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ORIGINAL INVESTIGATION

Role of preexisting inhibitory control deficits vs. drug use history in mediating insensitivity to aversive consequences in a rat model of polysubstance use

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Abstract

Rationale The nature and predictors of insensitivity to aversive consequences of heroin + cocaine polysubstance use are not well characterized.

Objectives Translational methods incorporating a tightly controlled animal model of drug self-administration and measures of inhibitory control and avoidance behavior might be helpful for clarifying this issue.

Methods The key approach for distinguishing potential contributions of pre-existing inhibitory control deficits vs. drug use history in meditating insensitivity to aversive consequences was comparison of two rat strains: Wistar (WIS/Crl), an outbred strain, and the spontaneously hypertensive rat (SHR/NCrl), an inbred strain shown previously to exhibit heightened cocaine and heroin self-administration and poor inhibitory control relative to WIS/Crl.

Results In separate tasks, SHR/NCrl displayed greater impulsive action and compulsive-like behavior than WIS/Crl prior to drug exposure. Under two different schedules of drug delivery, SHR/NCrl self-administered more cocaine than WIS/Crl, but self-administered a similar amount of heroin + cocaine as WIS/Crl. When half the session cycles were punished by random foot shock, SHR/NCrl initially were less sensitive to punishment than WIS/Crl when self-administering cocaine, but were similarly insensitive to punishment when self-administering heroin + cocaine. Based on correlation analyses, only trait impulsivity predicted avoidance capacity in rats self-administering cocaine and receiving yoked-saline. In contrast, only amount of drug use predicted avoidance capacity in rats self-administering heroin + cocaine. Additionally, baseline drug seeking and taking predicted punishment insensitivity in rats self-administering cocaine or heroin + cocaine.

Conclusions Based on the findings revealed in this animal model, human laboratory research concerning the nature and predictors of insensitivity to aversive consequences in heroin and cocaine polysubstance vs. monosubstance users is warranted.

Keywords Avoidance capacity · Cocaine · Heroin + cocaine · Inhibitory control capacity · Self-administration · Spontaneously hypertensive rat · Trait compulsivity · Trait impulsivity

Introduction

Polysubstance use in individuals with opioid dependence is on the rise. Over the past decade, co-use of heroin and cocaine has become more prevalent (Goodwin et al. 2021; Leri et al. 2003) and has contributed significantly to opioid overdose deaths (Lim et al. 2020). In a recent national sample of over 15,000 individuals entering treatment for opioid use disorder, 34% of this sample additionally used cocaine on a consistent basis (Cicero et al. 2020). Many individuals consume heroin + cocaine by injection, despite the risk of blood-borne diseases such as HIV/AIDS and hepatitis C (Harrell et al. 2012). Other risks associated with heroin + cocaine use include withdrawal/negative affect, poorer treatment outcome, loss of socioeconomic status, loss of relationships/family, arrest/imprisonment, overdose, and death (Williamson et al. 2006; Barocas et al. 2019). The persistence of drug use despite aversive consequences has been viewed as a cornerstone of addictive disorders (Hyman 2005; Leshner 1997). These negative outcomes

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occur repeatedly in the lives of those with substance use disorders, particularly those with polysubstance use, and appear to reflect cognitive/motivational insensitivity to aversive consequences, despite adequate warnings (Wilson and Vassileva 2016).

Understanding the nature and predictors of insensitivity to aversive consequences in heroin + cocaine polysubstance users holds the promise of aiding clinical intervention. Yet, few human studies have been conducted to assess contributing neuropsychological factors. It has been shown that participants with a prolonged history of either heroin + cocaine use or primarily cocaine use exhibit risky decision-making (Iowa gambling task), suggesting a reduced capacity to avoid aversive consequences (Verdejo-Garcia and Perez-Garcia 2007). In contrast, a prolonged history of primarily cocaine use was associated with response inhibition deficits (Go/N-Go; Stroop), whereas a prolonged history of heroin + cocaine use was not (Verdejo-Garcia et al. 2007b; Verdejo-Garcia and Perez-Garcia 2007). Later studies confirmed the findings in cocaine users (Verdejo et al. 2007a; Hester et al. 2013). A recent study showed that a high level of impulsivity, but not cocaine use, was a strong predictor of impairments in shock avoidance learning, suggesting that impulsivity might be a potential predisposing factor for insensitivity to aversive consequences in cocaine users (Ersche et al., 2016).

Despite these advances, it is difficult to know from cross-sectional evaluations of heroin + cocaine users whether impairments in avoidance capacity might arise from pre-existing inhibitory control deficits, chronic polysubstance use, or the interaction of these factors (Ivanov et al. 2008). Also unclear is if the pathway for predicting compulsive heroin + cocaine use, defined as persistence of drug use despite aversive consequences, is similar to or different from what has been suggested above for compulsive cocaine use (Ersche et al. 2016). Translational methods that incorporate a tightly controlled animal model of heroin + cocaine self-administration and measures of inhibitory control and operant avoidance behavior might be helpful for clarifying these issues. Moreover, inclusion of animals with a history of cocaine use is an important positive drug control for this experimental design, as this facet would establish the construct validity and translational relevance of our preclinical approach if impulsivity were found to be a strong predictor of impairments in avoidance capacity in animals self-administering cocaine. Importantly, prior research in outbred rats demonstrated that insensitivity to punished cocaine self-administration was associated with high pre-existing levels of impulsivity (Belin et al. 2008; Economidou et al. 2009). A key aspect of the approach for distinguishing the potential contributions of pre-existing inhibitory control deficits vs. drug use history in mediating insensitivity to aversive consequences was the comparison of two rat strains: outbred Wistar rats obtained from Charles River Laboratories with a strain designation of WIS/Crl and inbred spontaneously hypertensive rats obtained from Charles River Laboratories with a strain designation of SHR/NCrl. SHR/NCrl exhibit a heightened self-administration phenotype for a number of drugs, including cocaine (Harvey et al. 2011; Somkuwar et al. 2013; Jordan et al. 2014, 2016a, b) and heroin (Miller et al. 2018), as well as neuropsychological deficits involving behavioral flexibility, working memory, and inhibitory control (Harvey et al. 2011; Kantak et al. 2008; Sanabria et al. 2008; Somkuwar et al. 2016; Ibias and Pellon 2011) relative to WIS/Crl. Because both impulsivity and compulsivity are overlapping aspects of poor inhibitory control that can contribute to addictive behavior in people (Lee et al. 2019; Albertella et al. 2020), we examined non-overlapping measures of impulsive-like and compulsive-like behavior to differentiate their potential individual contributions to the levels of drug seeking and taking and avoidance capacity following drug exposure.

For drug self-administration, a paradigm wherein sensitivity to punishment by randomly presented foot shock was followed (Pelloux et al. 2007). Several reports have demonstrated insensitivity to punishment in subpopulations of animals self-administering cocaine (Belin et al. 2011; Xue et al. 2012; Pelloux et al. 2007) or various opioid drugs, including remifentanil, fentanyl, and oxycodone (Blackwood et al. 2019; Porter-Stransky ey al. 2017; Moussawi et al. 2020). The current study expanded this clinically relevant drug punishment approach by examining the potential role of pre-existing inhibitory control deficits vs. drug use history in mediating insensitivity to aversive consequences in an animal model of polysubstance use (heroin + cocaine). For the present study, the outcome of the operant avoidance test helped to discern the potential role of pre-existing inhibitory control deficits vs. drug use history in mediating insensitivity to aversive consequences. If pre-existing inhibitory control deficits were important, then trait impulsivity and/or trait compulsivity would correlate with avoidance accuracy in the operant avoidance task, regardless of drug use history (hypothesis 1). If drug use history was important, then drug use would correlate with avoidance accuracy in the operant avoidance task, regardless of pre-existing levels of impulsive action and/or compulsive behavior (hypothesis 2). If pre-existing inhibitory control deficits and drug use history were important, then trait impulsivity and/or trait compulsivity and drug use history would correlate with avoidance accuracy in the operant avoidance task (hypothesis 3). Comparing SHR/NCrl to WIS/Crl in this study provided a wide range of values for inhibitory control capacity, drug use, and avoidance accuracy upon which to determine the correlations among these targeted behavioral variables.

Materials and methods

Subjects

Thirty male SHR/NCrl strain rats (152–225 g; 8 weeks old on arrival from Charles River Laboratories, Wilmington, MA, USA) and thirty male WIS/Crl strain rats (251–275 g; 8 weeks old on arrival from Charles River Laboratories, Wilmington, MA, USA) were housed individually in ventilated cages under a 12-h light/dark cycle (08:00 h on; 20:00 h off) in a climate-controlled vivarium. Rats arrived in three cohorts over a 14-month period, with 10 SHR/NCrl and 10 WIS/Crl in each cohort. All procedures were conducted during the light phase based in part on the infrastructure of the laboratory environment. Importantly, cocaine (Phillips et al. 2013) and heroin + cocaine (Preston et al. 2016) use in people peaks after 5 pm, which is the diurnal equivalent of the light phase in rats, thus making it appropriate to conduct these procedures in rats during the light phase. During food-motivated procedures described below for inhibitory control capacity, rats were maintained at 80–85% of their expected free-feeding body weight. Furthermore, all procedures complied with the 8th edition of the NIH Guide for Care and Use of Laboratory Animals and were approved by the Boston University Institutional Animal Care and Use Committee.

Apparatus

Ten operant conditioning chambers (model ENV-008CT; Med Associates, St. Albans, VT, USA) were used for the four behavioral tasks and each was outfitted with two retractable levers, two white stimulus lights, a house light, a speaker, a pellet dispenser, and a syringe pump that were arranged as previously described (Szalay et al. 2013). Six of the chambers also were outfitted with a standalone aversive stimulator/scrambler module (model ENV-414S; Med Associates, St. Albans, VT, USA) that were used during the punished drug self-administration and operant avoidance procedures. Each chamber was enclosed in a sound attenuating cubicle with an exhaust fan.

Drugs

Cocaine hydrochloride and 3,6-diacetylmorphine hydrochloride (heroin) were obtained from the National Institute on Drug Abuse Drug Supply (Bethesda, MD, USA). Working solutions consisted of either cocaine (1.35 mg/ml), heroin + cocaine (0.081 mg/ml + 1.35 mg/ml), or vehicle (saline solution containing 3 IU heparin/ml). During sessions, rats self-administered either cocaine (0.25 mg/kg) or heroin + cocaine (0.015 mg/kg + 0.25 mg/kg), or they passively received the saline vehicle in a yoked manner (1.8 ml/min for 0.6 s/100 g body weight; yoked to rats self-administering cocaine). Yoked-saline rats received the same experience with lever retractions and insertions, stimulus light onsets and offsets, foot shocks, and time-out periods that were controlled by the rat self-administering drug, except that lever responses had no consequences and saline was infused instead of drug. The selection of cocaine and heroin doses was based on several considerations. First, 0.25 mg/kg cocaine previously was established as a relevant dose for revealing punishment resistance in a subset of Lister rats following a long self-administration training history (Pelloux et al. 2007). Second, SHR/NCrl and WIS/Crl rats will readily self-administer 0.25 mg/kg cocaine, a dose positioned on the descending limb of the cocaine dose–response curve when studied under a fixed-ratio schedule in these strains (Harvey et al. 2011; Somkuwar et al. 2013; Jordan et al. 2016a). Under these conditions, cocaine dose–response curves were shifted upward in SHR/NCrl compared to WIS/Crl. Third, in a small pilot study in two WIS/Crl rats, we determined that 0.015 mg/kg heroin was reinforcing, with rats self-administering 16.5 ± 2.5 infusions during 2-h daily sessions under a fixed-ratio schedule. This is similar to Harlan Sprague–Dawley WIS rats that self-administered approximately 14–16 infusions of 0.015 mg/kg heroin during the first 2 h of their daily 6-h sessions (Lynch and Carroll 1999). Fourth, a 0.015 mg/kg dose of heroin also is positioned on the descending limb of the heroin dose–response curve studied under a fixed-ratio schedule in several rat strains (Martin et al. 1998a, b; Hiranita et al. 2014; Hempel et al. 2020). The only published report with heroin self-administration in SHR/NCrl demonstrated a dose of 0.030 mg/kg heroin was readily self-administered (Miller et al. 2018) at levels lower than those reported in our pilot study for SHR/NCrl self-administering 0.015 mg/kg heroin. Fifth, the 0.015 mg/kg unit dose of heroin combined with 0.25 mg/kg cocaine in the present study is not likely analgesic nor likely to produce tolerance or physical dependence based on the results of past studies in rats that self-administered similar heroin unit doses prior to assessment of analgesia and physical withdrawal symptoms (Dai et al. 1989; De Vry et al. 1989). Other studies demonstrated that 0.013 mg/kg heroin + 0.25 mg/kg cocaine is highly reinforcing under a progressive ratio schedule (Cruz et al. 2011) and that heroin + cocaine combinations within this dose range are positioned on the descending limb of the heroin + cocaine dose–response curve when studied under a fixed-ratio schedule, similar to the positions of the heroin and cocaine doses alone (Smith et al. 2006). Collectively, these details suggest that 0.015 mg/kg heroin + 0.25 mg/kg cocaine would be an optimal dose combination to study the nature and predictors of insensitivity to the aversive consequences of heroin + cocaine polysubstance use in SHR/NCrl vs. WIS/Crl rats.

Procedures

Pre-existing inhibitory control capacity Differential reinforcement of low rate (DRL) procedures were implemented to measure impulsivity-like traits during 55-min sessions (Somkuwar et al. 2016; Kantak et al. 2021) in SHR/NCrl ($n = 30$) and WIS/Crl ($n = 30$). This task was selected because SHR/NCrl were shown previously to be more impulsive than WIS/Crl in this task (Somkuwar et al., 2016). Rats first were trained with a 5-s wait time that was incremented to a 30-s wait time for food pellet delivery subsequent to a lever press. A schedule-induced polydipsia (SIP) procedure with a fixed time (FT) 60-s schedule of non-contingent food pellet delivery was implemented to measure compulsivity-like traits during twelve 60-min sessions (Ibias and Pellon 2011; Kantak et al. 2021) in SHR/NCrl ($n = 30$) and WIS/Crl ($n = 30$). This task was selected because SHR/NCrl were shown previously to be more compulsive than WIS/Crl in this task (Ibias and Pellon, 2011). Further DRL and SIP task details and a timeline of all procedures are located in Supplemental Methods.

Drug self-administration Following the inhibitory control procedures, rats were returned to ad libitum feeding and i.v. catheters were surgically implanted (Szalay et al. 2013). Details for catheter maintenance are located in Supplemental Methods. Self-administration procedures measured drug use despite aversive consequences in SHR/NCrl and WIS/Crl utilizing a previously described tandem schedule (Pelloux et al. 2007; Kantak et al. 2021). Three groups were examined in each rat strain, including cocaine (0.25 mg/kg), heroin + cocaine (0.015 + 0.25 mg/kg), and yoked-saline. The testing of a yoked-saline (no-drug) group was necessary to discern if a reduced capacity to avoid aversive consequences in the operant avoidance procedure was associated with pre-existing inhibitory control deficits, drug use history, or an interaction of these factors (see hypotheses in "Introduction"). Phase 1 of drug self-administration measured acquisition of taking lever responses using a fixed ratio (FR) 1, 20-s time-out (TO) schedule during daily 2-h sessions. A total of 28 SHR/NCrl ($n = 11$ cocaine, $n = 10$ heroin + cocaine, and $n = 7$ yoked-saline) and a total of 21 WIS/Crl ($n = 8$ cocaine, $n = 5$ heroin + cocaine, and $n = 8$ yoked-saline) completed phase 1 training. Phase 2 measured acquisition of the seek-take chain, with rats trained up to a terminal tandem schedule consisting of a FR1, random interval (RI) 120-s response requirement on the seeking lever and a FR1, 600-s TO response requirement on the taking lever. Sessions lasted for 11 cycles, with each cycle culminating in a drug infusion, or 2 h, whichever occurred first. A total of 28 SHR/NCrl ($n = 11$ cocaine, $n = 10$ heroin + cocaine, and $n = 7$ yoked-saline) and a total of 19 WIS/Crl ($n = 6$ cocaine, $n = 5$ heroin + cocaine, and $n = 8$ yoked-saline) completed phase 2 training. Phase 3 measured punished drug self-administration using the FR1, RI 120-s; FR1, 600-s TO tandem schedule, with foot shock randomly presented (0.55 mA for 0.5 s) rather than insertion of the taking lever on half the cycles. Thus, this procedure involved risky decision-making concerning whether or not to respond on the seeking lever. A total of 27 SHR/NCrl ($n = 10$ cocaine, $n = 10$ heroin + cocaine, and $n = 7$ yoked-saline) and a total of 17 WIS/Crl ($n = 4$ cocaine, $n = 5$ heroin + cocaine, and $n = 8$ yoked-saline) completed phase 3 testing. Supplemental Methods contain further task and drug schedule details.

Avoidance capacity To determine the capacity to avoid aversive consequences, an operant avoidance task that measured avoidance accuracy (responses during the first 60 s of a 1000-Hz, 75-dB warning signal tone) and escape behavior (responses to terminate 0.5 s of 1.0 mA foot shock delivery after the warning signal elapsed) was used (Jiao et al. 2011). Foot shocks were delivered with an inter-shock interval of 3 s after the warning signal elapsed and were limited to a maximum of 5 per trial. Twenty trials per session (5 sessions) were conducted. A total of 27 SHR/NCrl ($n = 10$ cocaine, $n = 10$ heroin + cocaine, and $n = 7$ yoked-saline) and a total of 17 WIS/Crl ($n = 4$ cocaine, $n = 5$ heroin + cocaine, and $n = 8$ yoked-saline) completed operant avoidance testing. Supplemental Methods contain further task details.

Data analyses

Statistical analyses were conducted using SPSS version 26 software. To check for normality, quantile–quantile (Q-Q) plots were examined to determine if the residuals fell along an approximately straight line at a 45-degree angle for each group. To check for homogeneity of variance, the Mauchly test of sphericity was used for repeated measures analysis of variance (RM ANOVA) and the Levene test was used for non-repeated measures ANOVA. If Mauchly's test failed (significant p value), then the Greenhouse–Geisser correction was used to determine significance among the ANOVA factors. If the Levene test failed (significant p value) or if data were not normally distributed, then values were transformed to the square root of x prior to analysis to determine significance among the ANOVA factors.

Measures of impulsive action (percent response efficiency and burst responding under DRL 5-s and DRL 30-s schedules averaged over the last 3 sessions of each schedule) and compulsive-like behavior (ml/kg water consumed averaged over the last 3 SIP sessions) were analyzed by t test to compare performances in SHR/NCrl and WIS/Crl. SIP also was analyzed by 2-factor (strain × session number) RM ANOVA to evaluate the development of SIP between SHR/NCrl and WIS/Crl over the 12 sessions. Measures taken at the FR1 baseline (taking lever responses) and the FR1, RI 120-s;

FR1, 600-s TO baseline (seeking lever responses and seek-take cycles completed) were analyzed by 2-factor ANOVAs (strain × drug). Punished drug self-administration data (seeking responses, cycles completed, and foot shocks received) and operant avoidance data (percent avoidance accuracy and number of escape foot shocks) were analyzed by 3-factor RM ANOVAs (strain × drug × session number). Post hoc Tukey tests were used following significant ANOVA factors in all analyses.

Two-tailed Pearson correlation statistics were used to analyze the relationships between dependent measures in the cocaine/yoked-saline conditions and in the heroin + cocaine/yoked-saline conditions. The equation $\alpha' = 1 - (1 - \text{overall-}\alpha)^{1/k}$ was used to correct for multiple comparisons (Curtin and Schulz 1998) where k is the number of tests per matrix. Based on this equation, probability values ≤ 0.04 were considered significant.

Results

Pre-existing inhibitory control capacity

Across short and long DRL wait times, responding in SHR/NCrl was relatively more premature and non-productive, reflecting core features of impulsive action. Specifically, for the DRL 5-s wait time, response efficiency was lower ($t[58] = -2.97$, $p < 0.004$) and burst responding was greater ($t[58] = 3.05$, $p < 0.003$) in SHR/NCrl than WIS/Crl (Fig. 1a, b). Strain differences were more evident for the DRL 30-s wait time (Fig. 1c, d), with SHR/NCrl exhibiting lower response efficiency ($t[58] = -4.64$, $p < 0.00002$) and greater burst responding ($t[58] = 4.30$, $p < 0.00007$) than WIS/Crl. The total numbers of active lever responses (not shown) were greater in SHR/NCrl than WIS/Crl under the DRL 5-s schedule (549 ± 28 vs. 444 ± 29; $t[58] = 2.63$, $p < 0.011$) as well as under the DRL 30-s schedule (322 ± 15 vs. 169 ± 8; $t[58] = 12.17$, $p < 0.001$. The total numbers of inactive lever responses averaged 4 to 8% of the active lever responses (not shown) and were similar between SHR/NCrl and WIS/Crl under the DRL 5-s schedule (21 ± 2.4 vs. 27 ± 5.0; $t[58] = 1.19$, $p < 0.24$) as well as under the DRL 30-s schedule (18 ± 2.5 vs. 14 ± 2.4; $t[58] = 0.93$, $p < 0.36$).

Consummatory behavior in the SIP task was relatively more excessive in SHR/NCrl, reflecting a core feature of compulsive-like behavior. These data were expressed as ml/kg body weight because at the start of the SIP task at 17 weeks of age, WIS/Crl weighed 46% heavier than SHR/NCrl (386 ± 3 g vs. 264 ± 4 g). Analysis of ml/kg water consumption indicated that data were normally distributed (linear Q-Q plots), but that the variance among groups was not homogeneous (significant Mauchly's tests of sphericity; $p < 0.001$). Thus, the Greenhouse–Geisser correction was applied to determine significance among the factors. Although both strains consumed similar amounts of water at the start of the SIP task, SHR/NCrl developed polydipsia faster and to a greater extent than WIS/Crl. Across the 12 sessions (Fig. 1e), main effects of strain ($F[1, 58] = 14.0$, $p < 0.001$) and session number ($F[5.2, 304] = 28.5$, $p < 0.001$) as well as a strain × session number interaction ($F[5.2, 304] = 4.8$, $p < 0.001$) were revealed. Post hoc tests of the interaction demonstrated that relative to session 1, water consumption increased beginning on session 4 in SHR/NCrl ($ps < 0.001$), but not until session 8 in WIS/Crl ($ps < 0.05$). Relative to WIS/Crl, water consumption was greater in SHR/NCrl on sessions 4–12 ($ps < 0.04$). For the terminal three sessions combined (Fig. 1f), there were robust strain differences between SHR/NCrl and WIS/Crl ($t[58] = 3.90$, $p < 0.0003$). Similar strain differences over sessions additionally were obtained in a comparison of ml consumed across the 12 sessions (Fig. S1, Supplemental Results), again demonstrating the robustness of these strain differences.

Drug self-administration

FR1 baseline (phase 1) Analysis of taking response at baseline indicated normally distributed data (linear Q-Q plots) and homogeneity of variance among groups (non-significant Levene's test, $p < 0.531$). During the initial self-administration training phase, main effects of strain ($F[1, 43] = 33.7$, $p < 0.001$) and drug ($F[2, 43] = 7.4$, $p < 0.002$) and a strain × drug interaction ($F[2, 43] = 6.5$, $p < 0.004$) were revealed for the number of taking lever responses (Fig. 2a). Post hoc tests of the interaction indicated that SHR/NCrl made more responses on the taking lever than WIS/Crl for cocaine ($p < 0.001$) and yoked-saline ($p < 0.009$) but not for heroin + cocaine ($p < 0.25$). Together, these findings indicate that under the simple FR1 taking schedule, cocaine self-administration was greater in SHR/NCrl than WIS/Crl, whereas heroin + cocaine self-administration was similar in SHR/NCrl and WIS/Crl. Notably, the cocaine groups ($p < 0.008$) and the heroin + cocaine groups ($p < 0.003$) made more taking lever responses than the yoked-saline groups, demonstrating the reinforcing effect of cocaine and heroin + cocaine in both SHR/NCrl and WIS/Crl. It should be noted that heroin + cocaine self-administration training in SHR/NCrl and WIS/Crl was interrupted between late March and early June 2020 due to closure of on-campus research at Boston University related to the COVID-19 pandemic. Rats had just completed their FR1 baseline phase when the closure began. When the FR1 baseline was repeated upon our return, we found that responses on the taking lever for heroin + cocaine were statistically similar between strains both before and after the break (Table S1, Supplemental Results).

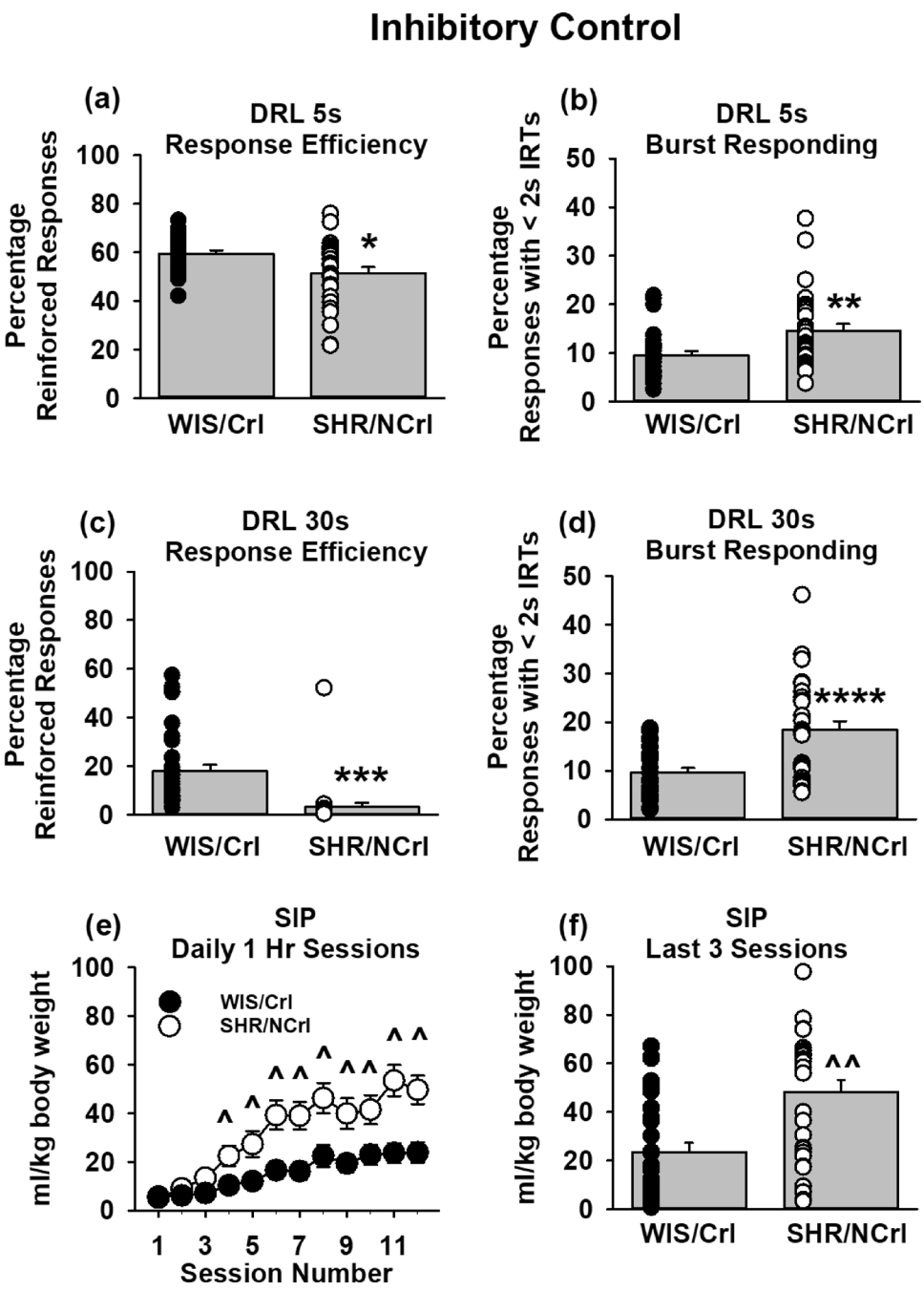

Fig. 1 Inhibitory control performance in SHR/NCrl and WIS/Crl male rats. For trait impulsivity (DRL 5-s and DRL 30-s testing; panels **a**–**d**), values are the mean ± SEM and individual rat data for percentage of reinforced responses (response efficacy) and percentage of responses with inter-response times of less than 2 s (burst responding) averaged over the last 3 daily sessions. For trait compulsivity (SIP testing; panels **e**, **f**), values are the mean ± SEM ml/kg water intake for each of the 12 daily sessions or the mean ± SEM and individual rat data for ml/kg water intake averaged over the last 3 daily sessions. *$p < 0.004$ comparing DRL 5-s response efficacy between SHR/NCrl and WIS/CRL; **$p < 0.003$ comparing DRL 5-s burst responding between SHR/NCrl and WIS/Crl; ***$p < 0.00002$ comparing DRL 30-s response efficiency between SHR/NCrl and WIS/Crl; ****$p < 0.00007$ comparing DRL 30-s burst responding between SHR/NCrl and WIS/Cr; ^$p < 0.04$ comparing ml/kg water intake between SHR/NCrl and WIS/Crl on sessions 4–12; and ^^$p < 0.0003$ comparing ml/kg water intake between SHR/NCrl and WIS/Crl on the last 3 daily sessions

FR1, RI 120-s; FR1, 600-s TO baseline (phase 2) After transition to the tandem schedule, analysis of seeking responses and cycles completed at baseline indicated normally distributed data (linear Q-Q plots) and homogeneity of variance among groups (non-significant Levene's test, $p < 0.163$ and $p < 0.146$, respectively). Main effects of strain ($F[1, 41] = 11.6$, $p < 0.001$) and drug ($F[2, 41] = 8.6$, $p < 0.001$) were revealed for the number of responses on the seeking lever (Fig. 2b). The strain × drug interaction was not significant ($F[2, 41] = 2.7$, $p < 0.078$). Post hoc Tukey tests of the main effects indicated that SHR/NCrl made more responses on the seeking lever than WIS/Crl across the three drug conditions ($p < 0.002$) and that there were more responses on the seeking lever for cocaine ($p < 0.002$) and heroin + cocaine ($p < 0.005$) compared to yoked-saline, again demonstrating the reinforcing effect of cocaine and heroin + cocaine in both SHR/NCrl and WIS/Crl. For the number of seek-take cycles completed (Fig. 2c), a main effect of strain ($F[1, 28] = 26.5$, $p < 0.001$) and a strain × drug interaction ($F[1, 28] = 6.5$, $p < 0.016$) was revealed. Post hoc Tukey tests of the interaction indicated that SHR/NCrl completed more cycles than WIS/Crl for cocaine ($p < 0.001$) but not for heroin + cocaine

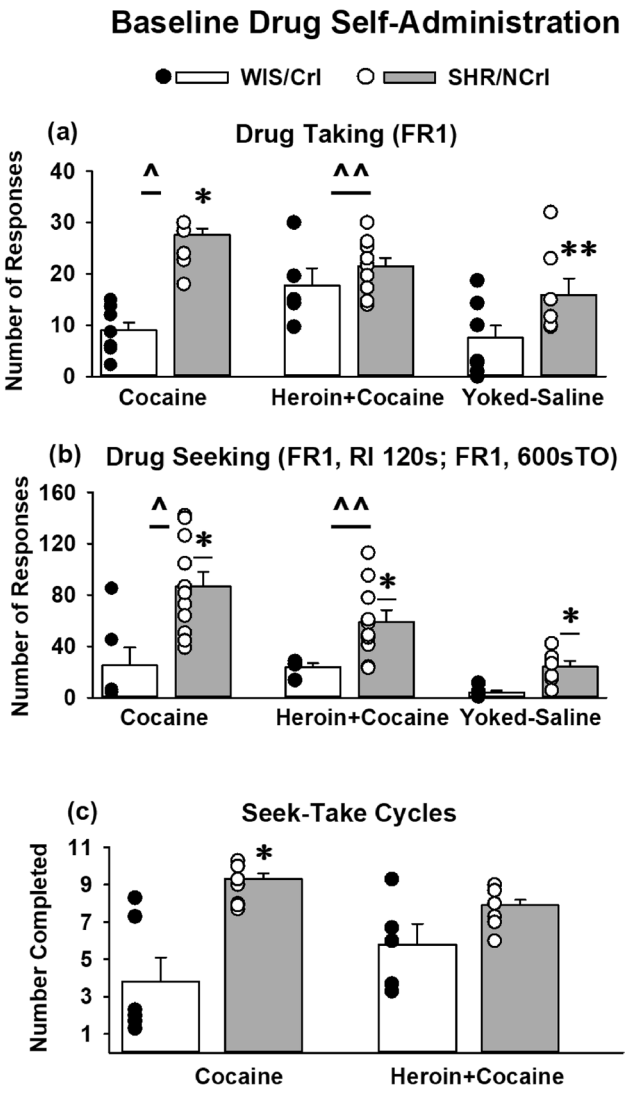

Fig. 2 Baseline drug self-administration performance in SHR/NCrl and WIS/Crl male rats under the FR1 drug-taking schedule and the FR1, RI 120-s; FR1, 600-s TO tandem schedule. Values are the mean ± SEM and individual rat data for the number of responses on the taking lever (panel **a**), number of responses on the seeking lever (panel **b**), and number of seek-take cycles completed (panel **c**), averaged over the last 3 daily sessions. In panel **a**, $*p < 0.001$ comparing SHR/NCrl cocaine to WIS/Crl cocaine; $**p < 0.009$ comparing SHR/NCrl yoked-saline to WIS/Crl yoked-saline; $\hat{}p < 0.008$ comparing cocaine to yoked-saline overall; and $\hat{\hat{}}p < 0.003$ comparing heroin + cocaine to yoked-saline overall. In panel **b**, $\underline{*}p < 0.002$ comparing SHR/NCrl to WIS/Crl across cocaine, heroin + cocaine, and yoked-saline drug groups overall; $\hat{}p < 0.002$ comparing cocaine to yoked-saline overall; and $\hat{\hat{}}p < 0.005$ comparing heroin + cocaine to yoked-saline overall. In panel **c**, $*p < 0.001$ comparing SHR/NCrl cocaine to WIS/Crl cocaine

($p < 0.089$). Together, these findings indicate that under the demanding FR1, RI 120-s; FR1, 600-s TO schedule, there were strain differences in drug-seeking responses (SHR/NCrl > WIS/Crl) for both cocaine and heroin + cocaine. However, strain differences in the amount of seek-take cycles completed depended on which drug was self-administered (SHR/NCrl > WIS/Crl for cocaine and SHR/NCrl = WIS/Crl for heroin + cocaine), as observed above under the FR1 schedule.

Punished drug self-administration (phase 3) Analysis of seeking responses during punished self-administration indicated that data were not normally distributed (non-linear Q-Q plots) and that the variance among groups was not homogeneous (significant Mauchly's tests of sphericity; $p < 0.001$). Data were transformed (square root of x) to achieve normality and the Greenhouse–Geisser correction was applied to determine significance among the factors. RM ANOVA revealed significant strain × session number ($F[4.5\ 158] = 8.4$, $p < 0.015$), drug × session number ($F[9, 158] = 8.4$, $p < 0.001$), and drug × strain ($F[2, 35] = 8.0$, $p < 0.001$) interactions for the number of responses on the seeking lever (Fig. 3a). Post hoc tests of strains across sessions indicated that SHR/NCrl emitted more seeking lever responses on session 1 than on sessions 2–8 ($ps < 0.001$) and on session 2 than on sessions 3–6 ($ps < 0.04$). WIS/Crl emitted more seeking lever responses on session 1 than on sessions 6–8 only ($ps < 0.05$). Post hoc tests of drugs across sessions indicated that cocaine rats ($ps < 0.001$) and heroin + cocaine rats ($ps < 0.001$), but not yoked-saline rats ($ps > 0.82$), emitted more seeking lever responses on session 1 than on sessions 2–8. Cocaine rats additionally emitted more seeking lever responses on session 2 than on sessions 4–8 ($ps < 0.01$). Post hoc tests of drugs across strains indicated that for session 1, SHR/NCrl emitted a greater number of seeking lever responses than WIS/Crl for cocaine ($p < 0.035$), but emitted a similar number of seeking lever responses as WIS/Crl for heroin + cocaine ($p < 0.49$). In rats receiving yoked-saline, responses on the seeking lever were low across all sessions, but were greater in SHR/NCrl than WIS/Crl ($p < 0.028$). It is important to note that in rats receiving yoked-saline, non-contingent responses on the seeking lever were exceptionally high (more than 20-fold) in 2 of 7 SHR/NCrl and in 1 of 8 WIS/Crl due to these three rats resting their forepaws on this lever as a strategy to lessen the impact of the randomly presented uncontrollable foot shock and its anticipation. Seeking lever responses in the majority of SHR/NCrl and WIS/Crl yoked-saline rats which did not utilize this strategy remained at low levels, similar to the levels observed above during the seek-take training baseline (Table S2, Supplemental Results). These outlier rats were removed from the above 3-factor RM ANOVA of punished seeking lever responses.

Analysis of cycles completed during punished self-administration indicated that data were normally distributed (linear Q-Q plots), but that the variance among groups was not homogeneous (significant Mauchly's tests of sphericity; $p < 0.001$). The Greenhouse–Geisser correction was applied

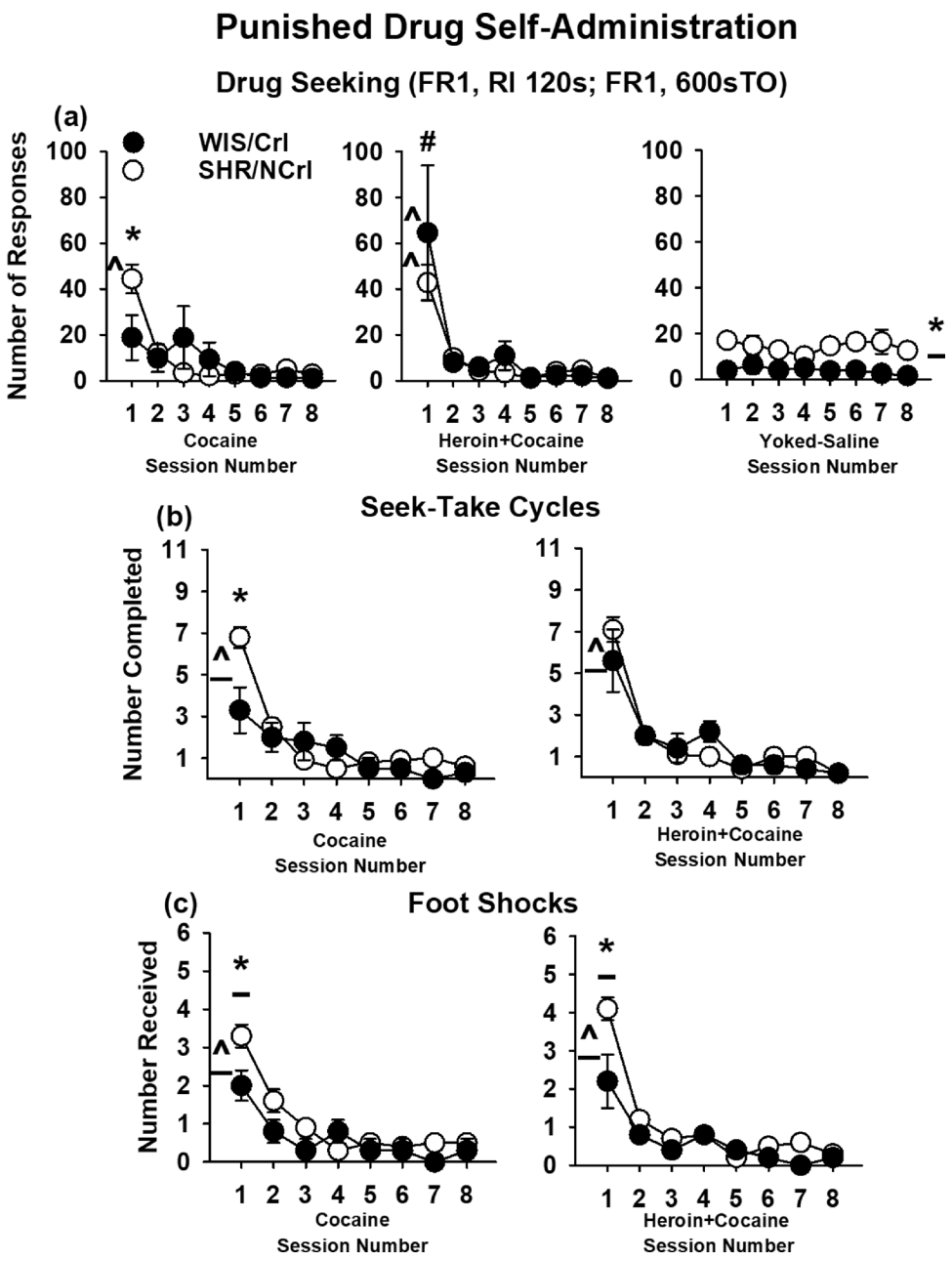

Fig. 3 Punished drug self-administration performance in SHR/NCrl and WIS/Crl male rats under the FR1, RI 120-s; FR1, 600-s TO tandem schedule. Values are the mean ± SEM number of responses on the seeking lever (panel **a**), number of seek-take cycles completed (panel **b**), and number of foot shocks received (panel **c**) across the 8 daily sessions. In panel **a**, $^{*}p < 0.047$ comparing SHR/NCrl cocaine to WIS/Crl cocaine on session 1; $\underline{^{*}}p < 0.005$ comparing SHR/NCrl yoked-saline to WIS/Crl yoked-saline overall; $^{\wedge}p < 0.001$ comparing session 1 to sessions 2–8 in SHR/NCrl self-administering cocaine and heroin + cocaine and in WIS/Crl self-administering heroin + cocaine; and $^{\#}p < 0.002$ comparing heroin + cocaine to cocaine in WIS/Crl. In panel **b**, $^{*}p < 0.005$ comparing SHR/NCrl cocaine to WIS/Crl cocaine on session 1; $\underline{^{\wedge}}p < 0.001$ comparing session 1 to sessions 2–8 overall. In panel **c**, $\underline{^{*}}p < 0.001$ comparing SHR/NCrl to WIS/Crl on session 1 overall; and $\underline{^{\wedge}}p < 0.001$ comparing session 1 to sessions 2–8 overall

to determine significance among the factors. RM ANOVA revealed a significant main effect of session number ($F[3.3, 83] = 56.9$, $p < 0.001$) and a strain × session number interaction ($F[3.3, 83] = 4.8$, $p < 0.003$) for the number of cycles completed (Fig. 3b). There were no significant differences in the number of cycles completed based on drug history, as neither the drug main effect ($F[1, 25] = 1.0$, $p < 0.34$) nor the interactions of drug × strain ($F[1, 25] = 0.7$, $p < 0.42$) or drug × session number ($F[3.3, 83] = 1.8$, $p < 0.14$) were significant. Post hoc tests across sessions indicated that SHR/NCrl and WIS/Crl completed more cycles on session 1 than on sessions 2–8 ($p < 0.001$). Post hoc tests between strains indicated that SHR/NCrl completed more cycles than WIS/Crl on session 1 overall ($p < 0.001$). However, a strain difference was more apparent for cocaine than for heroin + cocaine, based on visual inspection of Fig. 3b and t test analysis ($t[11] = 3.5$, $p < 0.005$ for cocaine and $t[13] = 1.1$, $p < 0.28$ for heroin + cocaine).

Analysis of foot shock received during punished self-administration indicated that data were normally distributed (linear Q-Q plots) and that the variance among groups was homogeneous (non-significant Mauchly's tests of sphericity; $p < 0.19$). RM ANOVA revealed significant main effects of strain ($F[1, 25] = 18.1$, $p < 0.001$) and session number ($F[7, 175] = 45.5$, $p < 0.001$) and a strain × session number interaction ($F[7, 175] = 4.4$, $p < 0.001$) for the number of cycles

completed (Fig. 3c). There were no significant differences in the number of foot shocks received based on drug history, as neither the drug main effect ($F[1, 25] = 0.31$, $p < 0.58$) nor the interactions of drug × strain ($F[1, 25] = 0.004$, $p < 0.95$) or drug × session number ($F[7, 175] = 0.74$, $p < 0.64$) were significant. Post hoc tests across sessions indicated that SHR/NCrl and WIS/Crl received more foot shocks on session 1 than on sessions 2–8 ($p < 0.001$). Post hoc tests between strains indicated that SHR/NCrl received more foot shocks than WIS/Crl on session 1 ($p < 0.001$).

We did not compare within-subject performances between seeking responses at baseline and on session 1 of punishment in this study because of attrition of 1 rat in the SHR/NCrl cocaine group and of 2 rats in the WIS/Crl cocaine group (see attrition numbers in "Materials and methods"). Consequently, the analyses for Figs. 2 and 3 emphasized how the stains and drugs differed for each phase of training separately. The suppression ratios (Pelloux et al. 2007) for rats that completed both phase 2 and phase 3 of self-administration training are reported in Table S3 (Supplemental Results). These data coupled with the number of seeking lever responses and cycles completed during the punishment phase suggest a profile whereby the behavior observed at session 1 of punishment was meaningful. Consideration of these data support the view that SHR/NCrl rats with a cocaine history were insensitive initially to punishment relative to WIS/Crl rats with a cocaine history because the SHR/NCrl were more willing than the WIS/Crl to risk receiving foot shock in order to seek and complete cycles for the opportunity to take cocaine. In contrast, the SHR/NCrl and WIS/Crl rats with heroin + cocaine histories exhibited similar profiles during punishment (high rates of drug seeking and seek-take cycles completed on session 1). Both strains equally succumbed to the influence of ongoing punishment in that drug-seeking and drug-taking responses were suppressed, particularly on sessions 3–8 after exposure to a prolonged history of either cocaine or heroin + cocaine self-administration. Importantly, the strain differences in sensitivity to punishment for cocaine rats and the lack of strain differences in sensitivity to punishment for heroin + cocaine rats on session 1 argue that the control of behavior under these two drug conditions is not identical. Nonetheless, in rats trained to self-administer heroin + cocaine, there is concern that animals were being punished under the analgesic properties of heroin throughout the session, making it possible that differential responses observed here were simply due to a difference in the sensitivity to the analgesic properties of heroin and/or conditioned tolerance to these analgesic properties. Consideration of the average latencies to the first delivery of the session during the three self-administration training and testing phases reported in Tables S4 and S5 (Supplemental Results) helps to lessen this concern. In addition, it is likely that the 0.015 mg/kg unit dose of heroin combined with cocaine in the present study was not analgesic and did not produce tolerance or physical dependence, based in part on the results of past studies in rats that self-administered similar heroin unit doses prior to assessment of analgesia and physical withdrawal symptoms (Dai et al. 1989; De Vry et al. 1989).

Avoidance capacity

Analysis of avoidance accuracy during the operant avoidance task indicated that data were normally distributed (linear Q-Q plots), but that the variance among groups was not homogeneous (significant Mauchly's tests of sphericity; $p < 0.001$). The Greenhouse–Geisser correction was applied to determine significance among the factors. RM ANOVA revealed significant main effects of drug ($F[2, 38] = 4.8$, $p < 0.014$), session number ($F[2.5, 95] = 46.8$, $p < 0.001$), and strain ($F[1,38] = 7.7$, $p < 0.009$) as well as a strain × drug interaction ($F[2, 38] = 3.3$, $p < 0.048$) for avoidance accuracy (Fig. 4a). Post hoc tests showed that overall, avoidance accuracy was lower in SHR than in WIS ($p < 0.009$). This strain difference was related predominantly to the yoked-saline condition, as the strain × drug interaction indicated that avoidance accuracy was similar between SHR/NCrl and WIS/Crl with a cocaine ($p < 0.209$) and heroin + cocaine ($p < 0.991$) history, whereas avoidance accuracy was lower in SHR/NCrl than in WIS/Crl with a yoked-saline history ($p < 0.001$). Moreover, avoidance accuracy was higher in SHR/NCrl with cocaine and heroin + cocaine histories relative to yoked-saline ($ps < 0.009$ and 0.001, respectively), whereas avoidance accuracy was similar in WIS/Crl receiving cocaine or heroin + cocaine, relative to yoked-saline ($ps < 0.790$ and 0.989, respectively). This indicates that the capacity to avoid harm was lower in SHR/NCrl than in WIS/Crl with no history of drug use, but that a prolonged history of cocaine or heroin + cocaine self-administration abolished this pre-existing strain difference. Post hoc tests of the session number main effect indicated that, overall, avoidance accuracy was lower on session 1 compared to sessions 2–5 ($p < 0.001$) and on session 2 compared to sessions 3–5 ($p < 0.001$). This indicates that avoidance learning improved in all groups over sessions, as there were no significant interactions of session number with strain and/or drug.

An inverse profile was observed for the number of foot shocks received (Fig. 4b), a relationship supported by the highly significant inverse correlation between avoidance accuracy and number of escape foot shocks reported in the cocaine/yoked-saline matrix ($r = -0.966$, $p < 2.8 \times E-017$; Table S6, Supplementary Results) and the heroin + cocaine/yoked-saline matrix ($r = -0.966$, $p < 4.4 \times E-016$; Table S7, Supplementary Results). Analysis of number of foot shocks received during the operant avoidance task

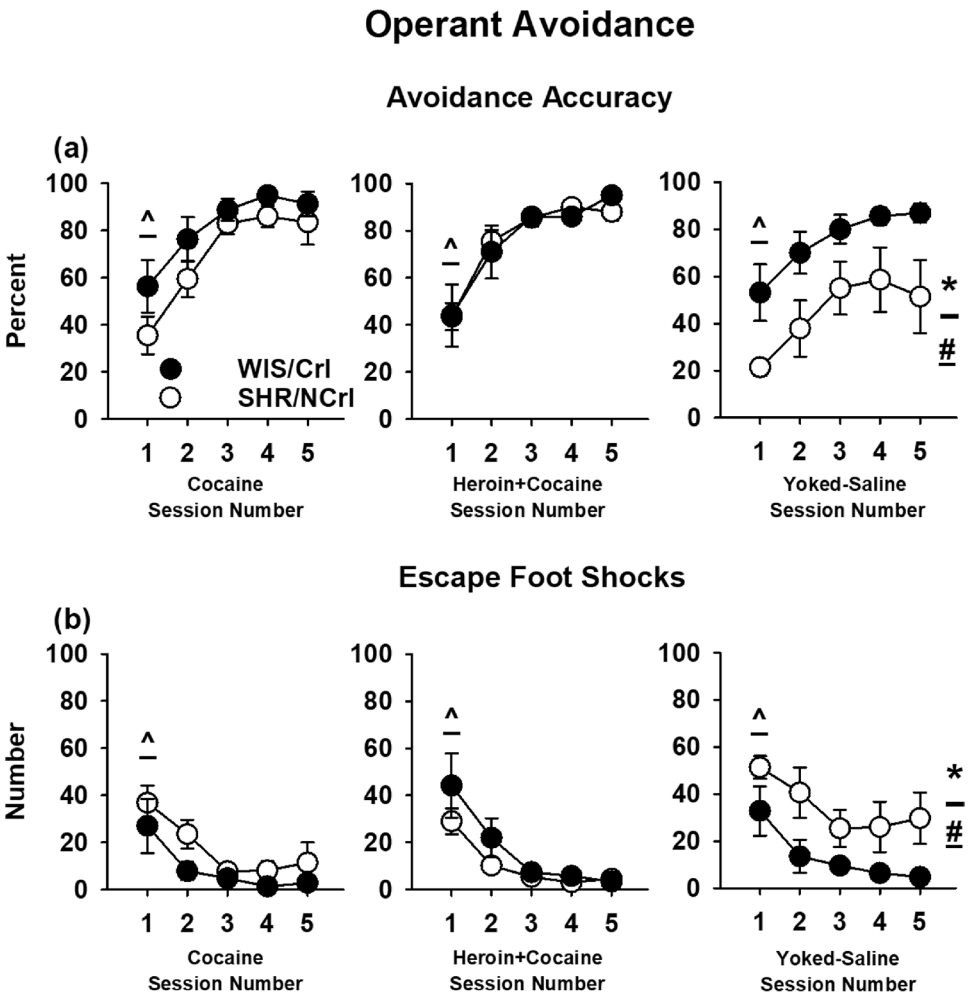

Fig. 4 Operant avoidance performance in SHR/NCrl and WIS/Crl male rats. Values are the mean ± SEM for percent avoidance accuracy (panel **a**) and number of escape foot shocks received (panel **b**) across the 5 daily sessions. In panel **a**, $\underline{*}p < 0.001$ comparing SHR/NCrl yoked-saline to WIS/Crl yoked-saline overall; $\underline{\hat{}}p < 0.001$ comparing session 1 to sessions 2–5 and comparing session 2 to sessions 3–5 overall; and $^{\#}p < 0.009$ and $p < 0.001$ comparing SHR/Crl cocaine and heroin + cocaine, respectively, to SHR/NCrl yoked-saline overall. In panel **b**, $\underline{*}p < 0.002$ comparing SHR/NCrl yoked-saline to WIS/Crl yoked-saline overall; $\underline{\hat{}}p < 0.001$ comparing session 1 to sessions 2–5 and comparing session 2 to sessions 3–5 overall; and $^{\#}p < 0.022$ and $p < 0.001$ comparing SHR/Crl cocaine and heroin + cocaine, respectively, to SHR/NCrl yoked-saline overall

indicated that data were normally distributed (linear Q-Q plots), but that the variance among groups was not homogeneous (significant Mauchly's tests of sphericity; $p < 0.001$). The Greenhouse–Geisser correction was applied to determine significance among the factors. RM ANOVA revealed significant main effects of drug ($F[2, 38] = 3.5$, $p < 0.042$) and session number ($F[2.1, 79] = 34.6$, $p < 0.001$) as well as a strain × drug interaction ($F[2,38] = 4.3$, $p < 0.021$). Post hoc tests of the strain × drug interaction indicated that the number of foot shocks received was similar between SHR/NCrl and WIS/Crl with a cocaine ($p < 0.238$) and heroin + cocaine ($p < 0.375$) history, whereas the number of foot shocks received was larger in SHR/NCrl than in WIS/Crl with a yoked-saline history ($p < 0.002$). Moreover, the number of foot shocks received was smaller in SHR/NCrl with cocaine and heroin + cocaine histories relative to yoked-saline ($ps < 0.022$ and 0.001, respectively), whereas the number of foot shocks received was similar in WIS/Crl with cocaine and heroin + cocaine histories relative to yoked-saline ($ps < 0.811$ and 0.896, respectively). Post hoc tests of the session number main effect indicated that, overall, there were more foot shocks received on session 1 compared to sessions 2–5 ($p < 0.001$) and on session 2 compared to sessions 3–5 ($p < 0.001$). The reduction in the number of foot shocks received across sessions supports the view that avoidance learning improved in all groups over sessions.

Predictors of avoidance capacity

The dependent measures used in the correlation analyses included trait impulsivity (DRL 30-s response efficiency averaged over the last 3 sessions), trait compulsivity (SIP averaged over the last 3 sessions), baseline drug taking (FR1 schedule averaged over the last 3 self-administration sessions), baseline drug seeking (tandem schedule averaged over the last 3 self-administration sessions), seek-take cycles completed during punished self-administration (session 1), and avoidance capacity (avoidance accuracy averaged over all 5 sessions). Among these variables, trait impulsivity in SHR/NCrl and WIS/Crl rats that subsequently

self-administered cocaine or received yoked-saline was the only significant predictor ($r = 0.375$, $p < 0.04$) of avoidance accuracy in the operant avoidance task (Fig. 5a). Of note, baseline drug taking in SHR/NCrl and WIS/Crl rats that had self-administered cocaine was not a significant predictor of avoidance accuracy ($r = -0.376$, $p < 0.19$). This supports hypothesis 1 that pre-existing level of inhibitory control is potentially an important factor for mediating the capacity to avoid harm, regardless of cocaine use history. In contrast, baseline drug taking was the only significant predictor ($r = 0.534$, $p < 0.04$) of avoidance accuracy in the operant avoidance task in SHR/NCrl and WIS/Crl that had self-administered heroin + cocaine (Fig. 5b). Of note, trait impulsivity in SHR/NCrl and WIS/Crl that subsequently self-administered heroin + cocaine or received yoked-saline was not a significant predictor of avoidance accuracy ($r = 0.300$, $p < 0.11$). This supports hypothesis 2 that heroin + cocaine use is potentially an important factor for mediating the capacity to avoid harm, regardless of pre-existing level of inhibitory control. These and other correlations that are depicted in Fig. 5a, b are discussed at length below.

Tables S6 and S7 (Supplemental Results) list the correlation coefficients for all dependent measures reported above for inhibitory control capacity, drug self-administration, and avoidance capacity.

Discussion

SHR/NCrl exhibit poor inhibitory control and heightened drug abuse liability

Animal models allow for tight control to discern the potential influence of pre-existing inhibitory control deficits and drug use history on subsequent impairments in the capacity to avoid aversive consequences. We confirmed that both impulsive action (DRL task) and compulsive-like behavior (SIP task) were characteristics of adult male SHR/NCrl (Sanabria and Killeen 2008; Ibias and Pellon 2011; Somkuwar et al. 2016). For the DRL 30-s wait time, which requires more inhibitory control than the DRL 5-s wait time for successful reward delivery, response efficiency was less than half and

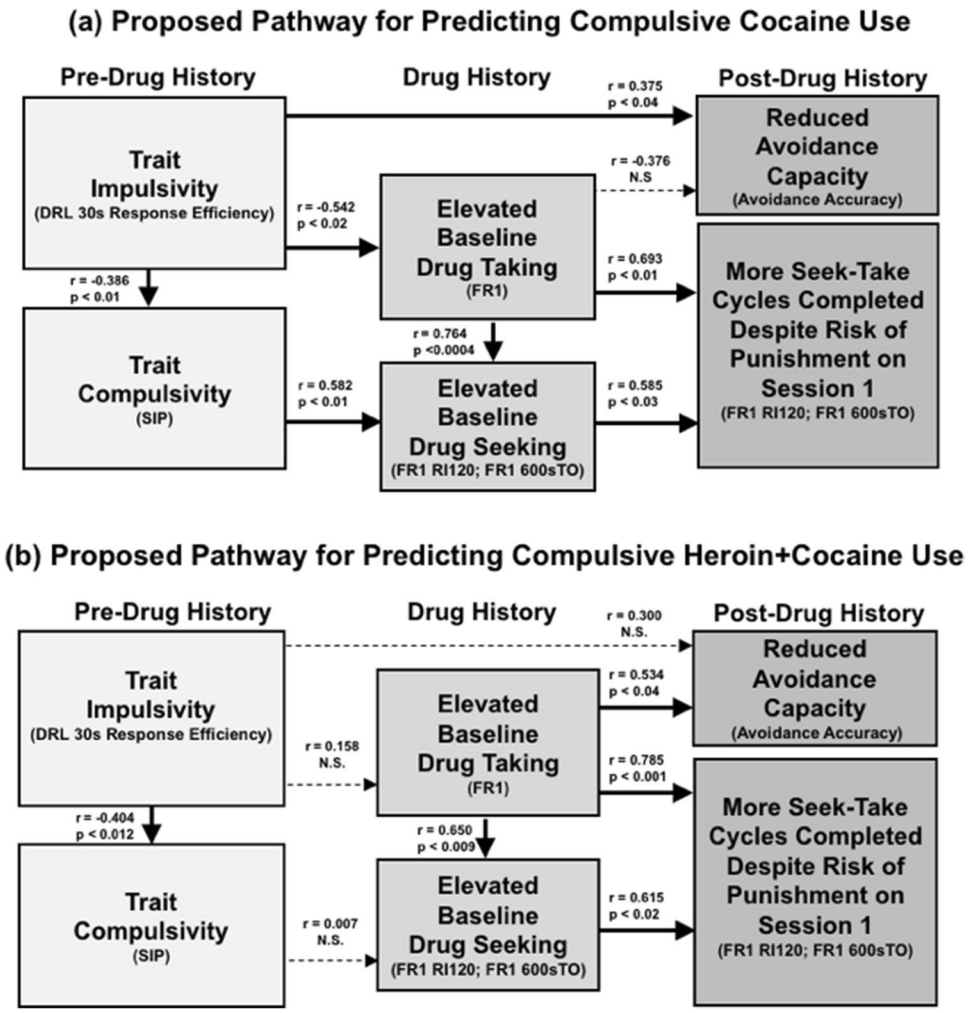

Fig. 5 Proposed pathways for predicting compulsive drug use are based on correlation analyses of selected dependent measures in SHR/NCrl and WIS/Crl receiving cocaine and yoked-saline (panel **a**) and heroin + cocaine and yoked-saline (panel **b**). Illustrated are correlations between pre-drug history measures (trait impulsivity and trait compulsivity), prolonged drug use history measures (baseline FR1 drug taking and baseline FR1, RI 120-s; FR1, 600-s TO drug seeking), and post-drug history measures (punished seek-take cycles on session 1 and avoidance accuracy in the operant avoidance task)

burst responding was double that of WIS/Crl, as was polydipsia in the SIP task. Notably, DRL 30-s performance correlated with SIP performance (see Fig. 5a, b, and Tables S6 and S7). This is not surprising given that impulsivity facilitates the development of compulsive behaviors, a transition likely controlled by the anterior insular cortex (Belin-Rauscent et al. 2016). Despite this, there was no overlap in what DRL 30-s and SIP performances predicted in SHR/NCrl and WIS/Crl. In cocaine and yoked-saline rats (Table S6), trait impulsivity but not trait compulsivity predicted poor avoidance capacity, with trait impulsivity also predicting drug taking and trait compulsivity predicting drug seeking. In heroin + cocaine and yoked-saline rats (Table S7), neither trait impulsivity nor trait compulsivity predicted poor avoidance capacity, drug seeking, or drug taking. Besides poor inhibitory control, SHR/NCrl also showed heightened drug self-administration behavior compared to WIS/Crl, as evidenced by strain differences in cocaine taking, cocaine seeking, and heroin + cocaine seeking. These findings add to the growing literature establishing greater abuse liability in SHR/NCrl for multiple drugs of abuse (Berger et al. 2010; Harvey et al. 2011; dela Pena et al. 2011; Somkuwar et al. 2013; Jordan et al. 2014; dela Pena et al. 2015; Jordan et al. 2016a; Jordan et al. 2016b; Miller et al., 2018).

Further consideration of the correlational analyses (Fig. 5a; Table S6) support the view that pre-existing impulsivity and compulsivity traits might potentially mediate different aspects of cocaine self-administration behavior (Dalley et al. 2011). A higher level of trait impulsivity (lower response efficiency) significantly predicted greater cocaine-taking responses at baseline, and a higher level of trait compulsivity (greater polydipsia) significantly predicted greater cocaine-seeking responses at baseline. However, neither measure of inhibitory control predicted baseline levels of heroin + cocaine taking and seeking (Fig. 5b; Table S7). These results support the possibility of a dissociable role of impulsivity on different aspects of cocaine vs. heroin self-administration, as previously reported in outbred rats. Specifically, Belin et al. (2008) reported that outbred rats with high levels of impulsive action escalated their cocaine self-administration to a greater degree than rats with low levels of impulsive action during long-access sessions. Economidou et al. (2009) reported that after long-access sessions and a second round of punished cocaine self-administration testing followed by a week of abstinence, outbred rats with high levels of impulsive action relapsed to cocaine seeking to a greater degree than rats with low levels of impulsive action. The distinct findings (prediction of greater cocaine-taking responses at baseline by impulsivity in the current study vs. prediction of greater compulsive cocaine use by impulsivity in prior studies) may relate to comparisons between inbred and outbred rats in the current study vs. comparisons exclusively within outbred rats in prior studies. Regarding heroin, McNamara et al. (2010) showed that impulsive action in high and low impulsive rats did not predict a greater tendency to self-administer heroin under an FR1 schedule, just like in the present study whereby impulsive action in high impulsive SHR/NCrl and low impulsive WIS/Crl did not predict a greater tendency to self-administer heroin + cocaine under an FR1 schedule. They additionally showed that escalation of heroin self-administration after 6-h long-access sessions and the propensity to reinstate heroin seeking following abstinence was not predicted by impulsive action. Schippers et al. (2012) examined rats with high and low impulsive choice to determine if this trait would impact acquisition of heroin self-administration (FR1–FR4 schedule), motivation to self-administer heroin (PR schedule), extinction of heroin self-administration, and reinstatement of heroin seeking following abstinence. They found that levels of impulsive choice did not predict any aspect of heroin taking or heroin seeking.

Another distinction we observed was a greater intake of cocaine and a similar intake of heroin + cocaine in SHR/NCrl relative to WIS/Crl under the FR1 drug-taking schedule. This difference appears to be related primarily to WIS/Crl self-administering twice as much heroin + cocaine than cocaine alone, with heroin + cocaine intake approaching levels measured in SHR/NCrl. Within the dose range of 0.18 to 0.38 mg/kg cocaine, an earlier report demonstrated that Sprague–Dawley rats, another outbred strain, self-administered more heroin + cocaine than cocaine alone under a FR1 choice procedure, with heroin + cocaine preference over cocaine alone disappearing when the Sprague–Dawley rats were tested under a more demanding progressive ratio schedule (Ward et al. 2005). The greater number of heroin + cocaine-seeking responses at baseline in SHR/NCrl than in WIS/Crl under the demanding tandem schedule in the current study is in line with this latter observation.

Compulsive drug use and avoidance capacity

Although elevated drug seeking and taking at baseline significantly predicted compulsive cocaine use (Fig. 5a; Table S6) and compulsive heroin + cocaine use (Fig. 5b; Table S7), there were differences in punished self-administration and operant avoidance tendencies that were related to rat strain and drug use history. Specifically, SHR/NCrl maintained cocaine seeking to a greater extent than WIS/Crl at the beginning of punishment testing, despite the risk of receiving foot shock instead of the opportunity for cocaine delivery (a type of passive avoidance deficit). During operant avoidance testing, the yoked-saline SHR/NCrl were less likely than the yoked-saline WIS/Crl to avoid foot shock (a type of active avoidance deficit). These findings confirm previous reports of a natural tendency for SHR/NCrl to exhibit both passive avoidance deficits (Knardahl and Karlsen 1984;

Gattu et al. 1997a, b; Kostyunina and Loskutova 2012; Grunblatt et al. 2015) and active avoidance deficits (Sutterer et al. 1980, 1981; Hecht et al. 1982; Goto et al. 1987; Kostyunina and Loskutova 2012) relative to WIS and other rat strains. Importantly, the strain difference in avoidance accuracy was not as evident in SHR/NCrl and WIS/Crl that had a history of cocaine or heroin + cocaine exposure, consistent with the ability of cocaine and morphine to improve active avoidance learning in rats (Satinder 1976; White et al. 1995). In contrast to cocaine-trained rats, both SHR/NCrl and WIS/Crl had relatively high levels of heroin + cocaine seeking at the beginning of punishment testing despite the risk of receiving foot shock instead of heroin + cocaine (a type of passive avoidance deficit), but had similar high accuracies for avoiding foot shock during operant avoidance testing (intact active avoidance). A small clinical literature provides tentative evidence for different profiles of fear acquisition and avoidance learning in cocaine-dependent (normal fear, deficient avoidance) and heroin-dependent (deficient fear, enhanced avoidance) adults who use drugs (Ersche et al. 2016; Basden et al. 2016; Sheynin et al. 2016), raising the potential translational importance of these drug group findings.

he strain and drug differences in compulsive drug use and avoidance capacity must be considered against potential strain differences in baseline sensitivity to punishing stimuli, given that a single punishing stimulus was used to measure compulsive drug use (0.55 mA foot shock) and avoidance capacity (1.0 mA foot shock). To begin, the response of SHR to foot shock is complex. One previous study reported that conditioned fear induced by foot shock training (1.5 mA) was lower in SHR compared to control strains (Ledoux et al. 1983), suggesting SHR have reduced baseline sensitivity to punishing stimuli. In the present study, reduced sensitivity to punishing stimuli in SHR/NCrl could potentially explain why yoked-saline SHR/NCrl had reduced avoidance accuracy compared to yoked-saline WIS/Crl and why SHR/NCrl made a greater number of cocaine-seeking responses despite punishment compared to WIS/Crl. However, this cannot explain why SHR/NCrl and WIS/Crl had a similar number of heroin + cocaine-seeking responses despite punishment. Another past study reported that behavioral reactivity (line crossings, rears, and jumps) to foot shock stress (2.5 mA) was greater in SHR/N compared to WIS/Crl (McCarty and Kopin, 1978) . In the present study, increased reactivity to punishing stimuli in SHR/NCrl could potentially explain why SHR/NCrl had a greater number of cocaine-seeking responses despite punishment compared to WIS/Crl but not why SHR/NCrl and WIS/Crl had similar avoidance accuracies. If SHR/NCrl were more reactive than WIS/Crl to foot shock during punished self-administration testing and operant avoidance testing, then SHR/NCrl might be expected to engage in greater lever pressing than WIS/Crl during both tests, which was not the case (Fig. 3a vs. Figure 4a). Importantly, cocaine and heroin + cocaine self-administration attenuated this strain difference in avoidance capacity. Consistent with this idea, previous research demonstrated that 15 mg/kg cocaine can reduce conditioned fear induced by 0.15 mA foot shock training in male Sprague–Dawley rats (Morrow et al. 1995). Inconsistent with this idea are findings showing that 0.03 mg/kg heroin can increase conditioned fear induced by 0.8 mA foot shock training (Leri et al. 2013). Collectively, it appears that any potential baseline differences in sensitivity to punishing stimuli cannot account for the present pattern of stain and drug history differences in compulsive drug use and avoidance capacity.

It remains possible that the correlation between impulsivity and avoidance capacity in rats with a history of cocaine self-administration and yoked-saline exposure could be driven by the third hidden trait not explored in the present investigation, given that SHR/NCrl receiving yoked-saline had pre-existing deficits in both measures. As cocaine self-administration produces a range of executive function deficits (Kantak 2020), several of which also are exhibited by SHR/NCrl (Kantak et al. 2008; Harvey et al. 2013; Jordan et al. 2016b), it is possible that one or more unexplored cognitive traits could have mediated the association we observed between high impulsivity and low avoidance capacity following cocaine self-administration and yoked-saline exposure.

Another concern for interpreting these findings is the small sample sizes for WIS/Crl receiving cocaine ($n = 4$) and heroin + cocaine ($n = 5$) during tests for punished self-administration and operant avoidance, which questions the reliability of any strain differences found in these behavioral measures. For rats self-administering cocaine, strain differences in punished self-administration occurred only on session 1 (of 8 sessions) and there were no strain differences during the 5 sessions of the operant avoidance task. For rats self-administering heroin + cocaine, there were no strain differences in punished self-administration across the 8 sessions and no strain differences across the 5 sessions of the operant avoidance task. Thus, for the most part, there were no strain differences for these two tests in rats with a cocaine and heroin + cocaine history. A concern for the reliability of the strain difference on day 1 of punished cocaine self-administration is lessened by the low variability observed in both WIS/Crl and SHR/NCrl (left panels in Fig. 3) despite the small sample size in the former strain and the large sample size in the latter strain.

Lastly, as both compulsive drug use and low avoidance accuracy reflect a reduced capacity to avoid harm, there is an expectation that compulsive cocaine use or compulsive heroin + cocaine use would negatively correlate with avoidance accuracy in the operant avoidance task. However, we did not observe a significant negative correlation between avoidance

accuracy and compulsive cocaine use (Table S1) or between avoidance accuracy and compulsive heroin + cocaine use (Table S2), and there may be several reasons for this. One possibility, as discussed above, may relate to the fact that the operant avoidance task measures active avoidance (emitting responses) and that the punished cocaine self-administration task measures passive avoidance (withholding responses). SHR/NCrl self-administering cocaine were less likely than WIS/Crl to avoid punishment. In the operant avoidance task, SHR/NCrl previously exposed to cocaine were equally likely as WIS/Crl to avoid punishment. In contrast, SHR/NCrl self-administering heroin + cocaine were equally likely as WIS/Crl to avoid punishment in both tasks. Thus, in cocaine-trained rats and in heroin + cocaine-trained rats, there was no inverse relationship between the passive avoidance behavior and the active avoidance behavior that would be a necessary condition to find a negative correlation between compulsive cocaine use and avoidance accuracy. In support, past studies in inbred mouse strains demonstrated that the correlation between active and passive avoidance behavior was low, with performance on one task not consistently predicting performance on the other task (Sprott and Stavnes 1974) . There also is evidence that active and passive avoidance behaviors in rats are uncorrelated as well (Myhrer, 1975), unless these behaviors represented are different facets of the same task (Vicens-Costa et al. 2011). We had selected an operant avoidance task (the active avoidance learning procedure) to measure harm avoidance capacity in rats because of its translational value. That is, an operant avoidance task was used successfully in a previous human laboratory study to establish that insensitivity to aversive consequences was associated with impulsivity but not drug use in cocaine users (Ersche et al. 2016). As our planned human laboratory studies in heroin and cocaine polysubstance and monosubstance users will utilize an operant avoidance task, it was important that we provided as many complementary features into the animal model to enhance translation. In retrospect, a passive avoidance learning procedure in rats might have been optimal for correlating harm avoidance capacity with the punished drug self-administration, given that this latter task in rats involves passive avoidance learning.

Proposed pathways for predicting compulsive drug use

Our findings suggest that there might be distinct etiologies for compulsive use of cocaine vs. heroin + cocaine. Trait impulsivity, which predicted reduced avoidance capacity in cocaine and yoked-saline exposed groups, also was associated with increased likelihood of greater cocaine intake at baseline that in turn increased the likelihood of rats making more risky cocaine-seeking choices to complete a greater number of cycles despite the risk of punishment on session 1. Greater risky cocaine-seeking choices are considered a behavioral marker of compulsive cocaine use (Pelloux et al. 2007; Economidou et al. 2009; Belin et al. 2011; Xue et al. 2012). Our findings in rats are consistent with past observations in experimental animals for whom the development of compulsive cocaine use (the number of seek-take cycles completed during the punishment phase) was observed in rats with high pre-existing levels of impulsivity (Belin et al. 2008; Economidou et al. 2009) and high pre-punishment levels of cocaine intake (Pelloux et al. 2007; Jonkman et al. 2012; Everitt et al. 2018). Based on the correlation analysis of the current study (Fig. 5a), we can extend this model to propose that trait impulsivity might directly reduce the capacity to avoid harm, and in situations when cocaine use is initiated, high impulsivity can trigger the kind of cocaine intake that gives rise to the development of compulsive cocaine use, an outcome also reflective of a reduced capacity to avoid harm. This model agrees with past observations in cocaine-dependent individuals in whom high levels of impulsivity (but neither compulsivity nor addiction to cocaine) predicted attenuated responding in a shock avoidance task (Ersche et al. 2016) and cocaine use severity (Moeller et al. 2001). Such agreement supports the construct validity and translational relevance of our preclinical approach to this clinical problem.

In contrast, predictive power of trait impulsivity for reduced avoidance capacity was eliminated in the correlation analysis of heroin + cocaine and yoked-saline exposed groups (Fig. 5b). This is likely due to the fact that rats with higher (SHR/NCrl) and lower (WIS/Crl) levels of impulsivity performed similarly in the operant avoidance task, as discussed above. Importantly, greater heroin + cocaine intake at baseline was strongly associated with a greater number of cycles completed during punished self-administration despite the risk of foot shock, suggesting that risky behavior during active heroin + cocaine self-administration might be due to the level of drug use and unrelated to any pre-existing deficits in inhibitory control. The lack of significant associations between impulsivity and baseline heroin + cocaine taking and between impulsivity and baseline heroin + cocaine seeking (Fig. 5b) suggest that these inhibitory control traits might not mediate the development of compulsive heroin + cocaine use as they might for the development of compulsive cocaine use. The only human laboratory study concerning correlations between heroin + cocaine use and risky behavior was one reported by Verdejo-Garcia and Perez-Garcia (2007) in which the authors hypothesized that the severity of primarily cocaine use and heroin + cocaine use would be associated with poorer performance in the Iowa gambling task (a task of risky decision-making). The authors reported that this correlation was not significant for either drug use profile. This inconsistency between rat and human findings may be related to the type of punisher used

(monetary loss in the Iowa gambling task in people vs. foot shock in the operant avoidance and self-administration tasks in rats). As reviewed above, Ersche et al. (2016) reported that high levels of impulsivity (but neither compulsivity nor addiction to cocaine) predicted attenuated responding in a shock avoidance task in people, consistent with our findings in rats self-administering cocaine and receiving yoked-saline. Complementary human laboratory studies are needed in heroin + cocaine polysubstance users, given our animal model revealed that there might be distinct etiologies for compulsive use of cocaine and heroin + cocaine.

Limitations

This study has some limitations. First, only male rats were evaluated, and secondly, a heroin alone self-administration drug group was not evaluated. There were logistical difficulties in running sufficient numbers of male and female SHR/NCrl and WIS/Crl in a longitudinal deep phenotyping study involving three drug groups plus a yoked-saline control due to the COVID-19-related laboratory closure that impacted the time and resources available to complete this study. Thus, the preclinical study was limited to males in order to facilitate comparisons with previous studies, which by and large employed males only, and to the heroin + cocaine and cocaine drug groups plus a yoked-saline control, which allowed evaluation of polysubstance drug use against a well-characterized monosubstance drug use condition. We fully acknowledge the importance of assessing both sexes and the effects of a heroin alone condition, and these aspects of the experimental design are incorporated into transition from the R21 animal phase to the R33 human subject phase of this project. A third limitation is that discerning the role of inhibitory control deficits vs. drug use history in mediating insensitivity to aversive consequences in rats with a prolonged history of cocaine and heroin + cocaine self-administration was based only on correlation analysis. Accordingly, the *potential* contribution of these factors was emphasized throughout. Although a causal relationship still needs to be established, the correlational outcomes emanating from this animal model will be useful for the design of our cross-sectional human laboratory experiments that seek to determine the nature and predictors of impaired harm avoidance in polysubstance and monosubstance users, specifically as they relate to heroin and cocaine use.

Conclusions

The human literature hypothesizes a feedforward cycle (i.e., an interaction) between pre-existing levels of impulsivity and drug use history on subsequent insensitivity to aversive consequences (Goldstein and Volkow 2002; Ivanov et al. 2008; Lopez-Caneda et al. 2014; Ersche et al. 2016; Just et al. 2019). Using an animal model, we found a unique role for trait impulsivity in potentially mediating avoidance capacity in rats self-administering cocaine and a unique role for drug use history in potentially mediating avoidance capacity in rats self-administering heroin + cocaine. These relationships observed in rats encourage investigation of similar associations between specific neurocognitive measures of inhibitory control and clinical deficits in avoidance capacity in those with heroin and cocaine use disorders. Human neurocognitive investigations tend to focus on drug use characteristics (e.g., type, duration, or amount of use) rather than the harmful behaviors that accompany drug use (risk of blood-borne diseases, loss of relationships/family, arrest/imprisonment, overdose, and death). Further documentation of the association between neurocognitive deficits and risky behaviors in those with substance use disorder, with attention to potential differences between single and dual substance users, has the potential to identify new mechanistic targets for cognitive rehabilitation/cognitive enhancement (Nielsen et al. 2018). To further translation, we also are in the process of utilizing this animal model to discover drug vulnerability genes by means of forward genetic mapping in an F2 reduced complexity cross between closely related but phenotypically different substrains of SHR (Bryant et al. 2020; Kantak et al. 2021), given the heightened drug abuse liability and co-presence of other drug vulnerability traits in the SHR/NCrl substrain.

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Declarations

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