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Punishment resistance for cocaine is associated with inflexible habits in rats

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Abstract

Addiction is characterized by continued drug use despite negative consequences. In an animal model, a subset of rats continues to self-administer cocaine despite footshock consequences, showing punishment resistance. We sought to test the hypothesis that punishment resistance arises from failure to exert goal-directed control over habitual cocaine seeking. While habits are not inherently permanent or maladaptive, continued use of habits under conditions that should encourage goal-directed control makes them maladaptive and inflexible. We trained male and female Sprague Dawley rats on a seeking-taking chained schedule of cocaine self-administration. We then exposed them to four days of punishment testing in which footshock was delivered randomly on one-third of trials. Before and after punishment testing (four days pre-punishment and ≥ four days post-punishment), we assessed whether cocaine seeking was goal-directed or habitual using outcome devaluation via cocaine satiety. We found that punishment resistance was associated with continued use of habits, whereas punishment sensitivity was associated with increased goal-directed control. Although punishment resistance for cocaine was not predicted by habitual responding pre-punishment, it was associated with habitual responding post-punishment. In parallel studies of food self-administration, we similarly observed that punishment resistance was associated with habitual responding post-punishment but not pre-punishment in males, although it was associated with habitual responding both pre- and post-punishment in females, indicating that punishment resistance was predicted by habitual responding in food-seeking

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CRediT authorship contribution statement

Bradley O. Jones: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Morgan S. Paladino:** Investigation, Writing – review & editing. **Adelis M. Cruz:** Investigation, Writing – review & editing. **Haley F. Spencer:** Investigation. **Payton L. Kahanek:** Investigation. **Lauren N. Scarborough:** Investigation. **Sandra F. Georges:** Investigation. **Rachel J. Smith:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

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females. These findings indicate that punishment resistance is related to habits that have become inflexible and persist under conditions that should encourage a transition to goal-directed behavior.

Keywords

Addiction; Compulsive; Footshock; Devaluation; Self-administration; Food

1. Introduction

Addiction is characterized by compulsive drug seeking and continued drug use despite negative consequences. In an animal model of compulsive drug use, a subset of rats continues to self-administer cocaine despite footshock consequences, indicating punishment resistance [1–4]. Compulsive drug use has been theorized to stem from a loss of control over habitual behavior, making habits maladaptive and inflexible [5–11]. Although habits are considered automatic and insensitive to changes in outcome value, they are not necessarily permanent or insensitive to consequences. Rather, habitual behavior is typically flexible in that it is overridden by goal-directed control under conditions of punishment or changes in context [9,12]. In contrast, habitual responding that persists despite conditions that should encourage goal-directed control may indicate that habits have become maladaptive and inflexible. Here we sought to directly assess the relationship between habitual cocaine seeking and punishment resistance in rats.

The role of cocaine-seeking habits in the development of punishment resistance has been unclear, partially due to limited methods for assessing habitual responding for intravenous (IV) cocaine. We recently developed a procedure to discriminate goal-directed and habitual responding in rats self-administering IV cocaine using outcome devaluation via satiety [13]. Goal-directed behavior is performed in direct pursuit of the outcome, and therefore sensitive to outcome devaluation, whereas habitual behavior is automatically elicited by conditioned stimuli and insensitive to outcome devaluation [14–16]. Using this novel outcome devaluation procedure for IV cocaine, we found that bilateral lesions of dorsolateral striatum (DLS) or dorsomedial striatum (DMS) caused goal-directed or habitual cocaine responding, respectively, similar to previous work with food rewards [13,15,17–22]. We also found that a random ratio (RR20) schedule of reinforcement biased toward goal-directed responding, while a random interval (RI60) schedule biased toward habitual responding, although this biasing effect was weaker for cocaine as compared to food rewards [13,15,16,18,21–24]. An advantage of this procedure is that it elicits devaluation temporarily without the need for additional training, easily allowing repeated testing at different time points (e.g., before and after footshock punishment testing).

While habitual responding develops in the majority of rats after extended training on cocaine self-administration [25,26], punishment resistance develops in only a subset of rats [2,3,27]. DLS is necessary for habitual responding for cocaine and is progressively recruited over extended cocaine training [13,25,28–32]. DLS may also play a role in punishment resistance for cocaine, considering that DLS inactivation increased sensitivity to footshock punishment [33]. Similar parallels between habits and punishment resistance have been observed for

alcohol. Extended alcohol exposure increased habitual responding and DLS control of self-administration, as well as punishment resistance despite footshock [34–39]. Animals whose alcohol seeking had become habitual and DLS-dependent after extended training showed continued alcohol seeking despite footshock, supporting a role for habits in punishment resistance [36,37]. In contrast, while extended training with food rewards leads to increased use of habits, it has not been shown to increase punishment resistance [3,4,39–43]. In summary, extended training with cocaine or alcohol results in habitual responding in the majority of animals, as well as punishment resistance in a subset of animals, and these two processes may be linked in addiction.

To investigate the relationship between habitual cocaine seeking and punishment resistance, we trained male and female rats to self-administer IV cocaine on a seeking-taking chained schedule of reinforcement, originally developed by Olmstead et al. [44,45] and used extensively to study punishment resistance [3,4,27,36,37,42,43,46–51]. Thus, we use the term “seeking” to refer to responding that is not immediately followed by reward (e.g., when responding on the initial link in a chained schedule, on a partial-reinforcement schedule, or under extinction conditions); “seeking” describes the behavior and not the underlying cognitive process, as is the convention in behavioral psychology [52]. We then exposed rats to four days of punishment testing and used outcome devaluation via cocaine satiety to assess whether seeking was goal-directed or habitual four days pre-punishment and at least four days post-punishment. We found that punishment resistance for cocaine was associated with habitual responding post-punishment but not pre-punishment in both males and females. In parallel experiments in which rats were trained to self-administer food instead, we also found that punishment resistance was associated with habitual responding post-punishment but not pre-punishment in males, although it was associated with habitual responding both pre- and post-punishment in females. Overall, these data indicate that punishment resistance is associated with inflexible habits, whereas punishment sensitivity is associated with increased goal-directed control.

2. Material and methods

2.1. Animals

Male and female Sprague Dawley rats (initial weight 225–250 g; Charles River, Raleigh, NC, USA) were single-housed in a temperature-and humidity-controlled facility accredited by AAALAC at Texas A&M University. Rats were housed under a reversed 12-h light/dark cycle (lights off at 6 a.m.), with food and water access ad libitum, except when noted below. All experiments were approved by the IACUC at Texas A&M and conducted according to specifications of the NIH as outlined in the Guide for the Care and Use of Laboratory Animals.

2.2. Surgery

For cocaine self-administration studies, rats were anesthetized via isoflurane (induction 5 %, maintenance 1–3 %), given a nonsteroidal anti-inflammatory analgesic (ketoprofen, 2 mg/kg, s.c.), and implanted with chronic indwelling IV jugular catheters, as previously described [53]. Beginning three days after surgery, catheters were flushed once daily with

0.1 ml of cefazolin (100 mg/ml) and 0.1 ml heparin (500 U/ml). Self-administration sessions began after at least five days of recovery from surgery.

2.3. Cocaine self-administration

Rats were trained to self-administer IV cocaine (0.5 mg/kg per infusion) on a seeking-taking chained schedule of reinforcement, in which completion of a random ratio (RR20) or random interval (RI60) schedule on the seeking lever gave access to the taking lever during daily 2-h sessions. RR20 and RI60 schedules were used due to their influence on the development of goal-directed and habitual responding, respectively [13,15,16,18,21–24]. Infusions of cocaine (pump speed of 70 μg/sec) were paired with 5-sec tone and light cues (78 dB, 2900 Hz; white stimulus light above the active lever). Operant conditioning chambers were housed in sound-attenuating cubicles and controlled via MED-PC IV (Med-Associates, St. Albans, VT). Cocaine HCl was obtained as a gift through the NIDA Drug Supply Program and diluted in sterile 0.9 % saline.

To train animals, self-administration began with fixed ratio (FR) 1 reinforcement, with only the taking lever available (criterion of 5 sessions ≥20 infusions). Rats were food-restricted (85–90 % of free-feeding weight) at the start of the experiment to increase general motivation and were placed back onto free feeding once they had at least two consecutive sessions where they earned ≥20 infusions. Training then progressed to a chained seeking-taking schedule with FR1 (seeking) - FR1 (taking) reinforcement (criterion of 2 days ≥15 infusions), during which completion of the seeking link of the chain led to retraction of the seeking lever and extension of the taking lever; completion of the taking link of the chain delivered cocaine and led to retraction of the taking lever and the start of the next trial. During the seeking link of the chain, a stimulus light ($S+$) was presented above the seeking lever and signaled availability. At the next stage, rats were given a 4-min time out between trials, such that completion of the taking link of the chain led to retraction of the taking lever and extension of the seeking lever, but with no $S+$ and no programmed consequence for responding (criterion of 2 days ≥15 infusions). Training then progressed to RR or RI seeking schedules, and the taking lever was available for only 60 sec or until an infusion was earned (FR1), whichever occurred first. Each animal was trained on only one schedule (either RR or RI). For the RI schedule, the first press on the seeking lever initiated the start of the random interval, and then the first press made following the random interval completed the schedule. Training for the seeking lever began at RR3 or RI10 (criterion of 2 days ≥15 infusions), progressed to RR10 or RI30 (criterion of 2 days ≥15 infusions), and then to the final schedule of RR20 or RI60 (criterion of 5 days ≥15 infusions). The MED-PC program determined the random ratio or interval for a given trial via a probability function (i. e., 0.05 probability per lever press for RR20; 0.0166 probability per second for RI60). Animals were removed from studies if they did not meet the minimum criteria after two weeks at a given stage of training.

2.4. Cocaine outcome devaluation

Once animals were trained on the final seeking-taking schedule, outcome devaluation was tested across consecutive days in a within-subject manner (devaluation and nondevaluation days, counterbalanced order). As described previously [13], on the day of outcome

devaluation, rats were placed into the operant conditioning chambers and after a 5-min habituation period, were given experimenter-administered IV cocaine, consisting of 10 μl (to fill the catheter volume) plus a dose that mimicked the estimated brain cocaine concentrations during self-administration, based on the average infusions of the 4 previous self-administration sessions. Rats were given either 1.0 mg/kg (average of 11–17 infusions during self-administration), 1.5 mg/kg (18–24 infusions), or 2.0 mg/kg (25–31 infusions), in increments of 0.5 mg/kg infusions separated by 20 sec. After a 60-sec waiting period, the seeking lever was available with *S*+ for 10 min under extinction conditions. On the day of nondevaluation, no infusions were administered but animals spent a similar amount of time in the chamber prior to starting the 10-min extinction test. Devaluation and nondevaluation responding was normalized per rat, such that the number of lever presses on one session was divided by the total lever presses on both sessions (e.g., devaluation lever presses / (devaluation lever presses + nondevaluation lever presses)). Each 10-min devaluation or nondevaluation test was followed by a 5-min period with no levers extended and then the start of a typical cocaine self-administration session. For acclimation purposes, at least two days prior to the first devaluation test, rats were given a 10-min extinction session similar to the nondevaluation day. If animals failed to meet a criterion of ≥10 presses during the nondevaluation test session, then both the devaluation and nondevaluation sessions were repeated; if they failed again, then they were removed from analyses.

2.5. Food self-administration

Separate groups of rats were trained to self-administer food pellets (45-mg plain purified pellets, Bio-Serv, Flemington, NJ). Rats were mildly food-restricted for the entire experiment but still gained weight. Rats were fed in the home cage each day >1 h after the operant conditioning session ended and were fed the maximum amount possible that also resulted in all food eaten before the next day's session (~50 g for males, ~20 g for females). Rats underwent the same training as described above for cocaine with a seeking-taking chained schedule of reinforcement (RR20 or RI60), except that a press on the taking lever resulted in delivery of a food pellet paired with tone and light cues. The first two training stages differed from cocaine in that the criterion was 3 days =30 pellets for FR1 taking and 2 days ≥20 pellets for FR1 seeking-taking; criterion for subsequent training stages was similar. Rats experienced a time out between trials, although only 1 min and the seeking lever was retracted. Sessions were limited to 1 h or 30 rewards, whichever occurred first, so that the total trials per session were comparable to cocaine studies.

2.6. Food outcome devaluation

Once animals were trained on the final seeking-taking schedule, outcome devaluation was tested in a within-subject manner via sensory-specific satiety (devaluation and nondevaluation days, counterbalanced order). Rats were allowed to free-feed on either 45-mg plain purified food pellets (for the devaluation day; the same pellets earned during self-administration) or 15 % sucrose solution (for the nondevaluation day) in the home cage for 1 h prior to being placed into the operant conditioning chamber. After a 5-min waiting period, the seeking lever was available for 10 min under extinction conditions, and then rats were returned to the home cage. A normal self-administration session took place the next day, and then the second test (devaluation or nondevaluation, depending

on counterbalanced order) took place the following day. Devaluation and nondevaluation responding was normalized per rat, as described above for cocaine outcome devaluation. Rats were acclimated to 15 % sucrose by giving it in the home cage overnight ≥ three days prior to the first devaluation test.

2.7. Footshock punishment

Once animals were trained on the final seeking-taking schedule (≥13 days for cocaine, ≥10 for food), and ≥4 days after outcome devaluation, they received four consecutive days of punishment sessions. Rats received a minimum of 26 total cocaine self-administration sessions, or 21 total food self-administration sessions, prior to punishment testing. During the punishment sessions, footshock (0.4 mA, 0.3 sec) was administered on 1/3 trials randomly, after completion of the seeking link and before extension of the taking lever. Rewards were still available on footshock trials. After the four days of punishment, rats returned to daily self-administration and were allowed to recover to baseline responding levels (≥4 sessions with ≥10 rewards) before outcome devaluation testing.

2.8. Estrous cycle evaluation

Estrous cycle was evaluated via vaginal smears and cytology. Daily swabbing took place starting several days before punishment and then through punishment testing. After the self-administration session, a cotton swab wet with filtered deionized water was used for vaginal swabbing and then smeared onto a glass slide. The phases of the estrous cycles were determined by viewing dried noncoverslipped slides under a microscope and categorizing as proestrus, estrus, metestrus, or diestrus according to the proportions of cells, as described by Ajayi & Akhigbe [54].

2.9. Shock sensitivity threshold testing

Rats were tested for shock sensitivity before all experimentation (with the exception of two male rats in cocaine group). Rats were placed into operant chambers and given a series of footshocks (0.3 sec duration, ≥ 10 sec inter-shock interval), in an ascending series of intensities from 0.1 to 1.0 mA in 0.1-mA steps. The rats were scored for their first flinch, jump, and vocalization to the footshock, as described by Maren et al. [55]. Following vocalization, the ascending series was repeated twice more, and scores across the three test sessions were averaged.

2.10. Data analyses

Animals were removed from all analyses if they failed to meet the criteria for self-administration (described in Methods). Data were analyzed using *t*-tests or 2-way or 3-way ANOVAs (with repeated measures when appropriate) as detailed in the Results, with Sidak's multiple comparisons tests used for post hoc analyses; post hoc results are shown on figures. Statistical results are reported for effects with significant p values (< 0.05). K-means clustering analysis was used to identify and separate sensitive and insensitive groups. Correlation analyses were evaluated via the Pearson correlation coefficient (r). Figures show means ± SEM.

3. Results

3.1. Cocaine self-administration

Male and female rats were trained on a seeking-taking chained schedule of self-administration for IV cocaine (2 h per day) and then exposed to four days of punishment testing (Fig. 1). Rats were trained on either an RR20 or RI60 schedule for the seeking lever because these schedules have been shown to influence the development of goal-directed and habitual responding [13,15,16,18,21–24]. For each rat, the four days before punishment were used as a baseline to assess the effects of punishment. Rats that completed ≥65 % of baseline trials in the fourth punishment session were considered punishment resistant, whereas rats that completed <65 % were considered punishment sensitive. We established this threshold of 65 % based on a larger population of male rats exposed to punishment and k-means clustering analysis identifying two clusters with a consistent split at 65 % (Fig. S1). A subset of these male rats is included in the following analyses.

Sensitive and resistant rats were significantly different in terms of percent trials completed during punishment, for both males (Fig. 2a; 2-way ANOVA: Group $F_{1,26} = 26.3$, $p < 0.0001$; Day $F_{11,286} = 34.4$, $p < 0.0001$; Group × Day interaction $F_{11,286} = 9.32$, $p < 0.0001$) and females (Fig. 2b; 2-way ANOVA: Group $F_{1,23} = 22.2$, $p < 0.0001$; Day $F_{11,253} = 22.9$, $p < 0.0001$; Group × Day interaction $F_{11,253} = 6.57$, $p < 0.0001$). Sensitive and resistant rats also differed in terms of total trials completed during punishment, but not before punishment, for males (Fig. 2c; 2-way ANOVA: Group $p = 0.09$; Day $F_{11,286} = 33.1$, $p < 0.0001$; Group × Day interaction $F_{11,286} = 9.63$, $p < 0.0001$) and females (Fig. 2d; 2-way ANOVA: Group $F_{1,23} = 7.06$, $p = 0.014$; Day $F_{11,253} = 21.7$, $p < 0.0001$; Group × Day interaction $F_{11,253} = 5.75$, $p < 0.0001$). Males and females were not significantly different from each other in terms of punishment resistance for cocaine, when comparing percent trials completed on the fourth day of punishment for all rats ($t_{51} = 0.63$, $p = 0.53$; male average 57.8% vs. female 53.0 %).

We used outcome devaluation via cocaine satiety to assess whether responding was goal-directed or habitual four days pre-punishment and at least four days post-punishment (once rats had recovered from punishment), with each rat given devaluation and nondevaluation sessions in a counterbalanced order. In male rats (Fig. 2e), both punishment-sensitive and -resistant rats were insensitive to outcome devaluation pre-punishment, indicating habitual responding. However, punishment-sensitive rats showed increased sensitivity to outcome devaluation post-punishment, indicating enhanced goal-directed control, while punishment-resistant rats remained habitual (2-way ANOVA: Devaluation $F_{1,52} = 12.7$, $p < 0.001$; Devaluation × Group interaction $F_{3,52} = 3.16$, $p = 0.03$). In female rats (Fig. 2f), punishment-sensitive rats were sensitive to outcome devaluation pre- and post-punishment, while punishment-resistant rats were insensitive to outcome devaluation pre- and post-punishment, indicating habitual behavior (2-way ANOVA: Devaluation $F1,46 = 20.2$, $p < 0.0001$). Raw data for devaluation testing is shown in Fig. S2.

Further statistical analyses were used to compare males and females, and to evaluate potential differences for rats trained on RR20 and RI60 schedules of reinforcement. We first compared males and females within the sensitive and resistant groups. We found a

significant main effect of Sex in the sensitive group (3-way ANOVA for Sex × Devaluation × Pre/post: Sex $F_{1,29} = 5.04$, $p = 0.033$), but no post hoc differences and no significant effects within the resistant group. We found support for the conclusion that sensitive rats showed increased goal-directed control in response to punishment because of a Devaluation × Pre/post interaction (Devaluation $F_{1,29} = 29.4$, $p < 0.0001$; Devaluation × Pre/post interaction $F_{1,29} = 8.45$, $p = 0.0069$), with post hoc analysis revealing significant sensitivity to devaluation post-punishment for males ($p < 0.0001$) and females ($p = 0.0048$). In contrast, resistant rats showed no significant main effects or interactions. We then compared rats trained on RR20 vs. RI60 schedules within the sensitive and resistant groups and found no effect of Schedule in either group (3-way ANOVAs for Schedule × Devaluation × Pre/post), which parallels our previous work showing that schedule only weakly influences strategy for cocaine seeking [13]. Although, the results again indicated increased goal-directed control in the sensitive group (Devaluation $F_{1,29} = 29.0$, $p < 0.0001$; Devaluation × Pre/post interaction $F_{1,29} = 7.29$, $p = 0.012$), with post hoc analysis revealing significant sensitivity to devaluation post-punishment for rats trained on RR20 ($p = 0.0003$) and RI60 ($p = 0.0027$). In contrast, resistant rats showed no significant main effects or interactions. Finally, a comparison of RR20 and RI60 for sensitivity to punishment on the fourth day revealed no difference ($t_{51} = 1.06$, $p = 0.29$).

We then determined whether habitual responding was predictive of punishment resistance. When rats were classified as goal-directed (<0.4 for normalized devalued responding) or habitual (≥0.4) based on pre-punishment outcome devaluation, there was no difference in terms of baseline responding or the fourth day of punishment, for male rats (Fig. 3a; 2-way ANOVA: Session $F_{1,26} = 58.5$, $p < 0.0001$; Session × Strategy interaction $p = 0.15$) or female rats (Fig. 3b; 2-way ANOVA: Session $F_{1,23} = 74.6$, $p < 0.0001$; Session × Strategy interaction $p = 0.44$). Similarly, when classified as goal-directed or habitual based on post-punishment outcome devaluation, there was also no difference in terms of baseline responding or the fourth day of punishment, for male rats (Fig. 3c; 2-way ANOVA: Session $F_{1,26} = 57.0$, $p < 0.0001$; Session × Strategy interaction $p = 0.13$) or female rats (Fig. 3d; 2-way ANOVA: Session $F_{1,23} = 76.3$, $p < 0.0001$; Session × Strategy interaction $p = 0.21$). However, we found that punishment resistance was correlated with habits post-punishment, but not pre-punishment. Specifically, responding on the fourth day of punishment (% baseline trials) correlated with devalued responding during outcome devaluation conducted post-punishment in males (Fig. 3e; $r = 0.35$, $p = 0.069$) and females (Fig. 3f, $r = 0.40$, $p = 0.045$). In contrast, punishment did not correlate with devalued responding conducted pre-punishment in males ($r = 0.24$, $p = 0.23$) or females ($r = -0.03$, $p = 0.87$). Interestingly, habitual responding was not required for punishment resistance, and some male and female rats that showed resistance (≥65 % on x-axis) also showed goal-directed responding post-punishment (<0.4 on y-axis).

3.2. Food self-administration

Separate groups of male and female rats were trained on a seeking-taking chained schedule of self-administration for food and then exposed to four days of punishment testing (Fig. 1). Food self-administration sessions were limited to 1 h or 30 rewards (whichever occurred first), so we used reward rate (pellets per min) to more accurately assess the effects of

punishment. For each rat, the four days before punishment were used as a baseline. Similar to cocaine, we used a threshold of 65 % on the fourth punishment session to identify rats that were resistant to punishment. Sensitive and resistant rats were significantly different in terms of percent baseline during punishment, for both males (Fig. 4a; 2-way ANOVA: Group $F_{1,31} = 18.1$, $p = 0.0002$; Day $F_{11,341} = 11.9$, $p < 0.0001$; Group × Day interaction $F_{11,341} = 6.37$, $p < 0.0001$) and females (Fig. 4b; 2-way ANOVA: Group $F_{1,20} = 16.3$, $p = 0.0006$; Day $F_{11,220} = 14.1$, $p < 0.0001$; Group × Day interaction $F_{11,220} = 6.36$, $p < 0.0001$). Sensitive and resistant rats also differed in terms of reward rate during punishment, but not before punishment, for males (Fig. 4c; 2-way ANOVA: Group $p = 0.11$; Day $F_{11,341} = 12.8$, $p < 0.0001$; Group × Day interaction $F_{11,341} = 7.12$, $p < 0.0001$) and females (Fig. 4d; 2-way ANOVA: Group $p = 0.99$; Day $F_{11,220} = 13.3$, $p < 0.0001$; Group × Day interaction $F_{11,220} = 6.61$, $p < 0.0001$).

Males were significantly more resistant than females for food, when comparing percent baseline on the fourth day of punishment for all rats ($t_{53} = 2.4$, $p = 0.020$; male average 79.2% vs. female 59.0 %). However, there was no significant difference between males and females for baseline reward rate during self-administration ($t_{53} = 1.9$, $p = 0.066$), despite large differences in weight between males and females at the time of punishment testing ($t_{53} = 19.2$, $p < 0.0001$; male average 470 g, female 295 g). We found that males were more resistant for food than cocaine ($t_{59} = 2.9$, $p = 0.0057$), but there was no difference in females for resistance to food and cocaine ($t_{45} = 0.69$, $p = 0.49$).

We used outcome devaluation via satiety to assess whether responding was goal-directed or habitual four days pre-punishment and at least four days post-punishment (once rats had recovered from punishment), with each rat given devaluation sessions (food pellets in home cage) and nondevaluation sessions (15 % sucrose in home cage) in a counterbalanced order. In male rats (Fig. 4e), both punishment-sensitive and -resistant rats were sensitive to outcome devaluation pre- and post-punishment, although sensitive rats showed even greater sensitivity post-punishment, indicating enhanced goal-directed control (2-way ANOVA: Devaluation $F_{1,62} = 73.6$, $p < 0.001$; Devaluation × Group interaction $p = 0.10$). In female rats (Fig. 4f), punishment-sensitive rats were sensitive to outcome devaluation pre- and post-punishment, while punishment-resistant rats were insensitive to outcome devaluation pre- and post-punishment, indicating habitual behavior (2-way ANOVA: Devaluation $F_{1,40} = 23.3$, $p < 0.0001$; Group $F_{3,40} = 640$, $p < 0.0001$; Devaluation × Group interaction $F_{3,40} = 5.55$, $p = 0.0028$). This mimicked what we observed with cocaine punishment in female rats. Raw data for devaluation testing is shown in Fig. S3.

Further statistical analyses were used to compare males and females within the sensitive and resistant groups. This analysis indicated significant effects for Sex within the sensitive group (3-way ANOVA for Sex × Devaluation × Pre/post: Sex $F_{1,19} = 683$, $p < 0.0001$; Sex × Pre/post $F_{1,19} = 14.8$, $p = 0.0011$) and the resistant group (Sex $F_{1,32} = 831$, $p < 0.0001$; Sex × Devaluation interaction $F_{1,32} = 6.29$, $p = 0.017$; Sex × Pre/post interaction $F_{1,32} = 125$, $p < 0.0001$), but no significant post hoc differences between males and females. Even though males tended to be goal-directed regardless of whether they were sensitive or resistant to punishment, we still observed that sensitive rats showed increased goal-directed control in response to punishment, as indicated by a significant interaction between Devaluation

and Pre/post (Devaluation $F_{1,19} = 47.1$, $p < 0.0001$; Pre/post $F_{1,19} = 30.1$, $p < 0.0001$; Devaluation × Pre/post interaction $F_{1,19} = 7.74$, $p = 0.012$), with post hoc analysis revealing significant sensitivity to devaluation pre-punishment for males ($p = 0.033$) and females ($p = 0.0029$) and post-punishment for males ($p < 0.0001$) and females ($p = 0.0001$). In contrast, resistant rats did not show a significant Devaluation × Pre/post interaction, and only showed significant main effects (Devaluation $F_{1,32} = 11.9$, $p = 0.0016$; Pre/post $F_{1,32} = 169$, $p < 0.0001$), with post hoc analysis revealing significant sensitivity to devaluation for males pre-punishment ($p = 0.0002$) and post-punishment ($p = 0.0008$) but not for females.

We then evaluated potential differences for rats trained on RR20 vs. RI60 within the sensitive and resistant groups. We found several effects for Schedule in the sensitive group (3-way ANOVA for Schedule × Devaluation × Pre/post: Schedule $F_{1,19} = 8.91$, $p = 0.0076$; Schedule × Devaluation interaction $F_{1,19} = 6.10$, $p = 0.023$; Schedule × Pre/post interaction $F_{1,19} = 17.7$, $p = 0.0005$), with post hoc analysis revealing significant sensitivity to devaluation for RR20 both pre-punishment ($p < 0.0001$) and post-punishment ($p < 0.0001$), and for RI60 post-punishment only ($p = 0.0043$). This parallels previous work showing an influence of schedule on strategy for food seeking [13,15,16,18, 21–24]. Within the resistant group, there was no main effect for Schedule, but a significant Schedule × Pre/post interaction ($F_{1,32} = 40.0$, $p < 0.0001$), with post hoc analysis revealing significant sensitivity to devaluation for RR20-trained rats both pre-punishment ($p = 0.0056$) and post-punishment ($p = 0.031$). We again observed support for the conclusion that sensitive rats showed increased goal-directed control in response to punishment, as indicated by a significant Devaluation × Pre/post interaction (Devaluation $F_{1,19} = 60.4$, $p < 0.0001$; Pre/post $F_{1,19} = 37.1$, $p < 0.0001$; Devaluation × Pre/post interaction $F_{1,19} = 6.36$, $p = 0.021$), while resistant rats only showed main effects without an interaction (Devaluation $F_{1,32} = 22.0$, $p < 0.0001$; Pre/post $F_{1,32} = 62.4$, $p < 0.0001$). Finally, a comparison of RR20 and RI60 for sensitivity to punishment on the fourth day revealed no difference ($t_{53} = 0.49$, $p = 0.63$). Therefore, RR20-trained rats were goal-directed pre- and post-punishment, regardless of whether they were sensitive or resistant to punishment, while RI60-trained rats were habitual pre-punishment but became goal-directed if they were sensitive to punishment.

We determined whether habitual responding was predictive of punishment resistance. When rats were classified as goal-directed (<0.4 for normalized devalued responding) or habitual (≥0.4) based on pre-punishment outcome devaluation, there was no difference in terms of baseline responding on the fourth day of punishment, for male rats (Fig. 5a; 2-way ANOVA: Session $F_{1,31} = 11.0$, $p = 0.0024$; Session × Strategy interaction $p = 0.61$) or female rats (Fig. 5b; 2-way ANOVA: Session $F_{1,20} = 28.4$, $p < 0.0001$; Session × Strategy interaction $p = 0.082$). When classified as goal-directed or habitual based on post-punishment outcome devaluation, male rats did not show a significant difference in terms of baseline responding or the fourth day of punishment (Fig. 5c; 2-way ANOVA: Session $F_{1,31} = 7.66$, $p = 0.0095$; Session × Strategy interaction $p = 0.12$). However, female rats showed a significant difference for the fourth day of punishment, indicating that the rats classified as habitual post-punishment showed greater punishment resistance (Fig. 5d; 2-way ANOVA: Session $F_{1,20} = 37.0$, $p < 0.0001$; Session × Strategy interaction $F_{1,20} = 8.96$, $p = 0.0072$). Similar to cocaine studies, we found that punishment resistance was correlated with habits post-punishment. Responding on the fourth day of punishment (% baseline

reward rate) correlated with devalued responding during outcome devaluation conducted post-punishment in males (Fig. 5; $r = 0.39$, $p = 0.024$), but not pre-punishment ($r = 0.16$, $p = 0.38$). In contrast, in females, punishment correlated with devalued responding conducted pre-punishment (Fig. 5f; $r = 0.44$, $p = 0.040$) and post-punishment ($r = 0.64$, $p = 0.0015$). Particularly for male rats, habitual responding was not required for punishment resistance, and some male rats that showed resistance (≥65 % on x-axis) also showed goal-directed responding post-punishment (<0.4 on y-axis).

3.3. Influences on punishment resistance

We ran correlations to determine whether punishment resistance was associated with and/or might be explained by differences in footshock sensitivity or weight. To determine sensitivity to footshock, we conducted footshock threshold testing (threshold for flinch, jump, and vocalization, or FJV) prior to any self-administration training. We found no difference for initial footshock sensitivity between punishment-resistant and -sensitive groups for cocaine or food in males or females (2-way ANOVAs of FJV vs. group, $p > 0.05$). For cocaine, we found a significant correlation in female rats for vocalization threshold and punishment resistance ($r = 0.59$, $p = 0.0021$), but no other correlations in females or males (Fig. 6a, b). For food, we found no correlations between footshock sensitivity and punishment in males or females (Fig. 6c, d).

We found no significant correlations between punishment sensitivity and animal weight on the first day of punishment; the average weights on the first day of punishment were: cocaine males (540 g), cocaine females (320 g), food males (470 g), and food females (300 g). The average weight gain from the start of self-administration to punishment testing was: cocaine males (200 g), cocaine females (50 g), food males (100 g), and food females (20 g). We also found no significant correlations between footshock sensitivity testing and the starting weight of the animals in females or males. These data indicate that differences in footshock sensitivity or punishment resistance were not related to differences in animal weight.

We ran correlations between punishment sensitivity and several other self-administration measures for cocaine and food in males and females. We found no significant correlations with the number of seeking presses in the final seeking-taking sessions prior to punishment testing ($p > 0.05$). We also found no correlations with self-administration rates during the final seeking-taking sessions (Fig. 6e–h), although we observed a significant correlation with early FR1 self-administration for food in females (Fig. 6 h; $r = 0.44$, $p = 0.039$) and a nearly significant correlation with early FR1 self-administration for cocaine in males (Fig. 6e; $r = -0.35$, $p = 0.07$). In other words, females that showed greater punishment resistance for food also self-administered food at a quicker rate under continuous reinforcement (FR1) conditions, which may indicate higher motivation for food. In contrast, males that showed greater punishment resistance for cocaine tended to self-administer less cocaine under continuous reinforcement conditions.

Finally, we also investigated possible influences of estrous cycle on punishment sensitivity in female rats. We categorized rats by cycle phase for each of the four days of punishment

and found no differences in punishment sensitivity for cocaine or food (Fig. S4), indicating that punishment sensitivity was not related to estrous cycle.

4. Discussion

We found that punishment resistance for cocaine was associated with habitual responding after, but not before, punishment. In other words, habits did not predict punishment resistance, but punishment resistance was related to the continued use of habits. We observed similar results with rats trained to self-administer food, with punishment resistance related to the continued use of habits, particularly in females. These data indicate that punishment resistance is associated with inflexible habits, whereas punishment sensitivity is associated with increased goal-directed control.

4.1. Punishment resistance and inflexible habits

These findings support the hypothesis that compulsive drug seeking is related to failure to control habits [5–10]. While habits themselves are not necessarily maladaptive or permanent, compulsive drug use may be related to a loss of control over habitual seeking, making them inflexible and maladaptive. This idea is corroborated by our finding that habitual cocaine seeking did not predict punishment resistance. Rather, punishment resistance was related to inflexible habits, whereas punishment sensitivity was related to increased goal-directed control over behavior. Interestingly, habitual behavior was not necessary for punishment resistance and a subset of resistant animals showed goal-directed cocaine seeking. This supports an alternative theory which posits that addiction is driven by excessive goal-directed choice and/or over-valuation of drug reward, and that habits are not necessary [56,57].

4.2. Punishment sensitivity and flexible habits

We observed that many rats showed a switch from habitual to goal-directed cocaine seeking when faced with footshock consequences, particularly when sensitive to punishment. Previous studies have also shown animals switching between goal-directed and habitual response strategies. Most commonly, these studies demonstrated a transition from goal-directed to habitual behavior, with the transition occurring gradually over time with progressive training for food [40,41,58,59], cocaine [25,26], or alcohol [34,37]. Similarly, a transition from DMS to DLS control over reward-seeking behavior has been depicted over training [25,29,34,60]. However, several recent studies from Bouton and colleagues demonstrated a transition from habitual to goal-directed responding, instead, and this transition occurred rapidly [12]. The circumstances that caused behaviors to become goal-directed include changes in context, changes in outcome, or unexpected food reinforcers, even when delivered in a different context [58,61–64]. Here, we found that the addition of an aversive outcome enhanced goal-directed responding, but only in animals that were sensitive to footshock punishment. Altogether, these findings indicate that habits generally are not permanent and that the goal-directed system can gain control over behavior.

Typically, habits are somewhat flexible. While habits are insensitive to changes in the value of the outcome, they are sensitive to changes in the outcome. Therefore, habits are

not completely inflexible and behavior is typically updated under certain circumstances, including after devaluation when an animal experiences the outcome in the devalued state [9,23,40,65,66]. For example, rats over-trained for food responding showed habitual behavior and insensitivity to outcome devaluation when tested under extinction conditions, but then became sensitive and reduced responding after several minutes of experiencing the food reward actually being delivered [9,40]. Lesions of DMS slowed learning of this effect, indicating that goal-directed processes are typically recruited and that the learning process in the habit system is slower [9]. Ostlund and Balleine [9] hypothesized that fast changes in performance (e.g., when faced with negative consequences) require a transition to goal-directed control, and that compulsive behavior in addiction may be related to a dominant habit system and difficulty reengaging goal-directed control. The data presented here support this hypothesis and indicate that the goal-directed and habitual systems function in parallel, such that both DMS and DLS encode the behavior. This explains why post-training inactivation of DMS or DLS leaves behavior intact but guided by the remaining system [18,23,25,34,36], and why habitual behavior can rapidly transition to being goal-directed [12].

We found that the addition of a footshock outcome enhanced goal-directed responding in punishment-sensitive rats. This may seem contradictory to previous work showing that stress biases toward habitual behavior in humans and animals (asreviewedby[10,67]). However, the impact of stress is dependent on the controllability (or escapability) of the stressor. While inescapable stress has negative long-term effects and recruits the habit system, escapable stress is protective against future insults and recruits the goal-directed system, including DMS and the prelimbic prefrontal cortex [68–73]. Previous work has implicated impairments in prelimbic function with punishment resistance [46,74–76]. Therefore, it is tempting to speculate that punishment-resistant rats may have a reduced ability to detect control (or contingency) of the footshock [77]. Further, because prelimbic cortex is necessary for the acquisition of goal-directed responding [78], reduced prelimbic function might impair the ability to recruit the goal-directed system.

We cannot rule out the possibility that individual differences in responding after experimenter-administered IV cocaine (i.e., differences in sensitivity to outcome devaluation) could be attributed to individual differences in cocaine satiety, rather than differences in the use of goal-directed and habitual strategies. However, this seems unlikely given that the IV cocaine doses used for devaluation are tailored to individual self-administration rates, and that sensitive and insensitive rats self-administer similar amounts of cocaine and experience similar brain cocaine concentrations, indicating comparable cocaine satiety [13]. Further, individual differences in cocaine satiety cannot fully explain why some rats showed increased sensitivity to outcome devaluation following punishment in the current study or why lesions of DMS or DLS affected sensitivity to outcome devaluation in our previous study [13]. We would not expect footshock punishment to change individual cocaine satiety, and even though many rats reduced responding and infusions during punishment, we ensured that rats returned to baseline responding before testing for post-punishment outcome devaluation. Likewise, we would not expect lesions of DMS or DLS to alter individual cocaine satiety; accordingly, we observed no differences in self-administered infusions with lesions, although we observed differences in sensitivity to

outcome devaluation [13]. Thus, it is unlikely that individual differences in cocaine satiety account for the observed differences in sensitivity to outcome devaluation.

4.3. Reward and sex differences

We observed punishment resistance with both cocaine and food self-administration, and even found that punishment resistance was greater for food than cocaine in male rats. In contrast, previous studies did not observe punishment resistance with food, even in rats with extended sucrose or chow self-administration [3,4,39,42,43]. In addition, punishment resistance for cocaine was observed with extended, but not limited, exposure to cocaine self-administration [2,3,27,79], although the pattern of intake is also an important consideration [80,81]. These discrepancies may be attributed to differences in methods, including footshock intensity, omission of cocaine on footshock trials, schedule of reinforcement, and criteria for resistance.

We found no sex difference in punishment resistance for cocaine, but found increased punishment resistance in males for food, as compared to females. Previous studies have shown female rats to be more sensitive to punishment for cocaine and more sensitive to punishment with risky food rewards [28,50,51,82,83]. Females also appeared to show greater punishment resistance for cocaine than food [50]. In contrast, we observed no significant difference for punishment resistance between food and cocaine for females but found a significant difference between food and cocaine for males. Sex differences in punishment sensitivity for food can likely be traced to sex differences in food motivation and eating. Although we found no sex difference in food reward rate during self-administration, male rats gained more weight than females across the course of the study, and previous work showed that male rats work harder than females to earn food rewards, even despite footshock risk [82,83]. We found that punishment-resistant rats were insensitive to outcome devaluation pre- and post-punishment in most groups we studied (males and females with cocaine, and females with food). However, male rats with punishment resistance for food were sensitive to outcome devaluation pre- and post-punishment, indicating goal-directed responding. Therefore, punishment resistance for food in male rats was not necessarily related to inflexible habits, and in some animals, seemed to be more related to goal-directed actions. Interestingly, punishment resistance for food in female rats was uniquely correlated with habitual responding pre- and post-punishment, whereas all other groups (males and females with cocaine, and males with food) were correlated with habitual responding post-punishment but not pre-punishment. Punishment resistance for food in females was also unique in that is showed a positive correlation with food reward rate under continuous reinforcement conditions (early FR1 training). Therefore, the female rats that eventually showed punishment resistance for food tended to be more motivated for food (faster reward rate) and less sensitive to outcome devaluation (i.e., more habitual).

4.4. Mechanisms of punishment resistance

The current data support the theory that punishment resistance is related to loss of control over habits [5–11]. However, it is important to note that support for this theory is not mutually exclusive with other theories of addiction (seecommentaryby[84]). There are multiple factors that contribute to drug seeking and addiction, and the factors may

differ across individuals (i.e. individual differences) or have a compound influence within an individual. We believe that these factors are shaped by a combination of individual vulnerability and drug experience. For example, with limited cocaine experience, we would expect very few rats to show punishment resistance. Then again, with even more cocaine self-administration experience than given in the current studies, we would likely see greater punishment resistance (e.g., more rats showing resistance and greater resistance within-subject). However, we would likely still have a subset of rats showing sensitivity to punishment. Therefore, we believe that punishment resistance reflects interactions between individual differences and drug-taking experience, analogous to the development of addiction in humans. Several factors have been hypothesized or considered for a possible influence on punishment resistance (via individual differences and/or drug experience), including habitual behavior, goal-directed behavior, high value of cocaine, low value for footshock, and reduced contingency learning [7,10,56,85–87].

Although we did not find that habits predicted punishment resistance for cocaine, previous work showed that punishment-resistant alcohol seeking was greater in rats with DLS-dependent alcohol seeking [47]. In addition, punished responding for cocaine was reduced by DLS inactivation [33], but not by inhibition of DMS direct pathway [88], further implicating DLS in punishment resistance. In contrast, support for the theory that addiction is related to excess goal-directed motivation comes from work indicating that habits are not prerequisite for punishment resistance [57], and that resistance was associated with strengthened activity in a pathway between orbitofrontal cortex and DMS [89,90]. In addition, punished responding for food in mice was associated with reward-related dopamine signals in DMS and not DLS, and responding was reduced by DMS manipulations [91]. We found that male rats showed goal-directed responding for food self-administration, regardless of whether they were punishment sensitive or resistant, while female rats showed habitual responding only if they were punishment resistant, which indicates that the mechanisms underlying punishment resistance may differ across reward type and sex. Therefore, both the habitual and goal-directed systems appear to be capable of driving expression of punishment resistance.

Punishment resistance could also be related to increased motivation (or value) for the reward or decreased sensitivity to the aversive consequence. In support of the former, punishment resistance was associated with higher break point on a progressive ratio schedule of reinforcement, as well as lower demand elasticity (i.e., high motivation) using behavioral-economic measures [2,92–94]. However, other work showed no association between punishment resistance and break point for cocaine or sucrose rewards, even though higher doses of cocaine drove greater resistance [50,51]. In the current study, we observed some evidence that punishment resistance for food in females was associated with increased food motivation, as resistance correlated with reward rate under continuous reinforcement conditions. Further, we observed a negative correlation between punishment resistance for cocaine in males and the amount of cocaine self-administered under continuous reinforcement conditions, which may be explained by differences in cocaine value or satiety. However, there is little support for punishment resistance being driven by decreased sensitivity to aversive consequences. Punishment-resistant alcohol seeking was not related to differences in footshock-induced fear [47]. Further, punishment-resistant

cocaine seeking was not correlated with punishment-resistant sucrose seeking, indicating that punishment resistance cannot simply be attributed to individual differences in footshock sensitivity [50,51]. We also found that punishment resistance for cocaine or food could not be explained by decreased sensitivity to footshock. Finally, studies using a conditioned-punishment task for food rewards found little evidence that punishment resistance was related to reward dominance or aversion insensitivity; instead, punishment resistance in rats and humans seemed most causally related to a lack of learning the punishment contingency and understanding the relationship between actions and aversive outcomes [77,95].

4.5. Conclusions and future directions

We found that punishment resistance for cocaine was associated with inflexible habits, whereas punishment sensitivity was associated with exerting goal-directed control. We did not find that habitual cocaine responding predicted punishment resistance. However, future studies with extended training of cocaine self-administration might reveal that habits become even more inflexible and predictive of punishment resistance. Future work might also further explore the hypothesis that punishment resistance is related to impaired contingency detection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

References

[1]. Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ, High impulsivity predicts the switch to compulsive cocaine-taking, Science (1979) 320 (2008) 1352–1355, 10.1126/science.1158136.

[2]. Deroche-Gamonet V, Belin D, Piazza PV, Evidence for addiction-like behavior in the rat, Science (1979) 305 (2004) 1014–1017, 10.1126/science.1099020.

[3]. Pelloux Y, Everitt BJ, Dickinson A, Compulsive drug seeking by rats under punishment: effects of drug taking history, Psychopharmacology. (Berl) 194 (2007) 127–137, 10.1007/s00213-007-0805-0. [PubMed: 17514480]

[4]. Vanderschuren LJMJ, Everitt BJ, Drug seeking becomes compulsive after prolonged cocaine self-administration, Science (1979) 305 (2004) 1017–1019, 10.1126/science.1098975.

[5]. Belin D, Belin-Rauscent A, Murray JE, Everitt BJ, Addiction: failure of control over maladaptive incentive habits, Curr. Opin. Neurobiol 23 (2013) 564–572, 10.1016/j.conb.2013.01.025. [PubMed: 23452942]

[6]. Everitt BJ, Neural and psychological mechanisms underlying compulsive drug seeking habits and drug memories–indications for novel treatments of addiction, Eur. J. Neurosci 40 (2014) 2163–2182, 10.1111/ejn.12644. [PubMed: 24935353]

[7]. Everitt BJ, Robbins TW, Drug addiction: updating actions to habits to compulsions ten years on, Annu. Rev. Psychol 67 (2016) 23–50, 10.1146/annurev-psych-122414-033457. [PubMed: 26253543]

[8]. Everitt BJ, Robbins TW, Neural systems of reinforcement for drug addiction: from actions to habits to compulsion, Nat. Neurosci 8 (2005) 1481–1489, 10.1038/nn1579. [PubMed: 16251991]

[9]. Ostlund SB, Balleine BW, On habits and addiction: an associative analysis of compulsive drug seeking, Drug Discov. Today Dis. Models 5 (2008) 235–245, 10.1016/j.ddmod.2009.07.004.

[10]. Smith RJ, Laiks LS, Behavioral and neural mechanisms underlying habitual and compulsive drug seeking, Prog. Neuropsychopharmacol. Biol. Psychiatry 87 (2018) 11–21, 10.1016/j.pnpbp.2017.09.003. [PubMed: 28887182]

[11]. Brown RM, Dayas CV, James MH, Smith RJ, New directions in modelling dysregulated reward seeking for food and drugs, Neurosci. Biobehav. Rev 132 (2022) 1037–1048, 10.1016/j.neubiorev.2021.10.043. [PubMed: 34736883]

[12]. Bouton ME, Context, attention, and the switch between habit and goal-direction in behavior, Learn. Behav 49 (2021) 349–362, 10.3758/s13420-021-00488-z. [PubMed: 34713424]

[13]. Jones BO, Cruz AM, Kim TH, Spencer HF, Smith RJ, Discriminating goal-directed and habitual cocaine seeking in rats using a novel outcome devaluation procedure, Learn. Mem 29 (2022) 447–457, 10.1101/lm.053621.122. [PubMed: 36621907]

[14]. Balleine BW, Dickinson A, Goal-directed instrumental action: contingency and incentive learning and their cortical substrates, Neuropharmacology 37 (1998) 407–419, 10.1016/s0028-3908(98)00033-1. [PubMed: 9704982]

[15]. Yin HH, Knowlton BJ, The role of the basal ganglia in habit formation, Nat. Rev. Neurosci 7 (2006) 464–476, 10.1038/nrn1919. [PubMed: 16715055]

[16]. Dickinson A, Actions and habits: the development of behavioural autonomy, Philosoph. Transact. Royal Soc. B: Biol. Sci 308 (1985) 67–78, 10.1098/rstb.1985.0010.

[17]. McNamee D, Liljeholm M, Zika O, O'Doherty JP, Characterizing the associative content of brain structures involved in habitual and goal-directed actions in humans: a multivariate FMRI study, J. Neurosci 35 (2015) 3764–3771, 10.1523/JNEUROSCI.4677-14.2015. [PubMed: 25740507]

[18]. Yin HH, Knowlton BJ, Balleine BW, Inactivation of dorsolateral striatum enhances sensitivity to changes in the action-outcome contingency in instrumental conditioning, Behav. Brain Res 166 (2006) 189–196, 10.1016/j.bbr.2005.07.012. [PubMed: 16153716]

[19]. Balleine BW, O'Doherty JP, Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action, Neuropsychopharmacology 35 (2010) 48–69, 10.1038/npp.2009.131. [PubMed: 19776734]

[20]. Corbit LH, Janak PH, Posterior dorsomedial striatum is critical for both selective instrumental and Pavlovian reward learning, Eur. J. Neurosci 31 (2010) 1312–1321, 10.1111/j.1460-9568.2010.07153.x. [PubMed: 20345912]

[21]. Gremel CM, Costa RM, Orbitofrontal and striatal circuits dynamically encode the shift between goal-directed and habitual actions, Nat. Commun 4 (2013) 2264, 10.1038/ncomms3264. [PubMed: 23921250]

[22]. Yin HH, Knowlton BJ, Balleine BW, Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning, Eur. J. Neurosci 19 (2004) 181–189, 10.1111/j.1460-9568.2004.03095.x. [PubMed: 14750976]

[23]. Yin HH, Ostlund SB, Knowlton BJ, Balleine BW, The role of the dorsomedial striatum in instrumental conditioning, Eur. J. Neurosci 22 (2005) 513–523, 10.1111/j.1460-9568.2005.04218.x. [PubMed: 16045504]

[24]. Dickinson A, Nicholas DJ, Adams CD, The effect of the instrumental training contingency on susceptibility to reinforcer devaluation, Quart. J. Experim. Psychol. Sect. B 35 (1983) 35–51, 10.1080/14640748308400912.

[25]. Zapata A, Minney VL, Shippenberg TS, Shift from goal-directed to habitual cocaine seeking after prolonged experience in rats, J. Neurosci 30 (2010) 15457–15463, 10.1523/JNEUROSCI.4072-10.2010. [PubMed: 21084602]

[26]. Leong KC, Berini CR, Ghee SM, Reichel CM, Extended cocaine-seeking produces a shift from goal-directed to habitual responding in rats, Physiol. Behav 164 (2016) 330–335, 10.1016/j.physbeh.2016.06.021. [PubMed: 27321756]

[27]. Jonkman S, Pelloux Y, Everitt BJ, Drug intake is sufficient, but conditioning is not necessary for the emergence of compulsive cocaine seeking after extended self-administration, Neuropsychopharmacology 37 (2012) 1612–1619, 10.1038/npp.2012.6. [PubMed: 22334124]

[28]. Bender BN, Torregrossa MM, Intermittent cocaine self-administration has sex-specific effects on addiction-like behaviors in rats, Neuropharmacology (2023) 109490, 10.1016/j.neuropharm.2023.109490. [PubMed: 36889433]

[29]. Murray JE, Belin D, Everitt BJ, Double dissociation of the dorsomedial and dorsolateral striatal control over the acquisition and performance of cocaine seeking, Neuropsychopharmacology 37 (2012) 2456–2466, 10.1038/npp.2012.104. [PubMed: 22739470]

[30]. Porrino LJ, Daunais JB, Smith HR, Nader MA, The expanding effects of cocaine: studies in a nonhuman primate model of cocaine self-administration, Neurosci. Biobehav. Rev 27 (2004) 813–820, 10.1016/j.neubiorev.2003.11.013. [PubMed: 15019430]

[31]. Porrino LJ, Lyons D, Smith HR, Daunais JB, Nader MA, Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains, J. Neurosci 24 (2004) 3554–3562, 10.1523/JNEUROSCI.5578-03.2004. [PubMed: 15071103]

[32]. Willuhn I, Burgeno LM, Everitt BJ, Phillips PEM, Hierarchical recruitment of phasic dopamine signaling in the striatum during the progression of cocaine use, Proc. Natl. Acad. Sci. USA 109 (2012) 20703–20708, 10.1073/pnas.1213460109. [PubMed: 23184975]

[33]. Jonkman S, Pelloux Y, Everitt BJ, Differential roles of the dorsolateral and midlateral striatum in punished cocaine seeking, J. Neurosci 32 (2012) 4645–4650, 10.1523/JNEUROSCI.0348-12.2012. [PubMed: 22457510]

[34]. Corbit LH, Nie H, Janak PH, Habitual alcohol seeking: time course and the contribution of subregions of the dorsal striatum, Biol. Psychiatry 72 (2012) 389–395, 10.1016/j.biopsych.2012.02.024. [PubMed: 22440617]

[35]. Corbit LH, Nie H, Janak PH, Habitual responding for alcohol depends upon both AMPA and D2 receptor signaling in the dorsolateral striatum, Front. Behav. Neurosci 8 (2014) 301, 10.3389/fnbeh.2014.00301. [PubMed: 25228865]

[36]. Giuliano C, Belin D, Everitt BJ, Compulsive alcohol seeking results from a failure to disengage dorsolateral striatal control over behavior, J. Neurosci 39 (2019) 1744–1754, 10.1523/JNEUROSCI.2615-18.2018. [PubMed: 30617206]

[37]. Giuliano C, Puaud M, Cardinal RN, Belin D, Everitt BJ, Individual differences in the engagement of habitual control over alcohol seeking predict the development of compulsive alcohol seeking and drinking, Addict. Biol 26 (2021) e13041, 10.1111/adb.13041. [PubMed: 33955649]

[38]. Lopez MF, Becker HC, Operant ethanol self-administration in ethanol dependent mice, Alcohol 48 (2014) 295–299, 10.1016/j.alcohol.2014.02.002. [PubMed: 24721194]

[39]. Radke AK, Jury NJ, Kocharian A, Marcinkiewcz CA, Lowery-Gionta EG, Pleil KE, McElligott ZA, McKlveen JM, Kash TL, Holmes A, Chronic EtOH effects on putative measures of compulsive behavior in mice, Addict. Biol 22 (2017) 423–434, 10.1111/adb.12342. [PubMed: 26687341]

[40]. Adams CD, Variations in the sensitivity of instrumental responding to reinforcer devaluation, Quart. J. Experim. Psychol. Sect. B 34 (1982) 77–98, 10.1080/14640748208400878.

[41]. Dickinson A, Balleine B, Watt A, Gonzalez F, Boakes RA, Motivational control after extended instrumental training, Anim. Learn. Behav 23 (1995) 197–206, 10.3758/BF03199935.

[42]. Limpens JHW, Schut EHS, Voorn P, Vanderschuren LJMJ, Using conditioned suppression to investigate compulsive drug seeking in rats, Drug Alcohol Depend 142 (2014) 314–324, 10.1016/j.drugalcdep.2014.06.037. [PubMed: 25060961]

[43]. Pelloux Y, Murray JE, Everitt BJ, Differential vulnerability to the punishment of cocaine related behaviours: effects of locus of punishment, cocaine taking history and alternative reinforcer availability, Psychopharmacology. (Berl) 232 (2015) 125–134, 10.1007/s00213-014-3648-5. [PubMed: 24952093]

[44]. Olmstead MC, Parkinson JA, Miles FJ, Everitt BJ, Dickinson A, Cocaine-seeking by rats: regulation, reinforcement and activation, Psychopharmacology (Berl) 152 (2000) 123–131, 10.1007/s002130000498. [PubMed: 11057515]

[45]. Olmstead MC, Lafond MV, Everitt BJ, Dickinson A, Cocaine seeking by rats is a goal-directed action, Behav. Neurosci 115 (2001) 394–402, 10.1037/0735-7044.115.2.394. [PubMed: 11345964]

[46]. Chen BT, Yau HJ, Hatch C, Kusumoto-Yoshida I, Cho SL, Hopf FW, Bonci A, Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking, Nature 496 (2013) 359–362, 10.1038/nature12024. [PubMed: 23552889]

[47]. Giuliano C, Peña-Oliver Y, Goodlett CR, Cardinal RN, Robbins TW, Bullmore ET, Belin D, Everitt BJ, Evidence for a long-lasting compulsive alcohol seeking phenotype in rats, Neuropsychopharmacology 43 (2018) 728–738, 10.1038/npp.2017.105. [PubMed: 28553834]

[48]. Zhou YQ, Zhang LY, Yu ZP, Zhang XQ, Shi J, Shen HW, Tropisetron facilitates footshock suppression of compulsive cocaine seeking, Int. J. Neuropsychopharmacol 22 (2019) 574–584, 10.1093/ijnp/pyz023. [PubMed: 31125405]

[49]. Limpens JHW, Damsteegt R, Broekhoven MH, Voorn P, Vanderschuren LJMJ, Pharmacological inactivation of the prelimbic cortex emulates compulsive reward seeking in rats, Brain Res 1628 (2015) 210–218, 10.1016/j.brainres.2014.10.045. [PubMed: 25451128]

[50]. Datta U, Martini M, Fan M, Sun W, Compulsive sucrose- and cocaine-seeking behaviors in male and female Wistar rats, Psychopharmacology (Berl) 235 (2018) 2395–2405, 10.1007/s00213-018-4937-1. [PubMed: 29947917]

[51]. Datta U, Martini M, Sun W, Different functional domains measured by cocaine self-administration under the progressive-ratio and punishment schedules in male Wistar rats, Psychopharmacology (Berl) 235 (2018) 897–907, 10.1007/s00213-017-4808-1. [PubMed: 29214467]

[52]. Handel SN, Smith RJ, Making and breaking habits: revisiting the definitions and behavioral factors that influence habits in animals, J. Exp. Anal. Behav (2023), 10.1002/jeab.889.

[53]. Smith RJ, See RE, Aston-Jones G, Orexin/hypocretin signaling at the orexin 1 receptor regulates cue-elicited cocaine-seeking, Eur. J. Neurosci 30 (2009) 493–503, 10.1111/j.1460-9568.2009.06844.x. [PubMed: 19656173]

[54]. Ajayi AF, Akhigbe RE, Staging of the estrous cycle and induction of estrus in experimental rodents: an update, Fertil. Res. Pract 6 (2020) 5, 10.1186/s40738-020-00074-3. [PubMed: 32190339]

[55]. Maren S, DeCola JP, Swain RA, Fanselow MS, Thompson RF, Parallel augmentation of hippocampal long-term potentiation, theta rhythm, and contextual fear conditioning in water-deprived rats, Behav. Neurosci 108 (1994) 44–56, 10.1037/0735-7044.108.1.44. [PubMed: 8192850]

[56]. Hogarth L, Addiction is driven by excessive goal-directed drug choice under negative affect: translational critique of habit and compulsion theory, Neuropsychopharmacology 45 (2020) 720–735, 10.1038/s41386-020-0600-8. [PubMed: 31905368]

[57]. Singer BF, Fadanelli M, Kawa AB, Robinson TE, Are cocaine-seeking “habits” necessary for the development of addiction-like behavior in rats? J. Neurosci 38 (2018) 60–73, 10.1523/JNEUROSCI.2458-17.2017. [PubMed: 29158359]

[58]. Thrailkill EA, Bouton ME, Contextual control of instrumental actions and habits, J. Exp. Psychol. Anim. Learn. Cogn 41 (2015) 69–80, 10.1037/xan0000045. [PubMed: 25706547]

[59]. Holland PC, Relations between Pavlovian-instrumental transfer and reinforcer devaluation, J. Exp. Psychol. Anim. Behav. Process 30 (2004) 104–117, 10.1037/0097-7403.30.2.104. [PubMed: 15078120]

[60]. Murray JE, Dilleen R, Pelloux Y, Economidou D, Dalley JW, Belin D, Everitt BJ, Increased impulsivity retards the transition to dorsolateral striatal dopamine control of cocaine seeking, Biol. Psychiatry 76 (2014) 15–22, 10.1016/j.biopsych.2013.09.011. [PubMed: 24157338]

[61]. Trask S, Shipman ML, Green JT, Bouton ME, Some factors that restore goal-direction to a habitual behavior, Neurobiol. Learn. Mem 169 (2020) 107161, 10.1016/j.nlm.2020.107161. [PubMed: 31927081]

[62]. Steinfeld MR, Bouton ME, Context and renewal of habits and goal-directed actions after extinction, J. Exp. Psychol. Anim. Learn. Cogn 46 (2020) 408–421, 10.1037/xan0000247. [PubMed: 32378909]

[63]. Bouton ME, Broomer MC, Rey CN, Thrailkill EA, Unexpected food outcomes can return a habit to goal-directed action, Neurobiol. Learn. Mem 169 (2020) 107163, 10.1016/j.nlm.2020.107163. [PubMed: 31927082]

[64]. Steinfeld MR, Bouton ME, Renewal of goal direction with a context change after habit learning, Behav. Neurosci 135 (2021) 79–87, 10.1037/bne0000422. [PubMed: 33119327]

[65]. Balleine BW, Killcross AS, Dickinson A, The effect of lesions of the basolateral amygdala on instrumental conditioning, J. Neurosci 23 (2003) 666–675, 10.1523/JNEUROSCI.23-02-00666.2003. [PubMed: 12533626]

[66]. Corbit LH, Balleine BW, The role of prelimbic cortex in instrumental conditioning, Behav. Brain Res 146 (2003) 145–157, 10.1016/j.bbr.2003.09.023. [PubMed: 14643467]

[67]. Schwabe L, Wolf OT, Stress-induced modulation of instrumental behavior: from goal-directed to habitual control of action, Behav. Brain Res 219 (2011) 321–328, 10.1016/j.bbr.2010.12.038. [PubMed: 21219935]

[68]. Maier SF, Amat J, Baratta MV, Paul E, Watkins LR, Behavioral control, the medial prefrontal cortex, and resilience, Dialogues Clin. Neurosci 8 (2006) 397–406, 10.31887/DCNS.2006.8.4/smaier. [PubMed: 17290798]

[69]. Maier SF, Watkins LR, Role of the medial prefrontal cortex in coping and resilience, Brain Res 1355 (2010) 52–60, 10.1016/j.brainres.2010.08.039. [PubMed: 20727864]

[70]. Amat J, Paul E, Watkins LR, Maier SF, Activation of the ventral medial prefrontal cortex during an uncontrollable stressor reproduces both the immediate and long-term protective effects of behavioral control, Neuroscience 154 (2008) 1178–1186, 10.1016/j.neuroscience.2008.04.005. [PubMed: 18515010]

[71]. Amat J, Paul E, Zarza C, Watkins LR, Maier SF, Previous experience with behavioral control over stress blocks the behavioral and dorsal raphe nucleus activating effects of later uncontrollable stress: role of the ventral medial prefrontal cortex, J. Neurosci 26 (2006) 13264–13272, 10.1523/JNEUROSCI.3630-06.2006. [PubMed: 17182776]

[72]. Amat J, Baratta MV, Paul E, Bland ST, Watkins LR, Maier SF, Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus, Nat. Neurosci 8 (2005) 365–371, 10.1038/nn1399. [PubMed: 15696163]

[73]. Amat J, Christianson JP, Aleksejev RM, Kim J, Richeson KR, Watkins LR, Maier SF, Control over a stressor involves the posterior dorsal striatum and the act/outcome circuit, Eur. J. Neurosci 40 (2014) 2352–2358, 10.1111/ejn.12609. [PubMed: 24862585]

[74]. Radke AK, Nakazawa K, Holmes A, Cortical GluN2B deletion attenuates punished suppression of food reward-seeking, Psychopharmacology. (Berl) 232 (2015) 3753–3761, 10.1007/s00213-015-4033-8. [PubMed: 26223494]

[75]. Verharen JPH, van den Heuvel MW, Luijendijk M, Vanderschuren LJMJ, Adan RAH, Corticolimbic mechanisms of behavioral inhibition under threat of punishment, J. Neurosci 39 (2019) 4353–4364, 10.1523/JNEUROSCI.2814-18.2019. [PubMed: 30902868]

[76]. Kasanetz F, Lafourcade M, Deroche-Gamonet V, Revest JM, Berson N, Balado E, Fiancette JF, Renault P, Piazza PV, Manzoni OJ, Prefrontal synaptic markers of cocaine addiction-like behavior in rats, Mol. Psychiatry 18 (2013) 729–737, 10.1038/mp.2012.59. [PubMed: 22584869]

[77]. Jean-Richard-Dit-Bressel P, Ma C, Bradfield LA, Killcross S, McNally GP, Punishment insensitivity emerges from impaired contingency detection, not aversion insensitivity or reward dominance, Elife 8 (2019), 10.7554/eLife.52765.

[78]. Ostlund SB, Balleine BW, Lesions of medial prefrontal cortex disrupt the acquisition but not the expression of goal-directed learning, J. Neurosci 25 (2005) 7763–7770, 10.1523/JNEUROSCI.1921-05.2005. [PubMed: 16120777]

[79]. Xue Y, Steketee JD, Sun W, Inactivation of the central nucleus of the amygdala reduces the effect of punishment on cocaine self-administration in rats, Eur. J. Neurosci 35 (2012) 775–783, 10.1111/j.1460-9568.2012.08000.x. [PubMed: 22304754]

[80]. Kawa AB, Bentzley BS, Robinson TE, Less is more: prolonged intermittent access cocaine self-administration produces incentive-sensitization and addiction-like behavior, Psychopharmacology (Berl) 233 (2016) 3587–3602, 10.1007/s00213-016-4393-8. [PubMed: 27481050]

[81]. James MH, Stopper CM, Zimmer BA, Koll NE, Bowrey HE, Aston-Jones G, Increased number and activity of a lateral subpopulation of hypothalamic orexin/hypocretin neurons underlies the expression of an addicted state in rats, Biol. Psychiatry 85 (2019) 925–935, 10.1016/j.biopsych.2018.07.022. [PubMed: 30219208]

[82]. Orsini CA, Willis ML, Gilbert RJ, Bizon JL, Setlow B, Sex differences in a rat model of risky decision making, Behav. Neurosci 130 (2016) 50–61, 10.1037/bne0000111. [PubMed: 26653713]

[83]. Jacobs DS, Moghaddam B, Prefrontal cortex representation of learning of punishment probability during reward-motivated actions, J. Neurosci 40 (2020) 5063–5077, 10.1523/JNEUROSCI.0310-20.2020. [PubMed: 32409619]

[84]. Epstein DH, Let's agree to agree: a comment on Hogarth (2020), with a plea for not-so-competing theories of addiction, Neuropsychopharmacology 45 (2020) 715–716, 10.1038/s41386-020-0618-y. [PubMed: 31969695]

[85]. Jean-Richard-Dit-Bressel P, Killcross S, McNally GP, Behavioral and neurobiological mechanisms of punishment: implications for psychiatric disorders, Neuropsychopharmacology 43 (2018) 1639–1650, 10.1038/s41386-018-0047-3. [PubMed: 29703994]

[86]. Lüscher C, Robbins TW, Everitt BJ, The transition to compulsion in addiction, Nat. Rev. Neurosci 21 (2020) 247–263, 10.1038/s41583-020-0289-z. [PubMed: 32231315]

[87]. Field M, Heather N, Murphy JG, Stafford T, Tucker JA, Witkiewitz K, Recovery from addiction: behavioral economics and value-based decision making, Psychol. Addict. Behav 34 (2020) 182–193, 10.1037/adb0000518. [PubMed: 31599604]

[88]. Yager LM, Garcia AF, Donckels EA, Ferguson SM, Chemogenetic inhibition of direct pathway striatal neurons normalizes pathological, cue-induced reinstatement of drug-seeking in rats, Addict. Biol 24 (2019) 251–264, 10.1111/adb.12594. [PubMed: 29314464]

[89]. Pascoli V, Hiver A, Van Zessen R, Loureiro M, Achargui R, Harada M, Flakowski J, Lüscher C, Stochastic synaptic plasticity underlying compulsion in a model of addiction, Nature 564 (2018) 366–371, 10.1038/s41586-018-0789-4. [PubMed: 30568192]

[90]. Hu Y, Salmeron BJ, Krasnova IN, Gu H, Lu H, Bonci A, Cadet JL, Stein EA, Yang Y, Compulsive drug use is associated with imbalance of orbitofrontal- and prelimbic-striatal circuits in punishment-resistant individuals, Proc. Natl. Acad. Sci. USA 116 (2019) 9066–9071, 10.1073/pnas.1819978116. [PubMed: 30988198]

[91]. Seiler JL, Cosme CV, Sherathiya VN, Schaid MD, Bianco JM, Bridgemohan AS, Lerner TN, Dopamine signaling in the dorsomedial striatum promotes compulsive behavior, Curr. Biol 32 (2022) 1175–1188, 10.1016/j.cub.2022.01.055, e5. [PubMed: 35134327]

[92]. Kasanetz F, Deroche-Gamonet V, Berson N, Balado E, Lafourcade M, Manzoni O, Piazza PV, Transition to addiction is associated with a persistent impairment in synaptic plasticity, Science (1979) 328 (2010) 1709–1712, 10.1126/science.1187801.

[93]. Bentzley BS, Jhou TC, Aston-Jones G, Economic demand predicts addiction-like behavior and therapeutic efficacy of oxytocin in the rat, Proc. Natl. Acad. Sci. USA 111 (2014) 11822–11827, 10.1073/pnas.1406324111. [PubMed: 25071176]

[94]. James MH, Bowrey HE, Stopper CM, Aston-Jones G, Demand elasticity predicts addiction endophenotypes and the therapeutic efficacy of an orexin/hypocretin-1 receptor antagonist in rats, Eur. J. Neurosci 50 (2019) 2602–2612, 10.1111/ejn.14166. [PubMed: 30240516]

[95]. Jean-Richard-Dit-Bressel P, Lee JC, Liew SX, Weidemann G, Lovibond PF, McNally GP, A cognitive pathway to punishment insensitivity, Proc. Natl. Acad. Sci. USA 120 (2023) e2221634120, 10.1073/pnas.2221634120. [PubMed: 37011189]

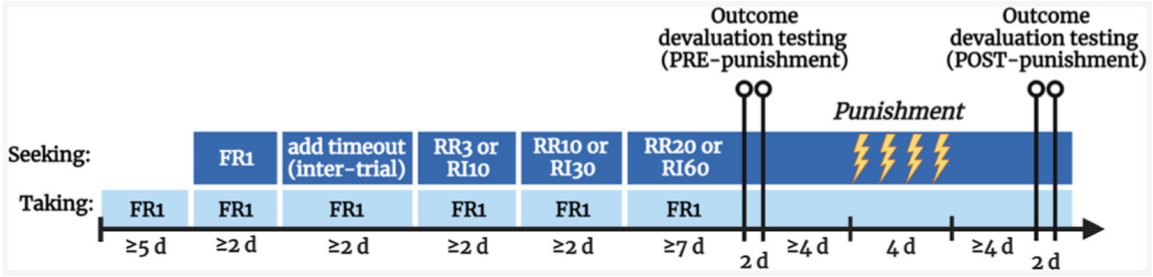

Fig. 1. |. Experimental timeline for self-administration training, outcome devaluation testing, and punishment.

Rats were trained to self-administer IV cocaine or food on a seeking-taking chained schedule of reinforcement as shown by the different stages, with the requirements for the seeking and taking levers shown for each stage, as well as the minimum number of days required at each stage. FR, fixed ratio; RI, random interval; RR, random ratio. After the final stage of training, rats were given outcome devaluation testing (devaluation and nondevaluation sessions counterbalanced across two days), before and after punishment testing. Punishment testing occurred on four days and was preceded by at least four days of baseline self-administration and followed by at least four days of self-administration prior to outcome devaluation testing. Created with BioRender.com.

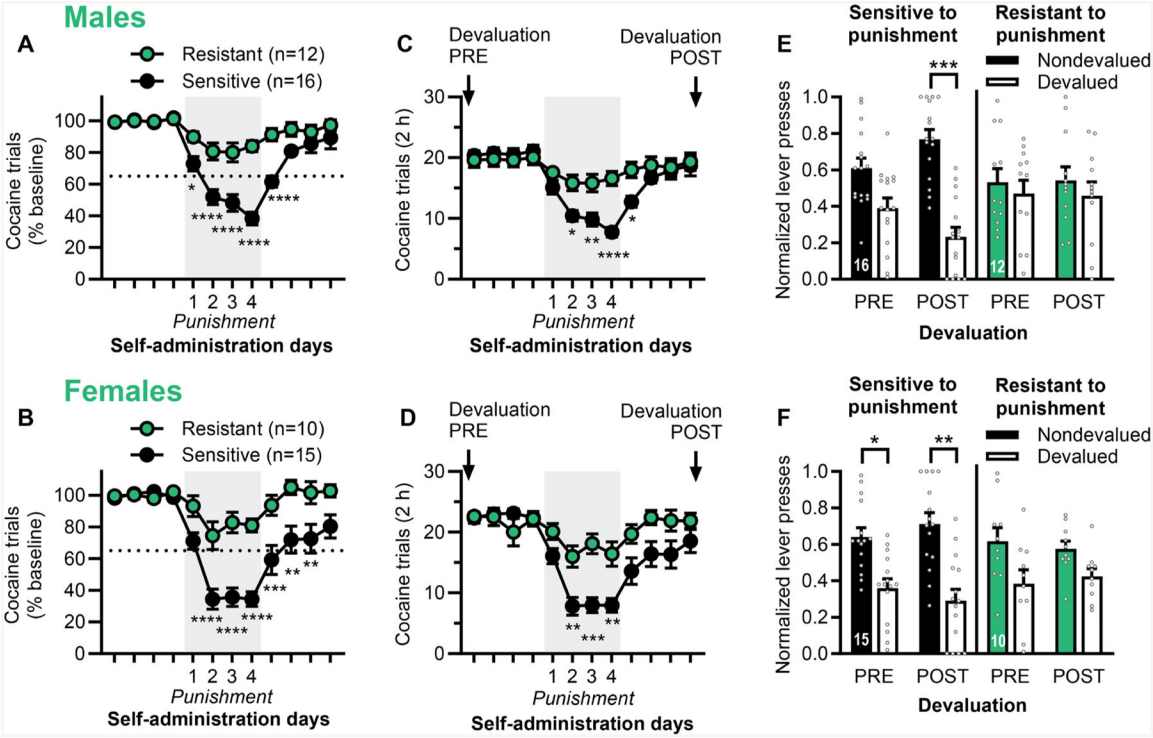

Fig. 2. |. Punishment resistance for cocaine self-administration is associated with inflexible habits.

A-B) Cocaine trials (% baseline) for the four days before, during, and after punishment testing for male rats (A) and female rats (B) categorized as punishment resistant or sensitive. C-D) Cocaine trials (total in 2 h) for male rats (C) and female rats (D). Labels indicate when outcome devaluation was conducted pre- and post-punishment. E-F) Outcome devaluation pre- and post-punishment for male rats (E) and female rats (F) that were sensitive or resistant to punishment. Normalized lever presses are shown for nondevalued and devalued sessions. *p* values < *0.05, **0.01, ***0.001, ****0.0001.

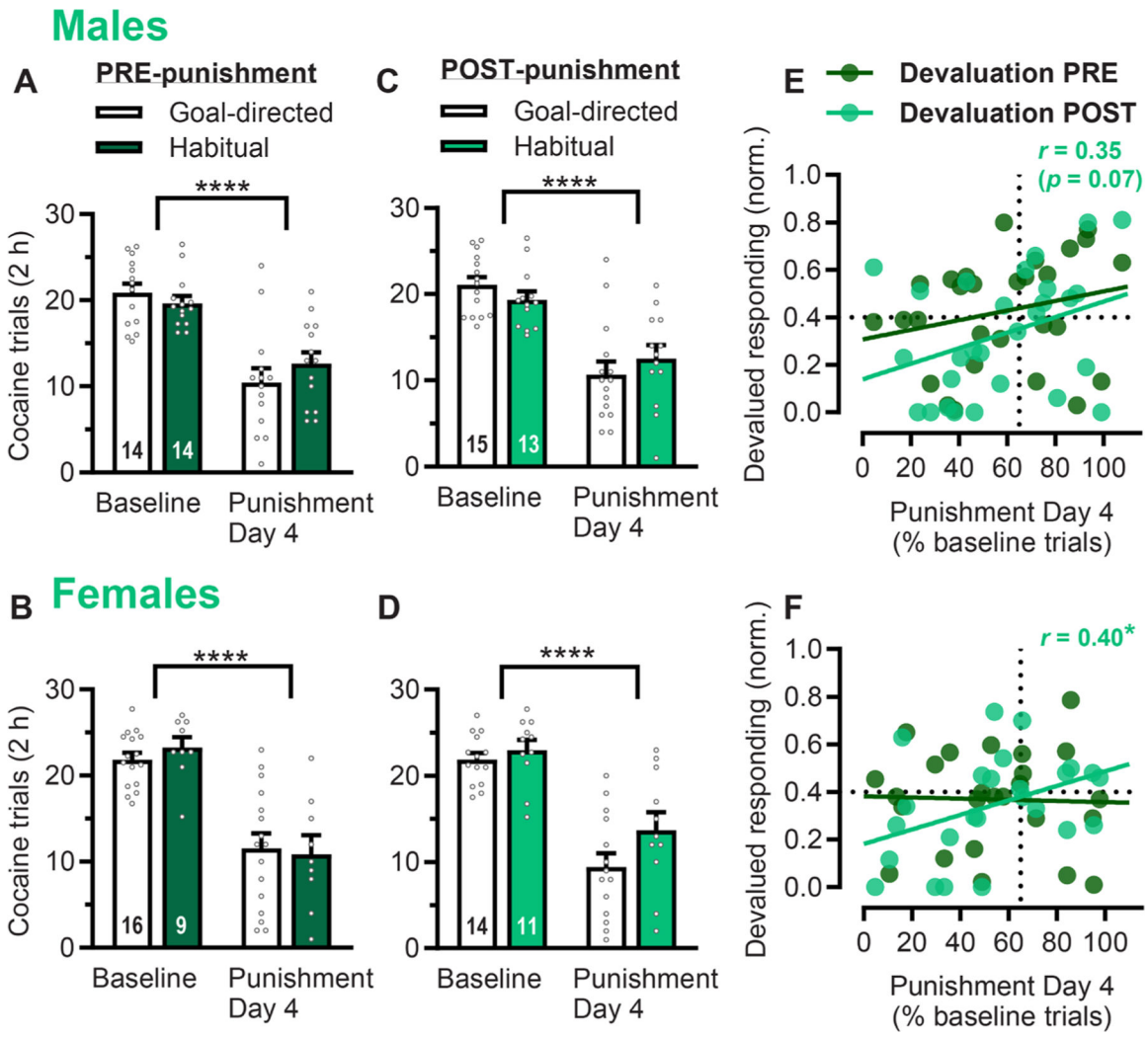

Fig. 3. |. Post-punishment but not pre-punishment cocaine habits are associated with punishment resistance.

A-B) Cocaine trials (total in 2 h) during baseline seeking-taking and punishment day 4 for male rats (A) and female rats (B) classified as goal-directed or habitual based on outcome devaluation conducted pre-punishment. C-D) Cocaine trials for male rats (C) and female rats (D) classified as goal-directed or habitual based on outcome devaluation conducted post-punishment. E-F) Relationship between punishment sensitivity (% baseline trials on Day 4; ≥65 % threshold considered resistant) and outcome devaluation (normalized devalued responding; ≥0.4 threshold considered habitual) for male rats (E) and female rats (F), with devaluation scores pre-punishment (dark green) and post-punishment (light green). *p* values < *0.05, ****0.0001.

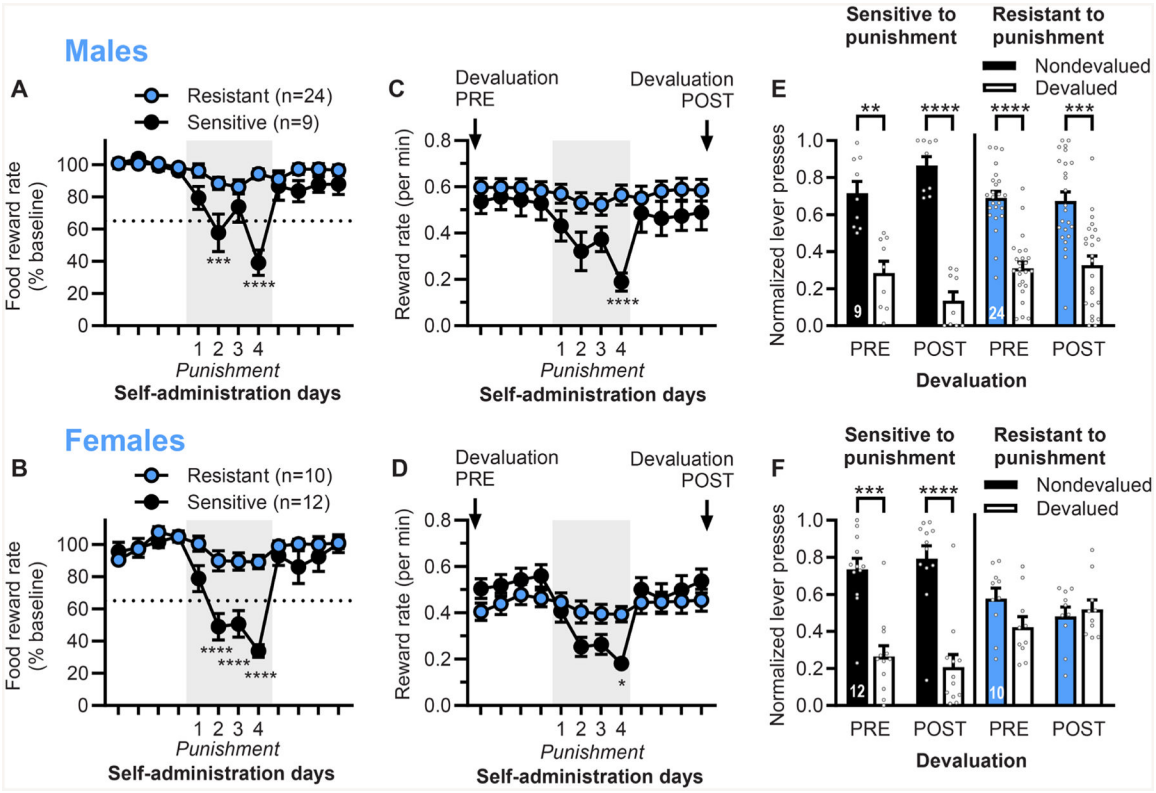

Fig. 4. |. Punishment resistance for food self-administration is associated with inflexible habits, particularly in female rats.

A-B) Reward rate for food (% baseline) for the four days before, during, and after punishment testing for male rats (A) and female rats (B) categorized as punishment resistant or sensitive. C-D) Reward rate (pellets/min) for male rats (C) and female rats (D). Labels indicate when outcome devaluation was conducted pre- and post-punishment. E-F) Outcome devaluation pre- and post-punishment for male rats (E) and female rats (F) that were sensitive or resistant to punishment. Normalized lever presses are shown for nondevalued and devalued sessions. *p* values < *0.05, **0.01, ***0.001, ****0.0001.

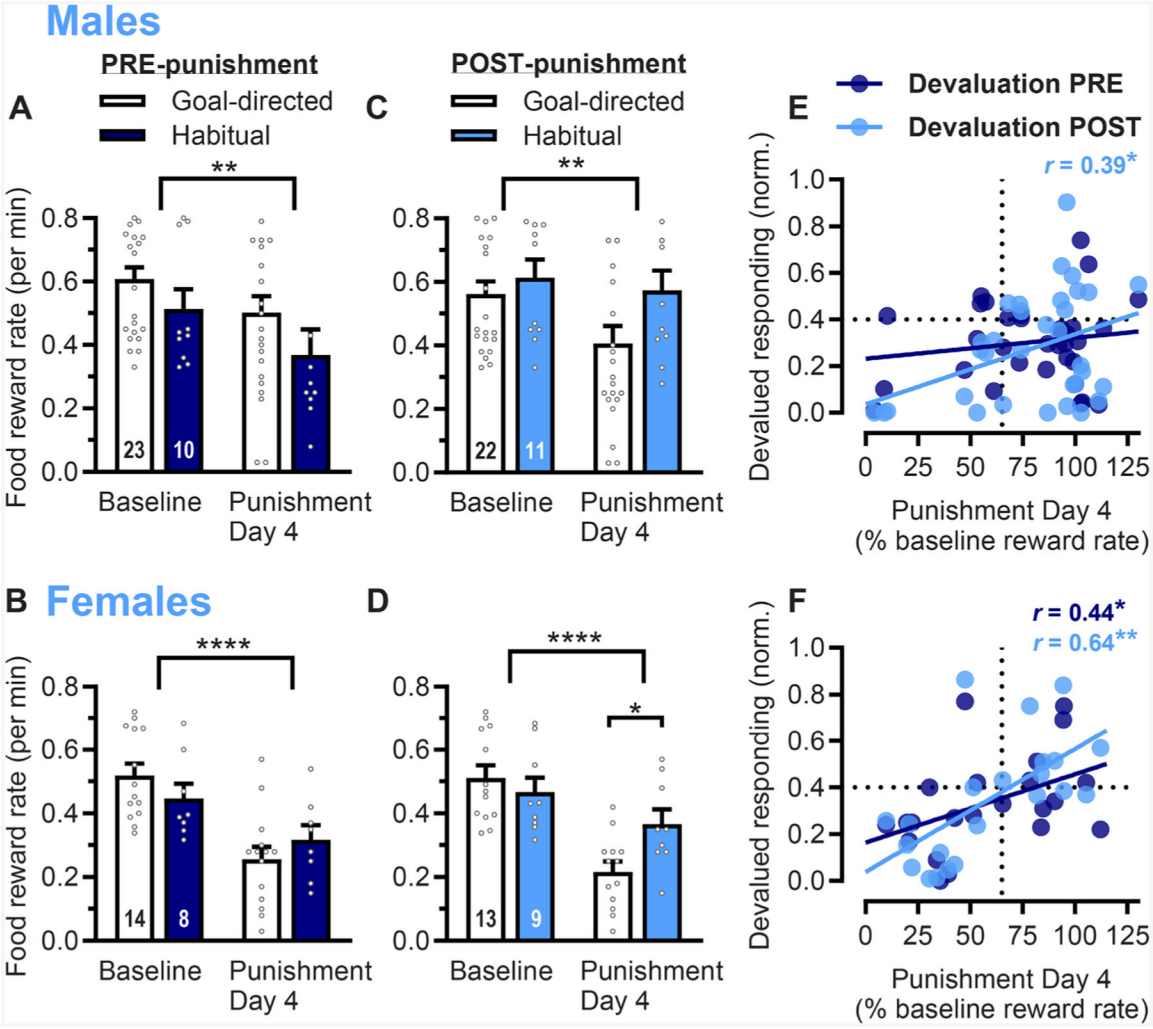

Fig. 5. |. Pre- and post-punishment food habits are associated with punishment resistance.

A-B) Reward rate for food (pellets per min) during baseline seeking-taking and punishment day 4 for male rats (A) and female rats (B) classified as goal-directed or habitual based on outcome devaluation conducted pre-punishment. C-D) Reward rate for male rats (C) and female rats (D) classified as goal-directed or habitual based on outcome devaluation conducted post-punishment. E-F) Relationship between punishment sensitivity (% baseline reward rate on day 4; ≥65 % threshold considered resistant) and outcome devaluation (normalized devalued responding; ≥0.4 threshold considered habitual) for male rats (E) and female rats (F), with devaluation scores pre-punishment (dark blue) and post-punishment (light blue). *p* values < *0.05, **0.01, ****0.0001.

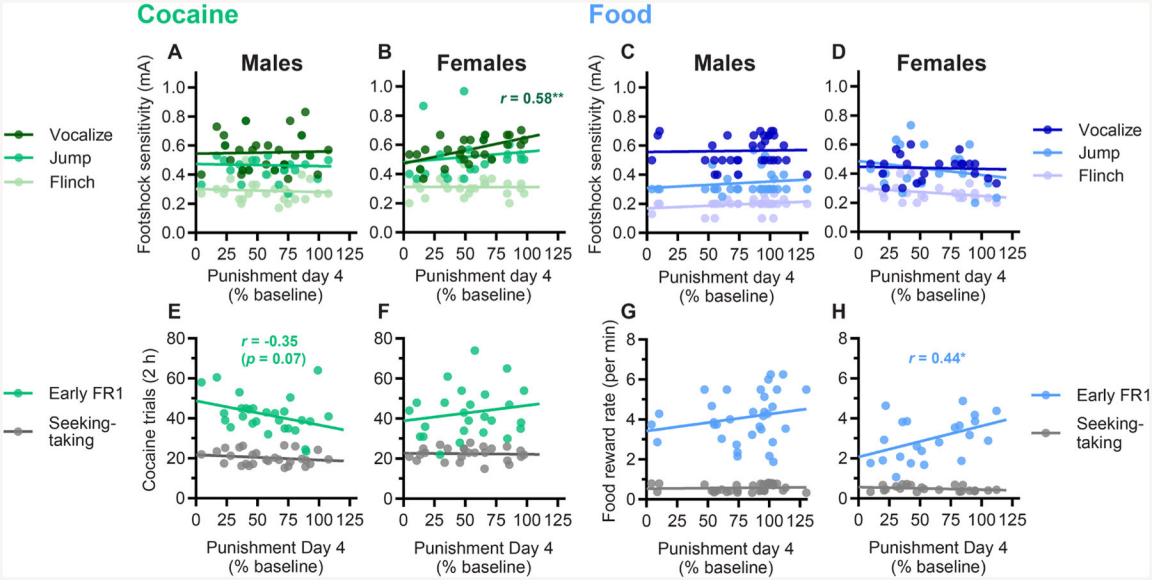

Fig. 6. |. Relationship between punishment resistance and footshock sensitivity (thresholds for flinch, jump, and vocalization) and self-administration rates.

A-B) Relationship between cocaine punishment sensitivity (% baseline trials) and footshock sensitivity in male rats (A) and female rats (B). C-D) Relationship between food punishment sensitivity (% baseline reward rate) and footshock sensitivity in male rats (C) and female rats (D). E-F) Relationship between cocaine punishment sensitivity (% baseline trials) and self-administration (cocaine trials in 2 h) during early FR1 training or final seeking-taking sessions in male rats (E) and female rats (F). G-H) Relationship between food punishment sensitivity (% baseline reward rate) and self-administration (food pellets per min) during early FR1 training or final seeking-taking sessions in male rats (G) and female rats (H). $p <$ *0.05, **0.01.