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HIGH TRAIT MOTOR IMPULSIVITY IS AN ANTECEDENT TO COCAINE-SEEKING BUT NOT OXYCODONE-SEEKING BEHAVIOR IN RODENTS

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by

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Dedication

To my ministry and family. These next few chapters are all for You.

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Relapse is a dynamic and essential barrier to abstinence in substance use disorders with behavioral endophenotypes (e.g. impulsivity) and exposure to environmental drug-associated cues along with complex neurobiology as precipitating factors. Impulsivity is expressed in different forms (e.g. motor impulsivity, impulsive choice) and is associated with both cocaine use disorder and opioid use disorder. Animal models of motor impulsivity and relapse vulnerability can be reasonably matched to provide valid translational approaches to help determine whether motor impulsivity is a factor leading to (i.e., trait) and/or resulting from abstinence from (i.e., state) drug use and relapse. We tested the hypotheses that abstinence from cocaine and oxycodone would have differential effects on trait motor impulsivity and drug-seeking behavior. We demonstrate that oxycodone- but not cocaine-abstinence altered trait motor impulsivity phenotypes. Additionally, motor impulsivity phenotypes predicted cocaine but not oxycodone drug-seeking. The findings presented here offer a glimpse into the complex relationship between trait and state motor impulsivity and drug-seeking behaviors during abstinence across classes of drugs of abuse.

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List of Abbreviations

SUD	Substance Use Disorder
CUD	Cocaine Use Disorder
OUD	Opioid Use Disorder
1-CSRT	One-Choice Serial Reaction Time
ITI	Intertrial Interval
HI	High Impulsive
LI	Low Impulsive
FA	Forced Abstinence
VITI	Variable ITI
FR	Fixed Ratio
mPFC	Medial Prefrontal Cortex
NAc	Nucleus Accumbens
VTA	Ventral Tegmental Area
NMDAR	N-methyl-D-aspartate Receptor

INTRODUCTION

The chronic, relapsing nature of substance use disorders (SUDs) presents one of the greatest pervasive health concerns in the United States, with cocaine use disorder (CUD) having no FDA-approved medication to date, and opioid use disorder (OUD) being declared a public health emergency (Califf et al., 2016). In 2017, the number of deaths linked to cocaine overdose increased dramatically in part due to the opioid overdose crisis (McCall Jones et al., 2017), which was precipitated by prescription opioid (e.g., oxycodone) misuse and abuse (National Center for Health Statistics; Center for Disease Control). While treatment can decrease morbidity and mortality associated with these disorders, only ~11% of those who needed treatment received care in 2017, with cost and inaccessibility cited as primary barriers (SAMHSA, 2018). Currently, treatment for CUD mainly involves cognitive behavioral therapy (Volkow, 2011). Pharmacological therapies are available for OUD (e.g. methadone, naltrexone, buprenorphine) that are used to manage withdrawal symptoms and abstinence maintenance; however, these therapies often encounter problems of compliance (Comer et al., 2010). Behavioral therapies begin to address abstinence maintenance for both OUD and CUD, but are limited in effectiveness to deter relapse and often do not address specific phases of the cycle of SUD (for reference, see Volkow and Boyle, 2018). Thus, the impact of drug abuse and dependence on the quality of health and society is massive, and the lack of useful therapeutic medications is considered an unaddressed gap that poses major challenges in the treatment of SUD (Hendershot et al., 2011; Volkow and Skolnick, 2012).

Relapse, in particular, is a dynamic process and an essential barrier to abstinence in SUDs with a culmination of factors precipitating it, such as behavioral endophenotypes and exposure to environmental cues previously associated with the drug-taking experience working alongside a complex neurobiology. One of the attributing behavioral

endophenotypes is impulsivity (Sanchez-Roige et al., 2019), a complex, multifaceted personality trait, generally defined as action without sufficient foresight and without regard to the negative consequences (Evenden, 1999; Moeller et al., 2001a). It is expressed in many different forms; the inability to withhold a response (i.e., motor impulsivity, impulsive action, rapid-response impulsivity) (Hamilton et al., 2015a), a lack of reflection on potential consequences , or aversion to a delayed reward (i.e., impulsive choice, delay discounting) (Hamilton et al., 2015b). Impulsivity is most likely both an antecedent and consequence of drug use and abstinence (for review, see Fineberg et al., 2014; Moeller et al., 2001b) and its roles as a vulnerability factor exhibits roughly equivalent overall predictive power in CUD and OUD (Loree et al., 2015; Stevens et al., 2014). Cocaine-dependent individuals present with high levels of impulsivity (Moeller et al., 2004; Moeller et al., 2002; Moeller et al., 2001b) and impulsivity positively correlates with dropout rates in clinical trials (Moeller et al., 2001a; Moeller et al., 2001b; Patkar et al., 2004). Acute intoxication from opioids does not affect impulsivity in healthy volunteers but for those who have a history of use and dependence, active intake of the highly misused prescription opioid oxycodone appears to increase levels of impulsivity (Baldacchino et al., 2015; Zacny and de Wit, 2009). While impulsivity does not appear to affect treatment outcomes in OUD, it is evident in active opioid intake and abstinence (Jones et al., 2016; Schippers et al., 2012; Verdejo-Garcia et al., 2008; Winstanley, 2011). Additionally, some studies suggest that abstinence from opioids may even decrease impulsivity over longer periods of abstinence (Li et al., 2012; Lou et al., 2012).

Reactivity to cues associated with the drug-taking experience (e.g. pipes, certain people, specific locations) is an additional relapse-like vulnerability factor associated with CUD (Anastasio et al., 2014b; Bauer and Kranzler, 1994; Cunningham and Anastasio, 2014; Sinha et al., 2003) and OUD (Back et al., 2014; Li et al., 2012; Liu et al., 2011; Lou et al., 2012; McHugh et al., 2014; Sell et al., 2000) where even subliminal presentation of drug-associated cues activates motivational neurocircuity (Wetherill et al., 2014). Further,

cue reactivity, a valuable clinical tool used to measure the effectiveness of therapies for SUDs (MacKillop and de Wit, 2012), is impacted by abstinence in a time-dependent manner (Li et al., 2012; Lou et al., 2012), associates with relapse (Back et al., 2010; Marissen et al., 2006), and is linked to impulsive behaviors (Coskunpinar and Cyders, 2013; Leung et al., 2017). Importantly, the propensity for drug-associated cues to trigger relapse-like behavior in animals (i.e., drug-seeking behavior, Kalivas and McFarland, 2003) correlates to inherent levels of motor impulsivity that differ among individuals, or trait motor impulsivity, (Anastasio et al., 2014b), presenting the possibility of trait motor impulsivity as a behavioral endophenotype of relapse vulnerability.

Preclinical assays of motor impulsivity and drug-seeking are reasonably matched to provide valid translational research outcomes, although few studies employ such tasks to address questions concerning the relationship between trait/state motor impulsivity and drug-seeking behaviors associated with extended abstinence from cocaine- or opioid-taking. While much research explores the relationship between SUD relapse-like behaviors and impulsivity in humans (Moeller et al., 2001a; Moeller et al., 2004; Moeller et al., 2002; Moeller et al., 2001b; Patkar et al., 2004) and laboratory animals (Anastasio et al., 2014b; Belin et al., 2008; Dalley et al., 2007), there remain gaps in knowledge for the role of trait (i.e., prior to exposure to drug) versus state (i.e., consequence of drug intake and abstinence) impulsivity in relationship to cocaine- or oxycodone-seeking behaviors. Using modified rodent behavioral tasks, this study addressed the impact of abstinence from cocaine or oxycodone self-administration on trait motor impulsivity and the link between trait motor impulsivity and drug-seeking behaviors.

First, we tested the hypothesis that abstinence from cocaine would induce a state of increased motor impulsivity in rats that are inherently more impulsive which would translate into increased relapse-like vulnerability, measured by drug-seeking behavior reinforced by cues previously associated with cocaine-taking (Anastasio et al., 2014b). Next, we tested the hypothesis that abstinence from oxycodone would induce an increased

state of motor impulsivity in both high and low inherent impulsive rats, but this increase in motor impulsivity would not influence drug-seeking behavior reinforced by cues previously associated with oxycodone-taking (Schippers et al., 2012). Overall, we propose that trait motor impulsivity plays a differential role in relapse vulnerability between these two classes of substances of abuse.

MATERIALS AND METHODS

ANIMALS

Male, outbred Sprague-Dawley rats (n=104; Envigo, Indianapolis, IN) weighing 250-275 grams upon arrival were pair-housed under a 12-hour light-dark cycle at a constant temperature (21-23^{o}C) and humidity (40-50%). Animals were acclimated to the colony room for seven days prior to the start of experiments. While training in the one-choice serial reaction time (1-CSRT) task, rats were food restricted and weighed daily with body weight maintained at 90% of free-feeding and water available *ad libitum* except during daily operant sessions. During cocaine and oxycodone self-administration and drug-seeking assays, food and water were available *ad libitum*. All experiments were carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals (2011) and with the University of Texas Medical Branch Institutional Animal Care and Use Committee approval.

DRUGS

(-)-Cocaine (National Institute on Drug Abuse Drug Supply Program, Bethesda, MD) and oxycodone hydrochloride (Millipore Sigma, St. Louis, MO) were dissolved in 0.9% NaCl.

MOTOR IMPULSIVITY ASSAY

One-choice serial reaction time (1-CSRT) task procedures took place in standard five-hole nosepoke operant chambers (Med Associates, Fairfax, VT) contained within a ventilated and sound-attenuating chamber. Each chamber is fitted with a houselight, a food tray, and an external pellet dispenser capable of delivering 45 mg pellets (Dustless Precision pellets, Bio-Serv, Frenchtown, NJ). The 1-CSRT task methodology is previously

described in detail (Anastasio et al., 2013; Anastasio et al., 2011; Anastasio et al., 2014b; Anastasio et al., 2019; Cunningham et al., 2013; Davis-Reyes et al., 2019; Fink et al., 2015; Sholler et al., 2019). Briefly, training began with pre-training stages in which rats were habituated to the test chamber and introduced to nosepoke responding for food pellets. During the first pre-training stage, all responses made in the correctly-lit, baited, center hole ("target") in a 30-minute period resulted in the illumination of the food tray light and presentation of a single food pellet. In the second pre-training stage, the number of correct responses were limited to 100 in a maximum of 30 minutes. Subsequent training stages involved lowering the stimulus duration with a limited hold of 5 seconds and an intertrial interval (ITI) of 5 seconds. The final stage of training and the stage in which rats were maintained had a 5-second limited hold, a 5-second ITI, and a 0.5-second stimulus duration. During maintenance, a maximum of 100 correct responses in a session resulted in a maximum of 100 reinforcers earned; incorrect, premature responses or omissions resulted in a 5-s time out period and a reduction in potential reinforcers earned.

The total number of responses (correct, incorrect, omissions, and premature) as well as the latency to the first response made and the time to finish the task were recorded. Rats were required to meet an acquisition criteria of a minimum of 50 correct responses, >80% accuracy [correct responses/(correct + incorrect) × 100], and <20% omissions (omitted responses/trials completed × 100) to move from one training stage to the next. Premature responses (total premature responses = target premature responses + non-target premature responses; "non-target" indicates premature response detected outside of the center nose poke hole) are the primary indication of motor impulsivity for identification of high (HI) or low (LI) impulsive phenotypes (Anastasio et al., 2014b; Anastasio et al., 2019; Davis-Reyes et al., 2019; Fink et al., 2015; Sholler et al., 2019). The number of reinforcers earned provides a measure of task competency as well as a secondary measure for motor impulsivity (Anastasio et al., 2014b; Anastasio et al., 2019; Davis-Reyes et al., 2019; Fink et al., 2015; Sholler et al., 2019). Accuracy (given as a percentage) is a general indication

of attentional capacity while omissions (given as a percentage) indicate the level of motivation to perform the task (Anastasio et al., 2014b; Anastasio et al., 2019; Davis-Reyes et al., 2019; Fink et al., 2015; Sholler et al., 2019).

After meeting stability criteria for the final training stage over three consecutive ITI5 sessions (with <20% variability), an ITI8 challenge session was conducted in which the ITI was 8-s for the entirety of the session (Anastasio et al., 2014b; Anastasio et al., 2019; Davis-Reyes et al., 2019; Fink et al., 2015; Sholler et al., 2019). Two separate cohorts of outbred rats were trained on the 1-CSRT task training (see experimental timeline, **Figure 1**) and, within each cohort (Cohort 1 N=48; Cohort 2 N=56), LI (N=10-11/cohort) and HI (N=12/cohort) were stratified as the top and bottom 33% (tertile split) of rats based upon premature responses on the ITI8 challenge session. Tertile splits were determined based on necessity for power analyses and utilization of this stratification method did not change the validity of the phenotypes nor the consistency of the 1-CSRT task output parameters across cohorts.

Following acquisition and maintenance of drug self-administration (see below for methodology and experimental timeline, **Figure 1**), rats were placed into a period of 30 days of forced abstinence (FA) from cocaine or oxycodone but were subjected to daily 1-CSRT task sessions (5-second limited hold, 5-second ITI, 0.5-second stimulus duration). During this time, neither drug nor drug-related cues were delivered to the rats. On FA Day 15 and FA Day 25, rats were subjected to a variable ITI (VITI) challenge session in which the intertrial interval varied from 2-8 seconds in random order to verify the reliability of responding in the 1-CSRT task (data not shown) (Dalley et al., 2002b). On FA Day 10 and FA Day 20, rats were subjected to an ITI8 challenge session to assess the impact of abstinence on trait motor impulsivity; the ITI8 session demands extra attentional effort to maintain inhibitory control and is used to more easily identify motor impulsivity phenotypes (Anastasio et al., 2014b; Anastasio et al., 2019; Besson et al., 2013; Dalley et al., 2002a; Davis-Reyes et al., 2019; Fink et al., 2015; Sholler et al., 2019).

DRUG SELF-ADMINISTRATION ASSAY

Following training in the 1-CSRT task (see experimental timeline, **Figure 1**), rats were anesthetized with a cocktail containing xylazine (8.6 mg/kg), acepromazine (1.5 mg/kg), and ketamine (43 mg/kg) in sterile saline (delivered intramuscular) prior to surgical implantation of indwelling catheters into the right jugular vein and attached to a cannula which exited dorsally (Anastasio et al., 2014a; Anastasio et al., 2014b; Cunningham et al., 2013; Cunningham et al., 2011; Neelakantan et al., 2017; Sholler et al., 2019). Rats received a 0.1 mL infusion of heparinized saline (10 U/mL; American Pharmaceutical Partners, East Schaumburg, IL), streptokinase (0.67 mg/mL; Millipore Sigma, St. Louis, MO), and ticarcillin disodium (66.67 mg/mL; Research Products International, Mt. Prospect, IL) into the catheter daily during surgical recovery and immediately following each drug self-administration session to ensure catheter patency throughout the duration of the studies; self-administration training began following a 7-day surgical recovery period (Anastasio et al., 2014a; Anastasio et al., 2014b; Cunningham et al., 2013; Cunningham et al., 2011; Neelakantan et al., 2017; Sholler et al., 2019).

Self-administration took place in standard operant chambers contained within a ventilated and sound-attenuated chamber (Med Associates, Fairfax, VT). Each chamber was equipped with two retractable levers, a stimulus light above each lever, and a houselight opposite the levers. Drug infusions were delivered through syringes that were loaded daily into infusion pumps (Med Associates, Inc.) located outside of the cubicles. The infusion pumps were connected to liquid swivels (Instech, Plymouth Meeting, PA) fastened to catheters via polyethylene 20 tubing encased inside a metal spring leash (Plastics One, Roanoke, VA).

Cocaine (Cohort 1, n=48) or oxycodone (Cohort 2, n=48) self-administration training consisted of daily 180-min sessions. During these sessions, rats were trained to self-administer intravenous (i.v.) cocaine (0.75 mg/kg/infusion) or oxycodone (0.1

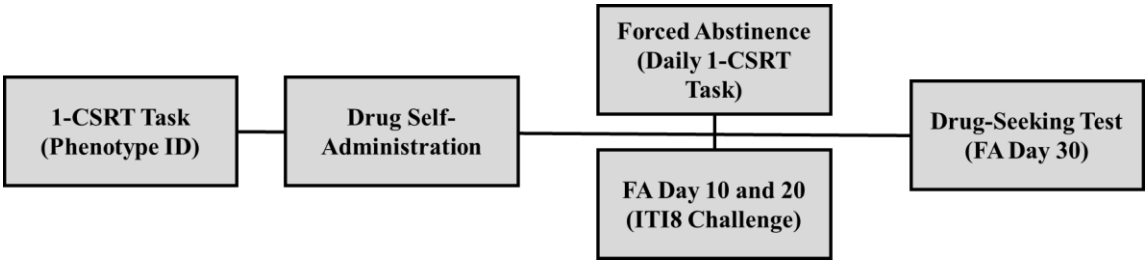
mg/kg/infusion) on a fixed ratio (FR) schedule of reinforcement. Scheduled responses on the active lever resulted in delivery of a drug infusion over a 6-sec period; each infusion was simultaneously paired with the illumination of the house and stimulus lights and activation of the infusion pump (i.e., discrete cue complex paired with drug delivery). Inactive lever presses were recorded but had no scheduled consequences. The stimulus light and infusion pump were inactivated following delivery of drug. The house light remained on to signal a timeout period (20 sec); lever presses committed during the timeout period had no scheduled consequences. Cocaine-trained rats were trained on a FR1 schedule of reinforcement and progressed to a FR5 schedule after achieving seven infusions/hr with <10% variability for three consecutive days (Anastasio et al., 2014a; Anastasio et al., 2014b; Cunningham et al., 2013; Cunningham et al., 2011; Sholler et al., 2019). Oxycodone-trained rats were trained on a FR1 schedule of reinforcement followed by a FR3 schedule and then progressed to a FR5 schedule after receiving five infusions/hr with <10% variability for three consecutive days (Neelakantan et al., 2017). Self-administration training consisted of 14 daily sessions for cocaine and 20-21 daily sessions for oxycodone. Once stable drug self-administration was acquired and maintained, rats were subjected to a 30-day period of FA during which self-administration training was terminated and daily 1-CSRT task training was reinitiated (see above for methodology and experimental timeline, **Figure 1**).

DRUG-SEEKING BEHAVIOR ASSAY

On FA Day 30, immediately following the daily 1-CSRT task, rats were reintroduced to the self-administration chambers and assayed in a drug-seeking test session comprised of two sequential components (see experimental timeline, **Figure 1**) (Anastasio et al., 2014a). The first part determined whether cocaine-abstinent or oxycodone-abstinent HI and LI rats would differentially respond to the drug-paired context in the absence of the discrete cue complex. During this 10-min session, responses on either the previously active

lever or inactive lever on an FR1 schedule of reinforcement were recorded with no scheduled consequence and no discrete cues delivered (e.g. stimulus light illumination, pump sounds) to assess the contextual reinforcement aspect of the test. Immediately after this initial 10-min session, the second component was initiated by the delivery of a single, non-response contingent, discrete cue complex (e.g., stimulus light illumination, pump sounds) and cue-reinforced drug-seeking behavior was assessed. During this 60-min cue-reinforced session, lever pressing on the previously active lever followed a FR1 schedule of reinforcement with responses reinforced by the discrete cue complex that was previously associated with delivery of either cocaine or oxycodone; inactive lever presses were recorded but produced no scheduled consequences (Anastasio et al., 2014a).

Figure 1. Schematic of Experimental Design



Rats were stratified as either high or low motor impulsive using the 1-CSRT task. Following phenotype identification, rats underwent jugular catheter implantation surgery and allowed to recover. Rats were then trained to self-administer either cocaine (Cohort 1) or oxycodone (Cohort 2) to stability. After acquiring and maintaining self-administration, rats were placed into forced abstinence (FA) for 30 days, during which daily 1-CSRT task training was re-initiated. Rats were subjected to 1-CSRT task ITI8 challenge sessions on FA Day 10 and FA Day 20. On FA Day 30, immediately following the daily 1-CSRT task session, drug-seeking behaviors were measured.

DATA AND STATISTICAL ANALYSES

Student's t-test was employed to analyze outcome measures of 1-CSRT task performance between phenotypes within each cohort and to analyze each outcome measure from the 1-CSRT task performance between cohorts (GraphPad Prism 7, La Jolla, CA). A

two-way repeated measure analysis of variance (ANOVA) with the factors of phenotype and training session and Sidak's correction for multiple comparisons was used for the comparison of HI and LI rats in the maintenance of drug self-administration (GraphPad Prism 7). Student's t-test was used to analyze total drug intake via self-administration between phenotypes (GraphPad Prism 7). A mixed model ANOVA with the within-subject factor of day and between-subject factor of phenotype was used to analyze outcome measures of 1-CSRT task performance between HI and LI rats during abstinence from drug self-administration (IBM SPSS Statistics, Version 23.0. Armonk, NY). A one-way ANOVA with a Sidak's multiple comparisons correction was employed to determine the effect of abstinence from drug on 1-CSRT task measures versus pre-drug performance (i.e., baseline) within phenotype (GraphPad Prism 7). Student's t-test was used to analyze previously active lever presses and inactive lever presses during the context-induced and cue-reinforced drug-seeking tests between HI and LI rats (GraphPad Prism 7). From Cohort 1, 15 rats were excluded from the final data analyses due to not meeting stable 1-CSRT task performance and/or catheter patency lost during the self-administration phase. From Cohort 2, 26 rats were excluded from the final data analyses due to not meeting stable 1-CSRT task performance and/or catheter patency lost during the self-administration phase. Significance was measured using $\alpha = 0.05$

RESULTS

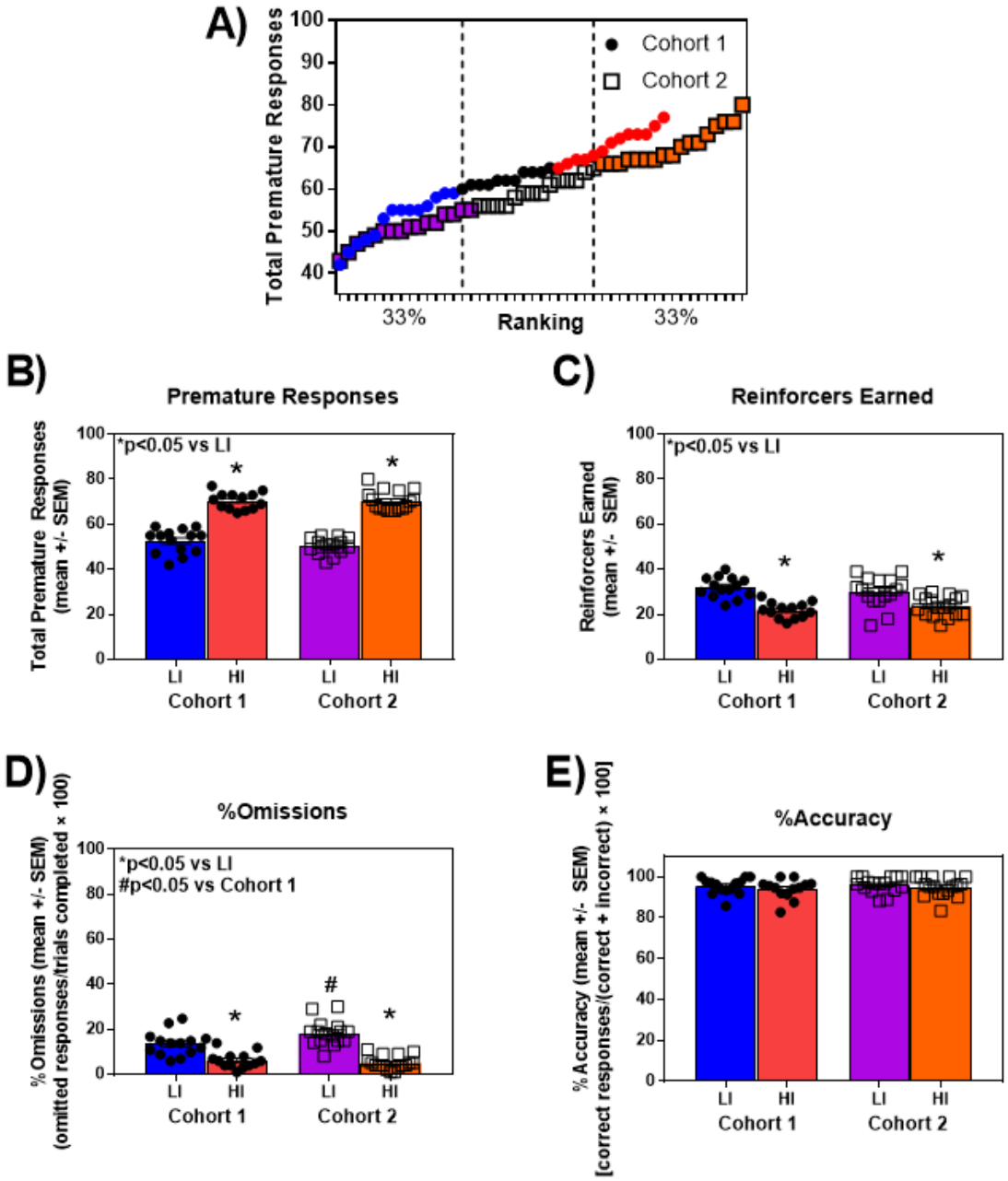
TRAIT MOTOR IMPULSIVITY PHENOTYPES ARE IDENTIFIABLE IN THE 1-CSRT TASK.

Figure 2 illustrates the premature responses, reinforcers earned, percent omissions, and percent accuracy on the 1-CSRT task ITI8 challenge for both cohorts of HI and LI rats utilized in this study. Male, outbred, Sprague-Dawley rats [Cohort 1 (n=48) and Cohort 2 (n=56)] were identified as HI or LI (n=13-17/phenotype/cohort) using a tertile split based upon rank ordering of total premature responses (**Figure 2A**). Within each cohort, HI and LI rats differed on levels of premature responses (Cohort 1: t_{25}=9.92, p<0.05; Cohort 2: t_{31}=14.54, p<0.05; **Figure 2B**), reinforcers earned (Cohort 1: t_{25}=6.6, p<0.05; Cohort 2: t_{31}=3.32, p<0.05; **Figure 2C**), and percent omissions (Cohort 1: t_{25}=4.22, p<0.05; Cohort 2: t_{31}=8.57, p<0.05; **Figure 2D**), but not percent accuracy (Cohort 1: t_{25}=0.84, n.s.; Cohort 2: t_{31}=0.74, n.s.; **Figure 2E**), as previously reported (Anastasio et al., 2013; Anastasio et al., 2011; Anastasio et al., 2014b; Anastasio et al., 2019; Cunningham et al., 2013; Davis-Reyes et al., 2019; Fink et al., 2015; Sholler et al., 2019). By nature of the task and response contingencies, HI rats completed the task faster than LI rats within each cohort (Cohort 1: LI=1229.5 ± 24.3 sec, HI=1124.4 ± 13.3 sec, t_{25}=4.75, p<0.05; Cohort 2: LI=1260.8 ± 20.4 sec, HI=1124.8 ± 9.7 sec, t_{31}=8.42, p<0.05). No difference between phenotypes within cohorts on the latency to first response was detected (Cohort 1: LI=1.00 ± 0.30 sec, HI=1.33 ± 0.36 sec, t_{25}=0.94, n.s.; Cohort 2: LI=1.21 ± 0.16 sec, HI=0.93 ± 0.21 sec, t_{31}=1.20, n.s.).

LI rats between cohorts did not differ on levels of premature responses (t_{28}=1.34, n.s; **Figure 2B**) or reinforcers earned (t_{28}=0.95, n.s; **Figure 2C**), did differ on percent omissions (t_{28}=2.29, p<0.05; **Figure 2D**), but did not differ on percent accuracy (t_{28}=0.48, n.s; **Figure 2E**), time to finish (t_{28}=0.48, n.s.) or latency to first response (t_{28}=1.35, n.s). The difference in percent omissions for LI rats between cohorts is below task criteria of <20% and did not influence the reliability of the identification of the phenotype. HI rats

between cohorts did not differ on levels of premature responses (t_{28}=0.15, n.s; **Figure 2B**), reinforcers earned (t_{28}=1.13, n.s; **Figure 2C**), percent omissions (t_{28}=0.94, n.s; **Figure 2D**), or percent accuracy (t_{28}=0.60, n.s; **Figure 2E**), time to finish (t_{28}=0.32, n.s.) or latency to first response (t_{28}=0.77, n.s.).

Figure 2. Stratification of Trait Motor Impulsivity in Outbred Rat Population Defined by Premature Responses, Reinforcers Earned, and Percent Omissions, but not Percent Accuracy



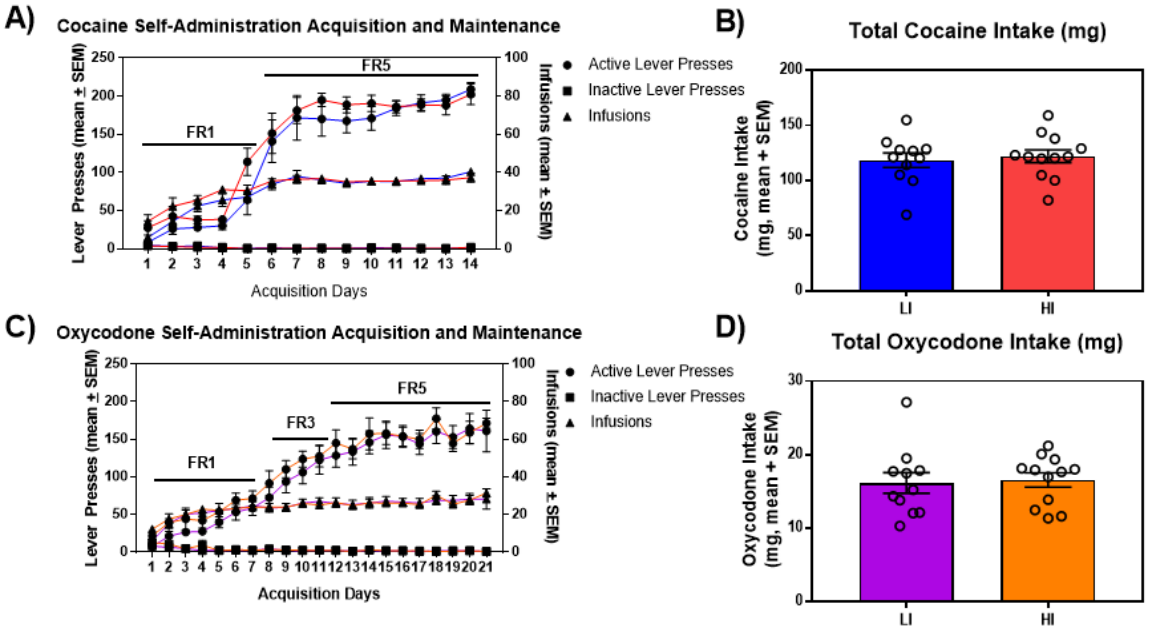
(A) Ordinal ranking of rats in Cohort 1 (circles) and Cohort 2 (squares) based on total premature responses on the ITI8 challenge session. The upper (Cohort 1, red; Cohort 2, orange) and lower tertile (Cohort 1, blue; Cohort 2, purple) of premature responders were identified as high (HI) and low (LI) impulsive, respectively. HI rats made (B) more premature responses (C) fewer reinforcers earned and (D) fewer percent omissions versus LI rats [(omitted responses/trials completed) x 100]. (E) No difference in percent accuracy

was observed between phenotypes [correct responses/ (correct + incorrect) x 100]. *p<0.05 vs LI rats; #p<0.05 vs Cohort 1.

TRAIT MOTOR IMPULSIVITY LEVELS DO NOT INFLUENCE COCAINE OR OXYCODONE SELF-ADMINISTRATION

Cohort 1 (LI N=11, HI N=12) and Cohort 2 (LI N=10, HI N=12) rats were employed to test the hypothesis that trait motor impulsivity is an antecedent to cocaine or oxycodone relapse-like behaviors in rodents. Following phenotype identification in the 1-CSRT task, Cohort 1 HI and LI rats were trained to self-administer cocaine to stability (**Figure 3A**). No differences between HI and LI rats in the acquisition and/or maintenance of cocaine self-administration were detected, as previously reported (Anastasio et al., 2014b). Across the last three training days, there was no main effect of phenotype ($F_{1,21}$=0.50, n.s.), a main effect of session ($F_{2,42}$=5.44, p<0.05) but no phenotype x session interaction ($F_{2,42}$=0.86, n.s.) for the total number of cocaine infusions (**Figure 3A**). Sidak's multiple comparison test indicated LI rats took ~three more infusions on Day 14 versus Days 12 and 13; however, this difference is less than the criteria for stability of <10% variability across days. Total cocaine intake for the entire self-administration phase did not differ between phenotypes (HI=122.0 ± 5.85 mg; LI=118.5 ± 6.62 mg; t_{21}=0.40, n.s., **Figure 3B**). Following phenotype identification in the 1-CSRT task, Cohort 2 HI and LI rats were trained to self-administer oxycodone to stability (**Figure 3C**) (Neelakantan et al., 2017). No differences between HI and LI rats in the acquisition and/or maintenance of oxycodone self-administration were detected. Across the last three training days, there was no main effect of phenotype ($F_{1,20}$=0.00, n.s.), session ($F_{2,40}$=2.68, n.s.) or a phenotype x session interaction ($F_{2,40}$=2.58, n.s.) for the total number of oxycodone infusions (**Figure 3C**). Total oxycodone intake for the entire self-administration phase did not differ between phenotypes (HI=16.56 ± 0.97 mg; LI=16.15 ± 1.40 mg; t_{21}= 0.24, n.s., **Figure 3D**).

Figure 3. Trait Motor Impulsivity does not Impact Acquisition of Cocaine or Oxycodone Self-Administration



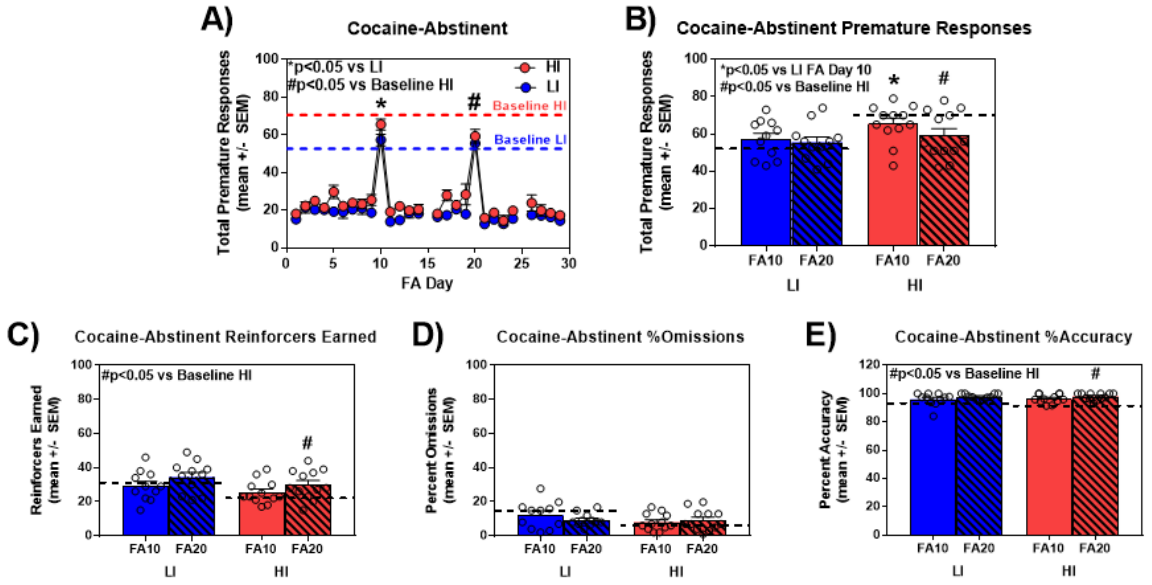
HI and LI rats did not differ in cocaine (A, B) or oxycodone (C, D) self-administration. (A, C) Average lever presses (circles), infusions (triangles), inactive lever presses (squares) in daily self-administration acquisition and maintenance training sessions are presented. Total drug intake (mg) for cocaine (B) or oxycodone (D) between phenotypes is presented.

DYNAMIC STATE OF ABSTINENCE FROM OXYCODONE, BUT NOT COCAINE SELF-ADMINISTRATION IMPACTS HIGH AND LOW TRAIT MOTOR IMPULSIVITY

Following stable cocaine or oxycodone self-administration, Cohort 1 and Cohort 2 rats were subjected to a period of forced abstinence from drug but during which daily 1-CSRT task sessions were re-initiated to test the hypothesis that the state of abstinence would influence the trait of motor impulsivity. **Figure 4A** demonstrates premature responses on the 1-CSRT task made by both HI and LI rats in FA from cocaine self-administration. The dashed line indicates the level of premature responding in cocaine-abstinent HI and LI rats prior to cocaine self-administration, i.e. "baseline" performance (**Figure 4A**). On FA Day 10 and FA Day 20, rats were subjected to an ITI8 challenge session. There was a main effect of phenotype ($F_{1,21}$=13.13, p<0.05), no main effect of day

($F_{2,42}$=2.05, n.s.), but a phenotype x day interaction ($F_{2,42}$=4.66, p<0.05) for premature responses (**Figure 4B**). Planned comparisons revealed that premature responses for cocaine-abstinent LI rats did not differ between baseline, FA Day10, and FA Day 20 (n.s., **Figure 4B**). Planned comparisons revealed that premature responses for cocaine-abstinent HI rats did not differ between baseline and FA Day 10 but were lower on FA Day 20 versus baseline ($F_{2,33}$=4.12, **Figure 4B**). Premature responses on FA Day 10 were higher in cocaine-abstinent HI versus cocaine-abstinent LI rats (t_{21}=1.92, p<0.05); no difference between phenotypes in premature responses on FA Day 20 was detected (t_{21}=0.79, n.s.).

Figure 4. Cocaine-Abstinent HI Rats Maintain High Impulsivity versus Cocaine-Abstinent LI Rats



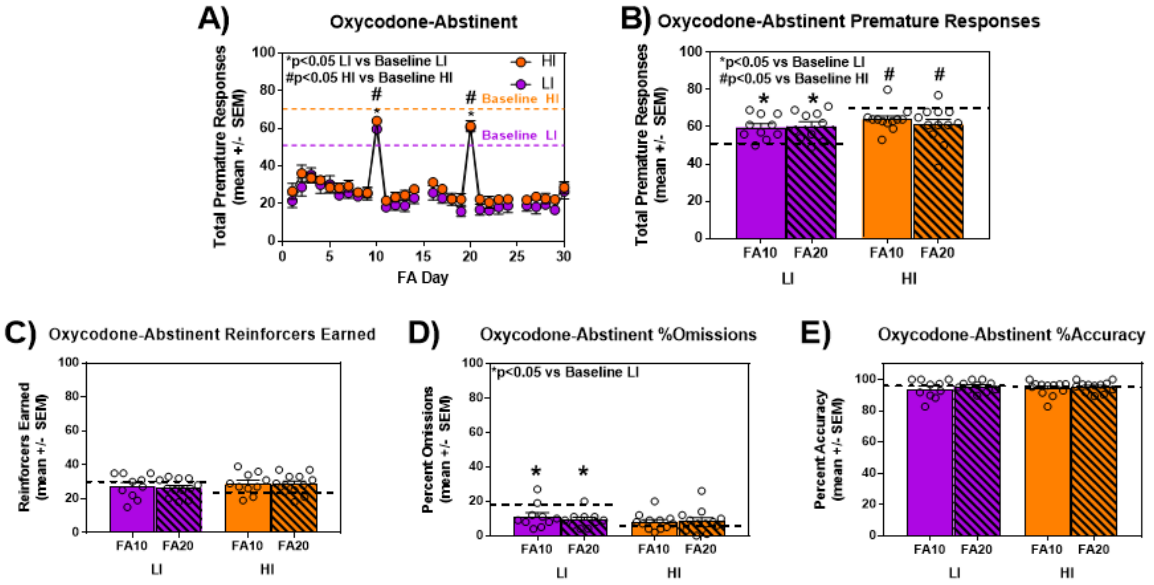
(A) Total premature responses were measured during daily 1-CSRT task maintenance in the cocaine abstinence period. (A,B) HI rats (red circles) have higher premature responses during ITI8 challenges on FA Day 10 but not FA Day 20 versus LI rats (blue circles). LI rats did not differ from their baseline performances (dashed line). HI rats had lower premature responses on FA Day 20 versus baseline. No differences were detected between HI rats and LI rats on (C) reinforcers earned, (D) percent omissions, or (E) percent accuracy on FA Days 10 and 20, but HI rats had more reinforcers earned and greater accuracy on FA Day 20 versus baseline. *p<0.05 vs cocaine-abstinent LI rats; #p<0.05 vs baseline.

For reinforcers earned in cocaine-abstinent rats, there was a main effect of phenotype ($F_{1,21}$=6.71; p<0.05), a main effect of day ($F_{2,42}$=6.28; p<0.05), but no phenotype x day interaction ($F_{2,42}$=1.41, n.s.; **Figure 4C**). Planned comparisons revealed that reinforcers earned for cocaine-abstinent HI rats did not differ between baseline and FA Day 10 but were higher on FA Day 20 versus baseline ($F_{2,33}$=4.59, **Figure 4C**). Reinforcers earned on FA Day 10 (t_{21}=1.16, n.s.) and FA Day 20 (t_{21}=1.16, n.s.) were not different between cocaine-abstinent HI and LI rats. There was a main effect of phenotype ($F_{1,21}$=7.63, p<0.05), no main effect of day ($F_{2,42}$=0.34, n.s.), but a phenotype x day interaction ($F_{2,42}$=3.85, p<0.05; **Figure 4D**) for percent omissions. Further analysis did not show differences between cocaine-abstinent HI and LI rats on percent omissions. For accuracy, there was no main effect of phenotype ($F_{1,21}$=0.02, n.s.), a main effect of day ($F_{2,42}$=7.29, p<0.05), and no phenotype x day interaction ($F_{2,42}$=0.38, n.s.; **Figure 4E**). Abstinence from cocaine did not alter latency to the first response on FA Day 10 (LI=1.18 ± 0.38 sec, HI=0.83 ± 0.27 sec) or FA Day 20 (LI=1.18 ± 0.54 sec, HI=0.58 ± 0.23 sec) versus baseline performance (LI=1.00 ± 0.30 sec, HI=1.33 ± 0.36 sec); there was no main effect of phenotype ($F_{1,21}$=0.48, n.s.), no main effect of day ($F_{2,42}$=0.32, n.s.), and no phenotype x day interaction ($F_{2,42}$=0.92, n.s.). Abstinence from cocaine did not alter time to finish the task on FA Day 10 (LI=1258.9 ± 77.9, HI=1241.9 ± 95.1 sec) or FA Day 20 (LI=1190.8 ± 15.9, HI=1227.5 ± 55.9) versus baseline performance (LI=1229.5 ± 24.3 sec, HI= 1124.4 ± 13.3.8 sec); there was no main effect of phenotype ($F_{1,21}$=0.38, n.s.), no main effect of day ($F_{2,42}$=0.80, n.s.), and no phenotype x day interaction ($F_{2,42}$=0.76, n.s.) for time to finish task.

Figure 5A demonstrates premature responses on the 1-CSRT task made by both HI and LI rats in FA from oxycodone self-administration. The dashed line shows the level of premature responding in oxycodone-abstinent HI and LI rats prior to oxycodone self-administration, i.e. “baseline” performance (**Figure 5A**). On FA Day 10 and FA Day 20, rats were subjected to an ITI8 challenge session. There was a main effect of phenotype

($F_{1,20}$=17.07, p<0.05), no main effect of day ($F_{2,40}$= 0.25, n.s.), but a phenotype x day interaction ($F_{2,40}$=14.37, p<0.05) for premature responses (**Figure 5B**). Planned comparisons revealed that premature responses for oxycodone-abstinent LI rats were higher on both FA Day10 and FA Day 20 versus baseline ($F_{2,27}$=7.31, p<0.05; **Figure 5B**). Planned comparisons revealed that premature responses for oxycodone-abstinent HI rats were lower on both FA Day 10 and FA Day 20 versus baseline ($F_{2,33}$=4.96, **Figure 5B**). No difference in premature responses on FA Day 10 (t_{20}=1.624, n.s.) or FA Day 20 (t_{20}=0.22, n.s.) between oxycodone-abstinent HI and LI rats was detected.

Figure 5. Oxycodone-Abstinent HI and LI Rats do not Maintain Original Trait Motor Impulsivity Phenotyping



(A) Total premature responses were measured during daily 1-CSRT task maintenance in the oxycodone abstinence period. (A, B) Premature responding during ITI8 challenges on FA Days 10 and 20 did not differ between HI (orange circles) and LI rats (purple circles). LI rats had higher premature responses while HI rats had lower premature responses on both FA Day 10 and 20. There were no overall differences between HI rats and LI rats on (C) reinforcers earned, (D) percent omissions, or (E) percent accuracy. LI rats had lower omissions compared to baseline on FA Days 10 and 20. *p<0.05 vs baseline LI; #p<0.05 vs baseline HI.

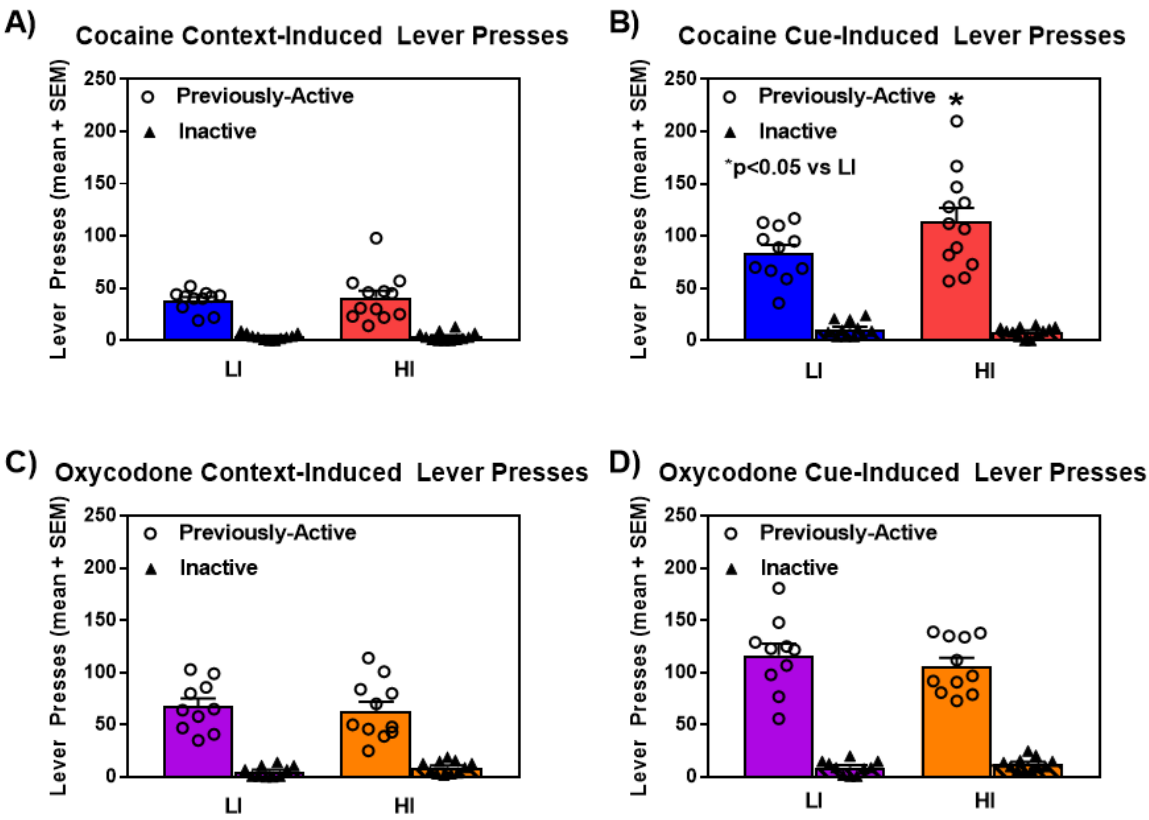
For reinforcers earned in oxycodone-abstinent rats, there was no main effect of phenotype ($F_{1,20}$=3.43, n.s.), no main effect of day ($F_{2,40}$=0.90, n.s.), and no phenotype x day interaction ($F_{2,40}$=1.87, n.s.; **Figure 5C**). There was a main effect of phenotype ($F_{1,20}$=12.5, p<0.05), no main effect of day ($F_{2,40}$=1.68, n.s.), but a phenotype x day interaction ($F_{2,40}$=8.37, p<0.05; **Figure 5D**) for percent omissions. Planned comparisons showed that percent omissions for oxycodone abstinent LI rats were lower than baseline on both FA Day 10 and FA Day 20 ($F_{2,27}$=6.00, p<0.05; **Figure 5D**). There was no main effect of phenotype ($F_{1,20}$=0.01, n.s.), no main effect of day ($F_{2,40}$=0.77, n.s.), and no phenotype x day interaction ($F_{2,40}$=0.09, n.s.; **Figure 5E**) for percent accuracy. Abstinence from oxycodone did not alter latency to the first response on FA Day 10 (LI=1.79 ± 0.72 sec, HI=1.72 ± 0.59 sec) or FA Day 20 (LI=1.68 ± 0.51 sec, HI=0.97 ± 0.37 sec) versus baseline performance (LI=1.21 ± 0.16 sec, HI=0.93 ± 0.21 sec); there was no main effect of phenotype ($F_{1,20}$=,0.83 n.s.), no main effect of day ($F_{2,40}$=1.12, n.s.), and no phenotype x day interaction ($F_{2,40}$=0.25, n.s.) for latency to first. Abstinence from oxycodone decreased LI time to finish the task on FA Day 10 (LI=1175.0 ± 16.1 sec) and FA Day 20 (LI=1177.1 ± 11.0 sec) versus baseline performance (LI=1260.8 ± 20.4 sec), but not HI rats on FA Day 10 (HI=1163 ± 9.9 sec) or FA Day 20 (HI=1166.4 ± 17.9 sec) versus baseline performance (HI=1124.8 ± 9.7 sec). There was a main effect of phenotype ($F_{1,20}$=14.42, p<0.05), no main effect of day ($F_{2,40}$=1.91, n.s.), but a phenotype x day interaction ($F_{2,40}$=14.89, p<0.05) for time to finish task.

TRAIT MOTOR IMPULSIVITY ASSOCIATES WITH COCAINE, BUT NOT OXYCODONE DRUG-SEEKING BEHAVIOR ON FA DAY 30

A two-component drug-seeking test was employed to test the hypothesis that trait motor impulsivity predicts cue-induced cocaine-seeking, but not oxycodone-seeking, behaviors following an extended period of abstinence. During the context-induced portion

of the test on FA Day 30, cocaine-abstinent HI rats did not differ from cocaine-abstinent LI rats in the number of previously active (t_{21}=0.38, n.s.) or inactive (t_{21}=0.07, n.s.;) lever presses made (**Figure 6A**). Following the delivery of a discrete, non-contingent cue, cocaine-abstinent HI rats displayed higher previously active lever presses that were reinforced by the discrete cue complex compared to cocaine-abstinent LI rats (t_{21}=1.9, p<0.05; **Figure 6B**). Inactive lever presses did not differ between cocaine-abstinent HI and LI rats during the cue-reinforced test session (t_{21}=1.02, n.s.; **Figure 6B**). Oxycodone-abstinent HI rats did not differ from oxycodone-abstinent LI rats in the number of previously active (t_{19}=0.36, n.s.) or inactive (t_{19}=1.57, n.s.;) lever presses made during the context-induced test session on FA Day 30 (**Figure 6C**). Following the delivery of a discrete, non-contingent cue, no differences in previously active (t_{19}=0.76, n.s.) or inactive (t_{19}=1.24, n.s.;) lever presses between oxycodone-abstinent HI and LI rats were detected during the cue-reinforced portion of the test (**Figure 6D**).

Figure 6. Trait Motor Impulsivity is Associated with Cue-Reinforced Cocaine- but Not Oxycodone-Seeking Behavior



(A) Context-induced drug-seeking is not different between cocaine-abstinent LI (blue) and HI (red) rats on FA Day 30. (B) Cocaine cue-reinforced drug-seeking is greater in cocaine-abstinent HI versus LI rats. (C) Context-induced drug-seeking is not different between oxycodone-abstinent LI (purple) and HI (orange) rats on FA Day 30. (D) Oxycodone cue-reinforced drug-seeking does not differ between oxycodone-abstinent HI and LI rats. *p<0.05 vs cocaine-abstinent LI rats.

DISCUSSION

We demonstrated identification and stratification of trait motor impulsivity using an outbred rat population, as previously reported (Anastasio et al., 2014b; Anastasio et al., 2019; Davis-Reyes et al., 2019; Fink et al., 2015; Sholler et al., 2019). There were no differences in performance on the 1-CSRT task between the Cohorts 1 and 2, allowing for confidence in the comparison of the two drug classes between phenotypes in this study. Trait motor impulsivity phenotypes did not exhibit differences in cocaine (Anastasio et al., 2014b; Belin et al., 2008; Economidou et al., 2009; but see Dalley et al., 2007) or oxycodone self-administration acquisition, maintenance or total drug intake. While cocaine-trained rats took a greater amount of cocaine in a shorter period of time than oxycodone-trained rats this is mostly likely due, in part, to the different criteria for stable self-administration between cocaine and oxycodone (Anastasio et al., 2014a; Anastasio et al., 2014b; Cunningham et al., 2013; Cunningham et al., 2011; Neelakantan et al., 2017; Sholler et al., 2019). Levels of motor impulsivity for cocaine-abstinent HI and LI rats did not differ from baseline performance except for cocaine-abstinent HI rats on FA Day 20. Conversely, abstinence from oxycodone shifted levels of motor impulsivity for both oxycodone-abstinent HI and LI rats. Finally, high inherent motor impulsivity was associated with higher cocaine cue-reinforced cocaine-seeking, but not oxycodone-seeking behavior.

Our data shows that higher trait motor impulsivity exists prior to and is not dramatically altered by the state of abstinence from cocaine self-administration (but see, Caprioli et al., 2013; Dalley et al., 2007; Economidou et al., 2009) but is impacted by the state of abstinence from oxycodone self-administration. Further, high cocaine-abstinent impulsive rats in extended abstinence may be more vulnerable to cocaine-associated discrete cues (also see Anastasio et al., 2014b) as opposed to oxycodone-associated discrete cues, similar to (Schippers et al., 2012). Interestingly, re-exposure to the drug-paired

context did not evoke differences between cocaine-abstinent or oxycodone-abstinent HI and LI rats, suggesting that context-induced drug memories, regardless of the drug of abuse, do not evoke drug-seeking behavior in a phenotype-specific manner. Trait motor impulsivity and the propensity to engage in relapse-like behaviors are intertwined in a cause-and-effect relationship. Preclinical studies report that high trait motor impulsivity predicts escalation of cocaine self-administration, compulsive cocaine-taking (Dalley et al., 2007), cocaine-seeking behavior following punishment-induced abstinence (Economidou et al., 2009) as well as cocaine-seeking following forced abstinence from cocaine self-administration (Anastasio et al., 2014b; Sholler et al., 2019). Conversely, trait motor impulsivity in rodents does not predict heroin self-administration or cue-induced heroin-seeking following abstinence (McNamara et al., 2010) and both high and low impulsive choice rats exhibit an escalation of heroin self-administration over time (McNamara et al., 2010; Schippers et al., 2012). Our dataset adds to the literature that high trait motor impulsivity predicts relapse vulnerability during extended abstinence in cocaine preclinical models and while motor impulsivity may develop during and following sustained, continued opioid abuse, trait levels of motor impulsivity per se do not predict the initiation of oxycodone use or vulnerability to opioid relapse-like behaviors in preclinical models.

We also discovered that trait motor impulsivity is differentially impacted by the state of abstinence from cocaine and oxycodone self-administration. Cocaine-abstinent rats maintained their original phenotyping (i.e. HI rats had higher premature responses versus LI rats on several days of abstinence.) Additionally, both cocaine-abstinent HI and LI rats did not differ significantly from baseline ITI8 performance with the exception of cocaine-abstinent HI rats on FA Day 20, similar to previous work in which over time, abstinence from cocaine decreases premature responding in the 5-CSRT task (Caprioli et al., 2013; Dalley et al., 2007; Economidou et al., 2009). However, oxycodone-abstinent rats did not maintain their original phenotyping and premature responses between HI rats and LI rats

were not different on any FA day. Interestingly, oxycodone-abstinent LI rats showed an increase from baseline premature responding, while oxycodone-abstinent HI rats showed a decrease in responding. These findings for both cocaine-abstinent and oxycodone-abstinent rats are unlikely the result of impaired attentional capacity, motivational properties, or general disturbances in motor behaviors as evident by a lack of significant effect on additional measures in the 1-CSRT task. While these data may appear inconsistent with previous findings in which abstinence from cocaine and heroin self-administration did not alter impulsivity on the 5-CSRT task (Dalley et al., 2005), levels of premature responding in this task can be at a "floor level" due to low working memory demands (Dalley et al., 2005; Hamilton et al., 2015a). Nonetheless, our findings support the hypothesis that pre-existing differences in impulsivity are an antecedent to cocaine-associated relapse-like behaviors that are also susceptible to the consequences of drug intake and abstinence. Further, we propose that the lack of association between trait motor impulsivity and opioid-seeking is most-likely related to transient changes in levels of motor impulsivity in the opioid-abstinent rats (Peters et al., 2013). Taken together, the predictive power of the motor impulsivity endophenotype for psychostimulant versus opioid relapse-like behaviors is dissociable and may be governed by distinct neural mechanisms.

Drug use and abstinence produce long-term effects on neurocircuitry (Kalivas and O'Brien, 2008; Koob and Bloom, 1988; Koob and Volkow, 2016) and synaptic plasticity (Shen and Kalivas, 2013; Ungless et al., 2001) which can lead to unique patterns of gene expression (for review, see Blum et al., 2017), possibly contributing to long-term neuroadaptations. A commonality across cocaine and opioids is the generation of rewarding effects via stimulation of dopamine mesolimbic efflux in SUD neurocircuitry [e.g. medial prefrontal cortex (mPFC), nucleus accumbens (NAc), ventral tegmental area (VTA)], (Di Chiara and Imperato, 1988) albeit through a distinct initial molecular target for cocaine versus opioid receptor agonists (Koob and Bloom, 1988; Koob and Volkow, 2016; Wise and Bozarth, 1987). The mPFC, a region integral to decision-making and goal-

directed behavior, is important for inhibitory control highlighted as dysfunctional in SUD (Bechara et al., 2001; Goldstein et al., 2007) and exerts top-down control over the NAc, primarily through glutamatergic neurotransmission (Ceglia et al., 2004; Moghaddam and Adams, 1998; Sesack et al., 1989; Verma and Moghaddam, 1996). Dysregulation of the corticoaccumbal glutamatergic system is recruited during both cocaine- and opioid-mediated behaviors assessed in preclinical studies (Bobadilla et al., 2017; Kalivas, 2009; Kalivas and Volkow, 2011; Peters et al., 2013; Pomierny-Chamiolo et al., 2014; Spencer et al., 2016). Bossert and colleagues argue that while there are differences between cocaine and opioid conditioned responding, the ventral mPFC, in particular, is a region of interest in drug-seeking and speculate that activation of the ventral mPFC to NAc serves to suppress, i.e. "off-switch", cocaine-seeking, but promote, i.e., "on-switch", heroin-seeking (Bossert et al., 2007; Bossert et al., 2011; Crombag et al., 2008; Peters et al., 2013). The mPFC is also recruited to regulate impulsivity (for review, see Dalley et al., 2011) and chemogenetic activation of the ventral mPFC to NAc circuit attenuates basal motor impulsivity (Anastasio et al., 2019). We recently discovered that high trait motor impulsivity is linked to an ionotropic glutamate N-methyl-D-aspartate receptor (NMDAR) subunit imbalance within the mPFC and the trafficking of these receptors may lead to a cortical excitatory synapse characteristic of synaptic destabilization (Davis-Reyes et al., 2019). Taken together, it is wholly feasible that trait motor impulsivity and cocaine-seeking are neurobiologically linked, such that dysfunctional glutamatergic signaling in the ventral mPFC may decrease excitatory output to the NAc to underlie sensitivity to discrete cues and promote drug-seeking behavior.

Further, phenotype-distinct neuroadaptations during abstinence from oxycodone versus cocaine may trigger the recruitment of additional substrates or brain regions beyond the ventral mPFC, or result in the reversal of its output to the NAc, to explain why drug-seeking behavior is similar between oxycodone-abstinent phenotypes, but elevated in

cocaine-abstinent high impulsive rats (but see, Bossert et al., 2007; Bossert et al., 2011; Crombag et al., 2008). Future studies are warranted to investigate this hypothesis.

In summary, this study identified how trait motor impulsivity is differentially related to drug-seeking in preclinical models of CUD and OUD. A comprehensive understanding of the behavioral manifestation and association of different endophenotypes such as motor impulsivity, the role of which in relapse vulnerability is incompletely understood, is necessary to significantly advance the prevention and treatment of CUD and OUD. The findings presented here offer a glimpse into the complex relationship between trait motor impulsivity and drug-seeking behaviors as well as the influence of the state of abstinence on these behaviors and lend support for the relevance of considering an individual's inherent level of motor impulsivity in the diagnosis and/or treatment of SUDs. The consideration of individual differences in motor impulsivity may one day provide more accurate and tailored diagnoses and/or treatment for patients during the different stages of the SUD cycle across drugs of abuse (e.g. abstinence, active use, anticipation) and may ultimately lead to therapies aimed at modifying trait or state levels of impulsivity which could lead to prevention of relapse and maintenance of abstinence.

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Publications

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Abstracts

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