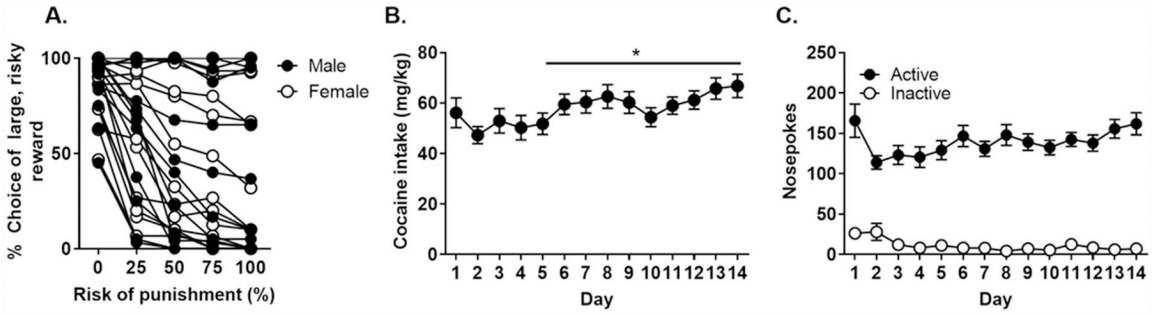

Fig. 4.

Performance in the Risky Decision-making Task and long-access cocaine self-administration. A. Distribution of individual values of choice performance in the Risky Decision-making Task in males and females. Each line represents data from a single rat. B. Cocaine intake across 14 days of long-access cocaine self-administration. Because there were no sex differences in cocaine intake, data from males and females were combined and presented as a group. The asterisk indicates that there was a significant increase in cocaine intake across days 6 through 14. C. Nosepoke behavior in the active and inactive hole across 14 days of long-access cocaine self-administration. Rats, irrespective of sex, preferred the active over the inactive nosepoke. For B and C, data are represented as the mean ± standard error of the mean.

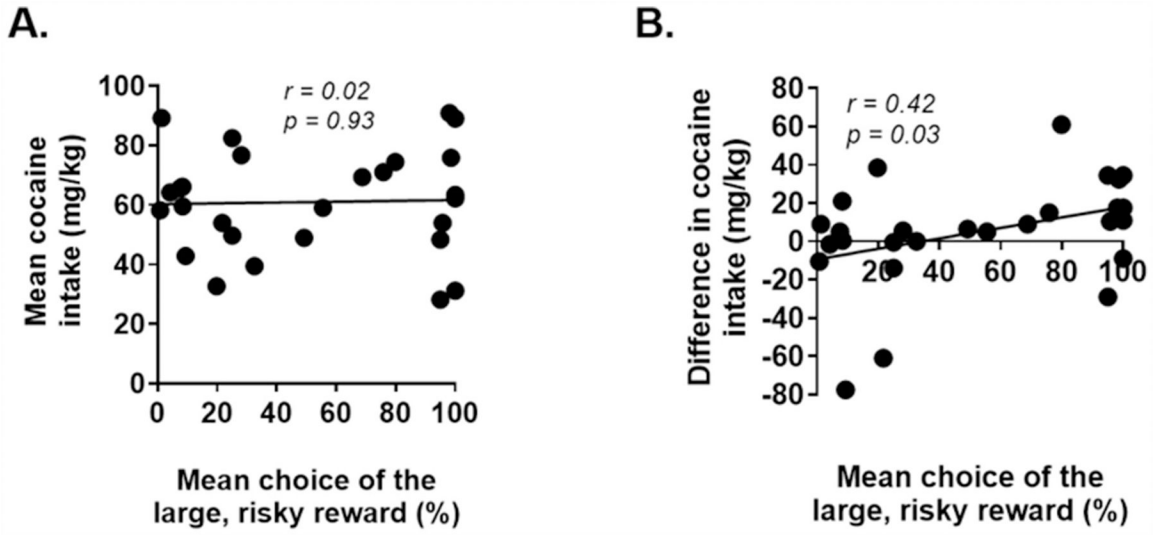

Fig. 5.

Relationships between risk preference and cocaine intake under long-access conditions. A. Relationship between risk preference and mean cocaine intake. B. Relationship between risk preference and difference in cocaine intake between days 6 and 14 (the period in which escalation occurred). Risk preference significantly predicted escalation of intake.

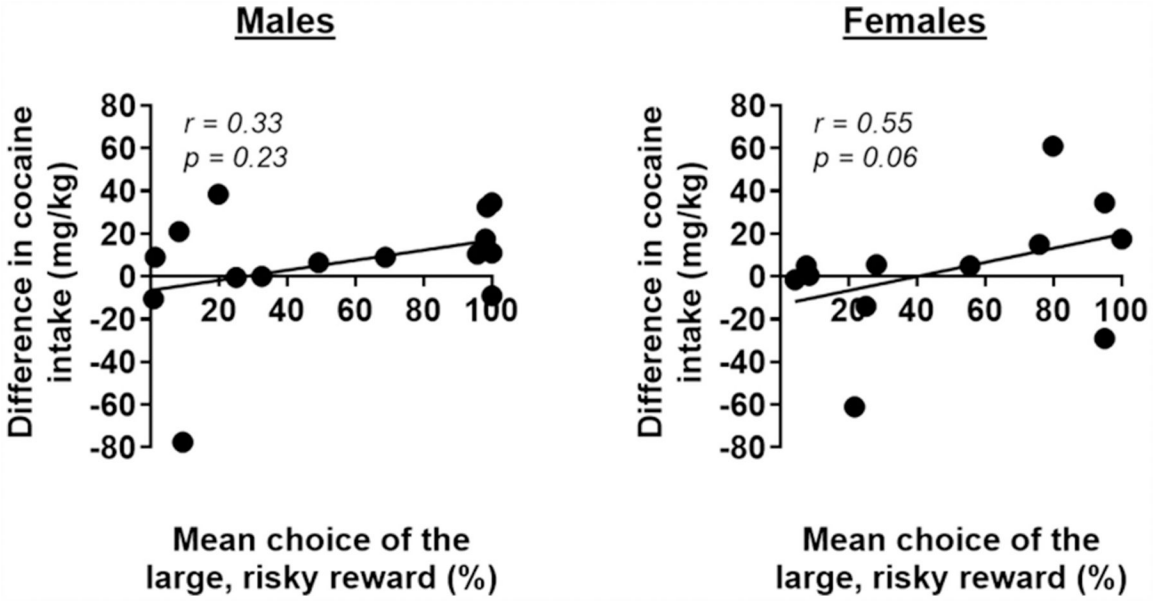

Fig. 6.

Relationships between risk preference and escalation of cocaine intake in males and females. While there was no association between risk preference and escalation of cocaine intake in males, there was a near-significant correlation in females, such that greater preference for the large, risky reward predicted greater escalation of cocaine intake in females.

Table 1

Mean (standard error of the mean) omissions, locomotor activity during intertrial intervals (ITIs), and locomotor activity during footshock delivery.

Experiment	Omissions	Locomotion (Locomotor units/ITI)	Shock reactivity (Locomotor uits/shock)
Experiment 1			
Male	0.50 (0.25)	54.59 (7.09)	3.20 (0.13)
Female	4.95 (1.52)	29.67 (5.48)	2.60 (0.36)
Experiment 2			
Male	1.27 (0.58)	60.25 (7.70)	2.61 (0.27)
Female	1.39 (0.80)	57.01 (10.00)	2.78 (0.24)