DIFFERENTIAL BEHAVIORAL EFFECTS OF ABSTINENCE FROM COCAINE SELF-ADMINISTRATION IN CUED AND UNCUED DELAY-BASED DECISION MAKING TASKS

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ABSTRACT

Metika L. Ngbokoli: Differential behavioral effects of abstinence from cocaine self-administration in cued and uncued delay-based decision making tasks
(Under the direction of Regina M. Carelli)

Decision making is an important cognitive process that can become dysfunctional when exposed to drugs of abuse. Those who suffer from substance use disorders often have increased rates of impulsivity, including delay discounting, a type of impulsivity comprised of magnitude and delay. Studies show prior cocaine experience can elicit differential behavioral effects related to magnitude of reward, and in the presence of a discrete cue shifts behavior towards the optimal reward. Here, we developed and tested two tasks to determine if delay-based decision making is similarly influenced by discrete cues. In the cued task, animals with prior cocaine self-administration were faster to press for reward, while in the uncued task, this effect disappeared. However, cocaine history had no effect on free choice behavior in either task. These findings indicate the presence of a discrete cue influences latency to respond, but not free choice behavior, in a delay-based decision making task.

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Introduction

Decision making is an important cognitive process for human survival and can become maladaptive when exposed to drugs of abuse (Roesch et. al, 2007). According to the 2018 U.S. National Survey on Drug Use and Health, approximately 164.8 million people aged 12 and up had used an abused substance (such as tobacco, alcohol, or illicit drugs) in the past month, with approximately 977,000 of them categorized as having a cocaine use disorder. Research shows that those who suffer from substance use disorders (SUDs) exhibit deficits in working memory, cognitive flexibility, and increased impulsivity (Butler & Le Foll, 2019).

Impulsivity, or lack of inhibitory control, can be defined as performing an action prematurely without thorough analysis of potential consequences (Dalley, Everitt, & Robbins, 2011). Those suffering from SUDs tend to have increased rates of impulsive behavior; this increased impulsivity holds for several drugs of abuse including heroin, methamphetamine, ethanol, nicotine, and cocaine (Cheng, Lu, Han, González-Vallejo, & Sui, 2012; Coffey, Gudleski, Saladin, & Brady, 2003; Crews & Boettiger, 2009; Grabski et al., 2016; Hoffman et al., 2006). While there are a number of different ways in which one can measure impulsivity in humans and animal models, one task commonly used is delay discounting.

Delay discounting is a way of measuring one's ability to delay gratification. In delay discounting tasks, both time and magnitude are modulated such that the value of a reward decreases as the time to reward increases (Kirby & Petry, 2004). In other words, the task is designed to determine if one prefers a small, immediate reward or a larger, delayed reward. As the delay for the larger reward increases, the value of that reward in turn becomes "discounted".

As such, impulsive individuals tend to choose the immediate reward more often as the delay to the larger reward increases.

Notably, the same holds true for those who suffer from SUDs. That is, people with SUDs tend to have heightened delay discounting (i.e., more impulsivity) than those without the illness (Bickel, Koffarnus, Moody, & Wilson, 2014; Bjork, Hommer, Grant, & Danube, 2004; Coffey et al., 2003; Hoffman et al., 2006). Further, preclinical research has shown that drug naïve animals with higher rates of delay discounting acquire self-administration of drugs faster (Anker, Perry, Gliddon, & Carroll, 2009) and have greater reinstatement of drug taking after a period of abstinence (Broos, Diergaarde, Schoffelmeer, Pattij, & De Vries, 2012). In addition, some preclinical studies reported that a history of repeated administration of cocaine increases rates of delay discounting in rats (Hernandez et al., 2014; Mendez, Simon, Hart, Mitchell, & Nation, 2010; Mitchell et al., 2014; Roesch et al., 2007; Simon, Mendez, & Setlow, 2007). However, these findings have not always been replicated (Broos et al., 2012; Moschak & Carelli, 2017).

Additional preclinical studies have examined the effects of cocaine history on behavior related to discrete components of a delay discounting task, namely, magnitude- and/or delay-based decision making. Rats without a history of cocaine exposure typically prefer high value (large reward/short delay) over low value options (Burton et al., 2018; Dandy & Gatch, 2009; Day, Jones, & Carelli, 2011; Mendez et al., 2010). However, a history of cocaine can alter these preferences. For example, Saddoris and colleagues examined the effects of cocaine history on behavior during a magnitude choice task (Saddoris, Sugam, & Carelli, 2017). Here, rats learned that one lever was associated with a small reward (1 pellet) and the other with a larger reward (2 pellets). Once learned, rats then had free choice trials where both the 1-pellet and 2-pellet levers were simultaneously extended into the chamber, and presses on the lever delivered the associated

reward. The authors found that rats that had a history of cocaine self-administration were unable to discriminate between a large and small reward (preferred both equally). In contrast, controls preferred the large over the small reward.

Interestingly, the effects of cocaine history on behavior may be related, in part, to the presence of discrete cues in decision making tasks. For example, in a study performed by Roesch and colleagues (2007) the effects of a history of cocaine was examined on a delay task and a magnitude task. That is, in this experiment, rats were trained and subsequently tested on two different tasks designed to manipulate either delay to reward or reward magnitude following abstinence from experimenter-administered cocaine (versus saline controls). Before testing, animals were trained with odors to determine side preference; one odor instructed the rat to go to one side of the chamber while the other instructed the rat to go to the opposite side for a reward. Once this was learned, a third novel odor, signifying the rat can choose either side, was introduced and animals were tested on the task where either delay or magnitude was manipulated. In the delay task, the delay to receive reward became increasingly larger (0.5s-10s) on the initially preferred side of the chamber while magnitude for both sides remained consistent. In the magnitude task, the size of the reward became increasingly larger (1-5 boli of sucrose) on the initially non-preferred side and there was no delay to reward. The cocaine-treated and saline-treated rats performed in a similar manner when delay lengths and reward magnitudes were equal at the two locations. However, animals with a history of cocaine (but not controls) were more likely to switch their responses to the alternative side when the delay to reward or reward size was increased.

As noted above, Saddoris et al., (2017) and Roesch et al., (2007) demonstrated that abstinence from cocaine resulted in differential effects in magnitude discrimination. It is

important to note that in the former, there was no discrete cue to signal availability of a reward and animals with a history of cocaine were unable to discriminate between large and small rewards while in the latter, there was a discrete cue and animals with a history of cocaine shifted behavior towards choosing the larger reward faster than their control counterparts. Collectively, these findings suggest that the presence of a discrete cue to signal availability of a reward may have an effect on magnitude-based decision making. Specifically, animals with a history of cocaine in the presence of a discrete cue shift behavior towards choosing the optimal option faster. The question then becomes: does this hold true for delay-based decision making?

Previous work in the Carelli lab has examined the effects of prior cocaine self-administration history on magnitude-based decision making and delay-discounting behavior (Moschak & Carelli, 2017; Saddoris et al., 2017) but we have not yet examined cocaine history on delay-based decision making. As such, the main goal of the present work was to determine if delay-based decision making is influenced by discrete cues signaling delay to reward and we designed two tasks to address this issue. In the first task, rats learned that a distinct visual cuelight illuminated for 5 s signaled the availability of either an immediate or delayed (4 s) reward of the same size, and then were given an opportunity to choose their preferred option. The second task was similar but without the 5 s visual cue. The two behavioral endpoints reflective of impulsive responding of interest were: 1) latency/speed to respond and 2) choice behavior. Our results revealed interesting differences between behavioral responding in the two tasks indicating an important role of cues in cocaine's actions on delay-based decision making.

Methods

Animals

Male Sprague-Dawley rats (Harlan; Task 1; cocaine *n*=7, saline *n*=6; Task 2; cocaine *n*=6, saline *n*=7) were obtained at ~2-3 months and weighed approximately 300-330g upon arrival. Rats were singly housed and kept at no less than 85% of their pre-experimental body weight with the exception of the week of postoperative care when they were given water and food *ad libitum*. During self-administration, animals were given 20mL of water a day while during behavioral testing, animals were fed 3 food pellets each day (Purina Laboratory Chow). Animal procedures were conducted in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals and were approved by the University of North Carolina at Chapel Hill Institutional Animal Care and Use Committee (IACUC).

Apparatus

Self-administration was completed in 30 x 25 x 19 cm operant chambers (Med Associates, St. Albans, VT) equipped with two retractable levers with cue lights above them on one side and a nosepoke location on the other. The chambers were also equipped with a receptacle programmed to deliver water located in between the two retractable levers. Cocaine infusions were delivered via a syringe pump located outside of the chambers and connected to the animals' catheter. For self-administration, the levers were retracted and only the nosepoke was enabled. Training and testing on the delay-based decision-making tasks were conducted in operant chambers located in another room. These chambers were 43 x 43 x 53 cm (Med

Associates, St. Albans, VT) and equipped with two retractable levers with cue lights above them and a foodcup located between the levers for delivery of sucrose pellets.

Experimental Timeline

Figure 1 shows a schematic diagram of the experimental timeline. First, the animals underwent intrajugular catheter surgery followed by a week of postoperative care. Next, the animals completed 14 consecutive days of either cocaine or water self-administration (yoked saline; see below for self-administration details) immediately followed by a 30-day experimenter-imposed abstinence. During abstinence, rats remained in their home cages without access to drug. Finally, after abstinence, the animals were trained on one of the delay-based decision-making tasks, followed by 4 test days, described below.

Surgery

Rats were deeply anesthetized using a mixture of 100 mg/kg ketamine hydrochloride and 10 mg/kg xylene and surgically prepared for implantation of a catheter into the right jugular vein as described in detail elsewhere (Moschak & Carelli, 2017). A subset of these animals (Task 1; cocaine n=3, saline n=4; Task 2; cocaine n=6, saline n=7) also received implantation of microelectrode arrays for electrophysiology in the nucleus accumbens core and prelimbic cortex in the same surgery. However, due to noise issues and low number of cells detected, those data are not included in this report.

Self-Administration

One week after surgery, animals began cocaine self-administration training. Rats were placed into the self-administration chambers and the catheter was connected to an infusion pump. Each nosepoke resulted in cocaine (0.33 mg in 0.2 ml of 0.9% saline, i.v.) or an equal volume of both saline (i.v.) and water (delivered to the reward receptacle) paired with a 30 s tone-houselight compound stimulus. Nosepokes during the 20 s post response period during the tone-houselight presentation were not reinforced. Of note, saline rats controlled both for the amount of fluid being infused intravenously and learning the operant task of nosepoking for reward. The animals were given 2-hour daily self-administration sessions over 14 consecutive days. All rats were mildly water-restricted (20 ml/d) but given ad libitum food access. Cocaine hydrochloride was obtained from the National Institute on Drug Abuse.

Abstinence

After two weeks of cocaine or water (yoked saline) self-administration sessions, the animals were placed on a 30-day experimenter-imposed abstinence period where they were given water and food *ad libitum* but remained in their home cages (no drug). After 30 days of abstinence, rats were trained on either the cued task (task 1) or the uncued task (task 2), described below.

Delay based decision making tasks

For the Cued Task (Task 1), rats were initially trained to press two distinct levers in which each response was reinforced on a fixed ratio 1 (FR1) schedule of reinforcement. Reinforced responses resulted in the delivery of a sucrose pellet to a centrally located food cup.

Animals were trained to a criterion of 50 presses on each response lever for two consecutive days. Next, rats were trained on a task that involved three types of contingencies (30 trials each) intermixed within 90 total trials per session. At this stage, a single sucrose pellet was available for each lever press throughout the session without any imposed delay to reinforcement. The first two trial types were classified as forced-choice trials. For one trial type, a single cue light was illuminated for 5 s over one lever, followed by extension of both levers. Responses on the cue light illuminated lever (within 10 s) were immediately reinforced with one sucrose pellet. During the other forced-choice trial type, the cue light over the other lever was illuminated for 5 s, followed by extension of both levers. Responses within 10s on the cue-associated lever were reinforced as above. For forced-choice trials, responses on the unsignaled lever were counted as errors and resulted in termination of the house light for the remainder of the trial period, with no reward delivery. No response to either lever within 10s was counted as an omission and also resulted in termination of the houselight with no reward delivery. During the third trial type, termed free choice trials, both cue lights were illuminated for 5 s, after which both levers were extended, and responses on either lever within 10 s were reinforced with one sucrose pellet. After a press on either lever, both levers were retracted, and a sucrose pellet was immediately delivered into the food receptacle. To move on to the test days, rats needed to maintain at least 3 days of stable accuracy (80% correct responses). Once stable behavior was achieved, a 4 s delay to reinforcement was imposed after a lever press on one of the levers and similar testing began for a total of 4 test days. Assignment of delay for the levers was counterbalanced across subjects. A schematic diagram of the cued task on the test days is shown in Figure 2.

For the Uncued Task (Task 2), rats were first trained that two distinct levers were each associated with delivery of 1 pellet on a FR1 schedule. When the rat performed 50 presses on

each lever within a 1-h session, the session terminated. If the rat failed to reach 100 total presses within the hour, it was run on the same contingency the next day. Animals were trained to a criterion of 50 presses on each response lever for two consecutive days. Next, the animals were trained on a task that involved three types of contingencies (20 trials each) intermixed within 60 total trials per session similar to task 1 but without the discrete 5 s cue preceding lever extension. The first two trial types were forced choice trial, during which either the right or the left lever was extended into the chamber without any preceding 5 s cuelight illumination above the levers. A response on the extended lever within 10s (FR1) resulted in the immediate delivery of a single sucrose pellet. Failure to respond within the 10s was counted as an error and resulted in the termination of the houselight for the remainder of the trial period, with no reward delivery. During the third trial type (free choice trials), both levers were extended into the chamber and response to either lever within 10s resulted in the immediate delivery of a single sucrose pellet. Failure to respond within 10 s was an omission and resulted in the termination of the houselight and end of the trial period with no reward delivery. In order to move on to test days, animals had to have at least 2 days of stable accuracy (80% correct responses). Once stable behavior was established, a 4s delay to reinforcement was imposed after a lever press on one of the levers and animals were run on this same task for 4 consecutive test days. A schematic diagram of the uncued task on the test days is shown in Figure 3.

Data analysis

For analysis of self-administration behavior, for each task (cued versus uncued) a two-way (group x day) ANOVA was used to compare total daily nosepokes for water (yoked saline) versus cocaine self-administration during the two-week training period, followed by Tukey's

post hoc tests.

For the two delay-based decision making tasks, separate unpaired t-tests were used to compare accuracy (% correct responding during forced delay and immediate trials) for rats with a history of water (yoked saline) versus a history of cocaine self-administration. For free choice trials, unpaired t-tests were used to examine if differences occurred in preference for pressing the delay lever in rats with a history of water versus cocaine self-administration for each task. Analysis of delay lever preference across days was also evaluated separately for each task using a repeated measures two-way (group x day) ANOVA with Bonferroni's post hoc correction for multiple comparisons. This analysis compared lever preference for the delayed reward using group and day as factors. Latency to press for reward was evaluated separately for forced and free choice trials using a two-way repeated measures ANOVA with Bonferroni's post hoc correction for multiple comparisons. This analysis compared latency to lever press using group (cocaine and saline) and trial type (delay and immediate) as factors. For all within-subjects analyses that did not pass Mauchly's test for sphericity, Geisser-Greenhouse adjusted degrees of freedom were used.

All analyses were considered to be significant at $\alpha = 0.05$. Statistical and graphical analyses were performed using GraphPad Prism 8.0 for Windows (GraphPad Software, La Jolla, CA).

Results

Self-administration behavior

Nose-poke responses for rats with a history of cocaine self-administration and control animals (water self-administration, yoked saline) were examined within the two tasks. For the cued task, a two-way ANOVA revealed no significant main effect of group ($F_{1,11}$= 0.2440, p = 0.6310), no main effect of day ($F_{3.22,35.42}$= 0.9761, p = 0.4195) and no significant interaction ($F_{13,143}$ = 0.4737, p = 0.9363) (Figure 4A). These findings indicate similar self-administration responding across days for each group in the cued task. For the uncued task, a two-way ANOVA revealed a significant main effect of group ($F_{1,11}$ = 6.972, p = 0.0230), no main effect of day ($F_{4.403,48.43}$ = 0.7746, p = 0.5581) and no significant interaction ($F_{13,143}$ = 1.249, p = 0.2510) (Figure 4B). The significant main effect of group in the Uncued task indicates that collapsed across days, nose poke responses for water (controls) was significantly higher than rats responding for cocaine.

History of cocaine self-administration does not affect free choice behavior but makes animals respond faster than controls when discrete cues are present

During forced choice delay trials in Task 1 (Cued Task), there was no significant difference in percent correct lever press responding during forced delay trials (t_{11} = 0.3731, p = 0.7162; Figure 5A), errors (t_{11} = 0.6992, p = 0.4990; data not shown), or omissions (t_{11} = 1,349, p = 0.2045; data not shown) between animals with a history of cocaine self-administration compared to water self-administration (yoked saline). Likewise, during forced choice

immediate trials, there was no significant difference found in percent correct lever press responses ($t_{11} = 0.7238$, $p = 0.4843$; Figure 5B), errors ($t_{11} = 0.6792$, $p = 0.5215$; data not shown), or omissions ($t_{11} = 1.108$, $p = 0.2917$; data not shown) between groups. When animals could freely choose either lever (i.e., free choice trials), behavior between groups was averaged and analyzed across all 4 test days (Fig. 5C) as well as across each individual test day (Fig. 5D). There was no significant difference in free choice behavior across groups averaged across all test days ($t_{11} = 0.8103$, $p = 0.4350$; Figure 5C). Likewise, a two-way ANOVA revealed a significant main effect of test day ($F_{1.785,19.63} = 5.304$, $p = 0.0169$), but no main effect of group ($F_{1,11} = 0.6565$, $p = 0.4350$), or interaction of day x group ($F_{3,33} = 0.7879$, $p = 0.5093$) (Figure 5D), indicating that both groups pressed the delay lever less over days (i.e., behavior improved).

Interestingly, animals with a history of cocaine self-administration were faster to press for reward (compared to water self-administration rats) on forced choice and free choice trials independent of trial type (delay versus immediate). Specifically, a two-way ANOVA revealed a main effect of group ($F_{1,11} = 4.624$, $p = 0.0428$), but no main effect of delay ($F_{1,11} = 0.1061$, $p = 0.7477$), or interaction of delay x group ($F_{1,11} = 0.03081$, $p = 0.8623$) during forced choice trials (Figure 5E). Likewise, animals with a history of cocaine were also faster to press for reward during free choice trials compared to water self-administration (saline yoked) rats. A two-way ANOVA revealed a main effect of group ($F_{1,11} = 4.679$, $p = 0.0417$), but no main effect of delay ($F_{1,11} = 0.003898$, $p = 0.9508$), or interaction of delay x treatment ($F_{1,11} = 0.1832$, $p = 0.6728$) (Figure 5F).

History of cocaine self-administration does not affect free choice behavior, response time or response latency in a delay-based decision making task without discrete cues

Similar to the Cued Task, in Task 2 (Uncued Task), there was no significant difference

in percent correct responding between animals with a history of cocaine self-administration compared to water self-administration (yoked saline) for both forced delay ($t_{11} = 0.2289$, $p = 0.8231$; Figure 6A) and forced immediate trials ($t_{11} = 0.5991$, $p = 0.5612$; Figure 6B). Likewise, there was no significant difference between groups for number of omissions made during forced delay ($t_{11} = 0.2289$, $p = 0.8231$; data not shown) or forced immediate trials ($t_{11} = 0.5991$, $p = 0.5612$, data not shown). Further, there was no significant difference in free choice behavior averaged across all 4 test days ($t_{11} = 0.9777$, $p = 0.3492$; Figure 6C) or when averaged across each test day (Figure 6D). Specifically, a two-way ANOVA revealed no main effect of day ($F_{1.878,20.03} = 0.4239$, $p = 0.6478$), group ($F_{1,11} = 0.1030$, $p = 0.3320$), or interaction effect of day x group ($F_{3,32} = 0.8944$, $p = 0.4547$, Figure 6D).

In contrast to the cued task, animals with a history of cocaine self-administration were not faster to press for reward during forced choice trials (Figure 6E). Here, there a two-way ANOVA revealed no main effect of trial type ($F_{1,11} = 1.098$, $p = 0.3172$;), group ($F_{1,11} = 0.6939$, $p = 0.4226$), or interaction ($F_{1,11} = 0.7958$, $p = 0.3915$). Similarly, there was no difference in latency to press during free choice trials between animals with a history of cocaine self-administration versus animals with a history of water self-administration (Figure 6F). Specifically, a two-way ANOVA revealed a significant main effect of trial type ($F_{1,11} = 5.890$, $p = 0.0336$), but not group ($F_{1,11} = 1.446$, $p = 0.2544$) or interaction ($F_{1,11} = 0.0006639$, $p = 0.9799$). These findings indicate that independent of drug, animals were faster to respond to free choice immediate trials versus free choice delay trials during the task.

Discussion

The objective of the present study was to determine if prior cocaine self-administration experience can differentially influence behavior during delay-based decision making dependent upon task cues. In the first task (cued), a discrete cuelight was illuminated for 5 s, after which rats could respond for an immediate versus delayed reward. In the second task (uncued), the cuelight was not presented, and rats could respond for immediate or delayed reward upon lever extension into the chamber. During the Cued task, when animals were presented with a cue light that signaled that they could respond for reward 5 s later, animals with a history of cocaine were faster to press for a reward than the water self-administration animals. In contrast, during the Uncued task, when there was no discrete cuelight present, there was no difference in latency to press for reward between animals with a history of cocaine self-administration and controls. Interestingly, prior cocaine experience did not influence free choice responding in either task. Collectively, these findings indicate that the presence or absence of a discrete cue light signaling reward availability 5 s later influences the effects of cocaine history on latency to respond independent of trial type in only cued but not uncued delay-based decision making tasks in rats.

During the Cued task, a 5s cue light indicated the availability of an immediate or delayed (4s) reward upon a lever press response. There was no difference between groups in choice behavior (% free choice trials in which animals chose the delayed reward), but animals with a history of cocaine self-administration were significantly faster to press for reward

regardless of trial type. This finding indicates that a history of cocaine may contribute to enhanced impulsive responding in the task. These findings are consistent with previous work implicating that those who suffer from SUDs are more likely to be more impulsive than those without drug history (Dalley et al., 2011; Winstanley et al., 2009). For example, previous work has shown that in the 5-choice serial reaction time task (5CSRTT), a task used to measure impulsivity, animals with a history of cocaine show increased rates of premature responses (behavioral inhibition) than their control counterparts (Broos, van Mourik, Schetters, De Vries, & Pattij, 2017; Winstanley et al., 2009). Collectively, these data suggest that behavioral inhibition is diminished following cocaine self-administration. The current findings demonstrate that a history of cocaine increases another specific type of impulsivity (latency to respond) without making rats more impulsive in choice trials when presented with a 5 s 'waiting period' before a response could be made for reward.

During the Uncued task, there was no cue light presented above the levers with lever extension serving as the only indicator of the availability of an immediate or delayed reward upon lever press. We found no difference between groups for choice behavior during free choice trials or latency to press for reward. These findings suggest that in the absence of a discreet cue, animals with a history of cocaine perform at similar levels as their control counterparts in all aspects of this particular task with similar levels of impulsive behavior. This occurred even though control rats previously pressed more for water self-administration compared to water controls across all sessions (Figure 4). The latter finding indicates that prior nose-poking experience for either cocaine or water self-administration did not differentially influence subsequent delay-based decision making behavior in this task.

As noted above, those who suffer from SUDs tend to be more impulsive than those who

do not. Impulsivity has also been shown to be a vulnerability marker for developing a SUD (Kozak et al., 2019; Kreek, Nielsen, Butelman, & LaForge, 2005), and has been linked with increased risky behaviors (Bakhshani, 2014; Gorini, Lucchiari, Russell-Edu, & Pravettoni, 2014). Interestingly, a study performed by Ferland et al., (2019) using a cued and uncued version of the rat gambling task to test impulsive behavior found that animals preferred more risky options in the cued version as opposed to the uncued version of the rat gambling task. Collectively, this suggests that, similar to delay-based decision making examined in the present study, the absence/presence of a discrete cue also influences responding in a risk-based decision making task, another form of impulsive behavior (Ferland et al., 2019). Their data suggests that the pairing of uncertain rewards with cues increases risky choice and also promotes a hypodopaminergic state in the nucleus accumbens (NAc). It is unclear however whether it is the NAc core or shell which is contributing to this hypodopaminergic state.

For the purpose of this study, the terms "Cued" and "Uncued" were employed to distinguish between the two tasks used, but it is important to note that the Uncued task is not entirely without a discrete cue. The term "uncued" refers to the fact that this particular task had no cue light to signify availability of a reward, but the lever extension does serve as a cue. Evidence shows there are differential effects in reward value tasks that have a discrete cue presentation immediately before reward availability versus those that do not. For example, examining dopamine signaling in the nucleus accumbens (NAc) of rats immediately following cue presentation have shown that phasic dopamine signaling predicted anticipated reward value (Day et al., 2011; Ostlund, Leblanc, Kosheleff, Wassum, & Maidment, 2014) while dopamine release in uncued tasks did not (Saddoris et al., 2017). Taken together, these studies reveal that there is evidence not only of behavioral differences but also neurobiological differences in cued

versus uncued tasks.

Within both tasks used in the present study, following a lever press response a 4s delay to reward was imposed. As mentioned previously, Roesch and colleagues (2007) examined the effects of a history of cocaine on a delay-based decision making task. During the task, they used a variety of delay periods ranging from 0.5s-10s, increasing delay to reward. It was at the 4s delay to reward where they saw the greatest difference in animal response, so we thought it was best to use that delay period in our study. Interestingly, at shorter (0.5, 2s, 3s) and longer (7s, 8s, and 9s) delay lengths, animals with a history of cocaine performed similarly to control animals during the delay task. Specifically, they both shifted behavior away from the initially preferred (delayed) side at similar rates. It remains unknown as to why the 4 s delay resulted in the largest difference in responding between cocaine versus control rats in that study. However, as mentioned previously, this task was executed using odor cues to signify availability of reward. It would be interesting to see if this pattern of behavior holds true in the absence of a discrete cue using our behavioral task design but for delay periods both longer and shorter than the 4s used in our task.

As used in our cued task, the 5s discrete cuelight period is an established feature in a number of studies in the Carelli lab (Day et al., 2011; Moschak & Carelli, 2017; Sackett, Moschak, & Carelli, 2019; Saddoris et al., 2015). It is during this 5s waiting period where animals make their decision to respond, and in a series of studies from the Carelli lab, it was during this 5 s waiting period where neural processing was altered in animals in decision making tasks. For example, in a study performed by Sackett et al., (2019), electrophysiological recordings were used to examine prelimbic cortex activity during a delay discounting task. They found that a subset of these neurons tracked the preferred reward during the cue

presentation and that this was differentially encoded in high and low impulsive animals. These animals were all drug naïve, so it would be interesting to see if this effect holds true or is even exaggerated in animals with a history of cocaine self-administration. Furthermore, it will be interesting to determine if neural processing in the PrL cortex, or its efferents such as the NAc core varies in activity when no discrete cues are present (e.g., using our uncued task) in animals with a history of cocaine self-administration versus controls.

Concluding Remarks

Taken together, these findings suggest that prior cocaine self-administration experience can produce differential effects in animal behavior during cued and uncued delay-based decision making tasks. Numerous studies have also shown that the NAc core is important for delay processing (Saddoris et al., 2015). Additionally, the prelimbic cortex, which projects to the NAc core is shown to exhibit numerous neuroadaptations following abstinence from cocaine (West, Saddoris, Kerfoot, & Carelli, 2014; Wolf, 2016) which have been associated with incubation of craving and implicated in delay discounting behavior (Churchwell, Morris, Heurtelou, & Kesner, 2009). It is unclear, however, the role of the PrL to NAc pathway when investigating the effects of cocaine self-administration on delay-based decision making. As previously mentioned, a subset of animals received implantation of microelectrode arrays for electrophysiology in the NAc core and prelimbic cortex, but these data were unable to be included in the current study due to noise issues and low cell count. Future studies will explore local field potential (LFP) of the PrL and NAc core as well as coherence between the two regions during both the cued and uncued delay-based decision making tasks.

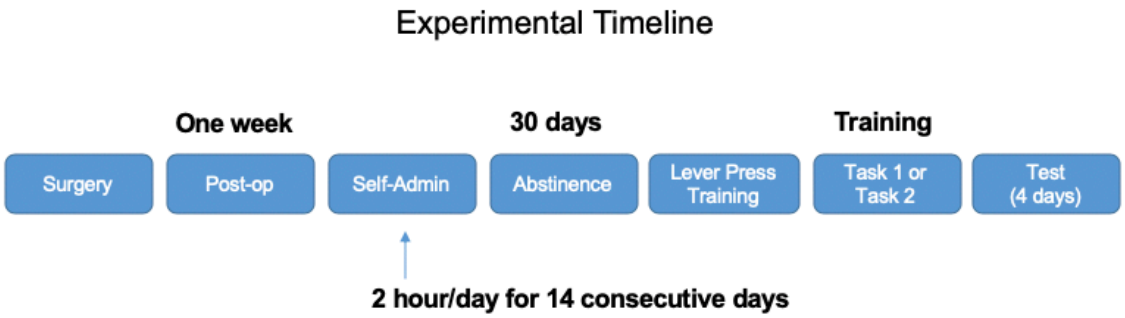

Figure 1. Schematic diagram of experimental timeline. Animals were prepared for surgery approximately one week after arrival to the animal facility. Following surgery, animals had one week of post-operative care then began self-administration of either cocaine or water (yoked saline) 2 hours a day for 14 consecutive days. After 30 days of experimenter-imposed abstinence in their home cages, animals then began lever press training. Finally, animals were trained on either the Cued Task (Task 1) or Uncued Task (Task 2) followed by 4 test days on their specific task.

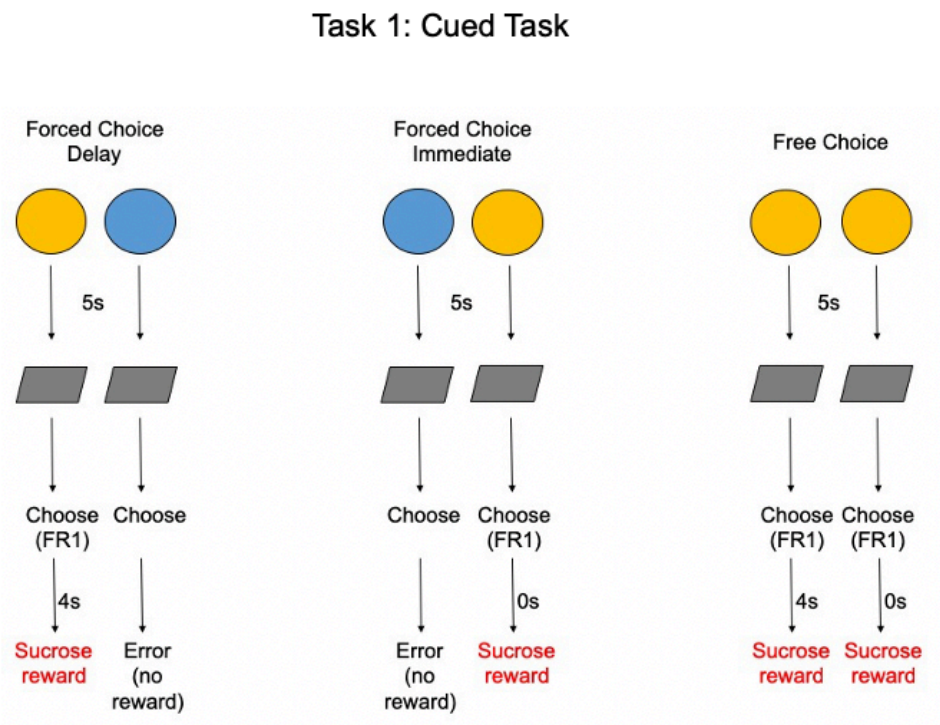

Figure 2. Schematic diagram of task 1: Cued delay based decision making task. **Left:** During forced choice delay trials, one cue light was illuminated for 5s followed by the extension of both levers. Presses on the signaled lever resulted in a reward delivery of 1 sucrose pellet after a 4s delay. Presses on the non-signaled lever resulted in termination of the trial, no reward delivery, and counted as an error. **Middle:** During forced choice immediate trials), one cue light was illuminated for 5s followed by the extension of both levers. Presses on the signaled lever resulted in a reward delivery of 1 sucrose pellet immediately. Presses on the non-signaled lever resulted in termination of the trial, no reward delivery, and counted as an error. **Right:** During free choice trials), both cue lights were illuminated for 5s followed by the extension of both levers. Responses were rewarded based on the contingency of the lever chosen. See text for additional details.

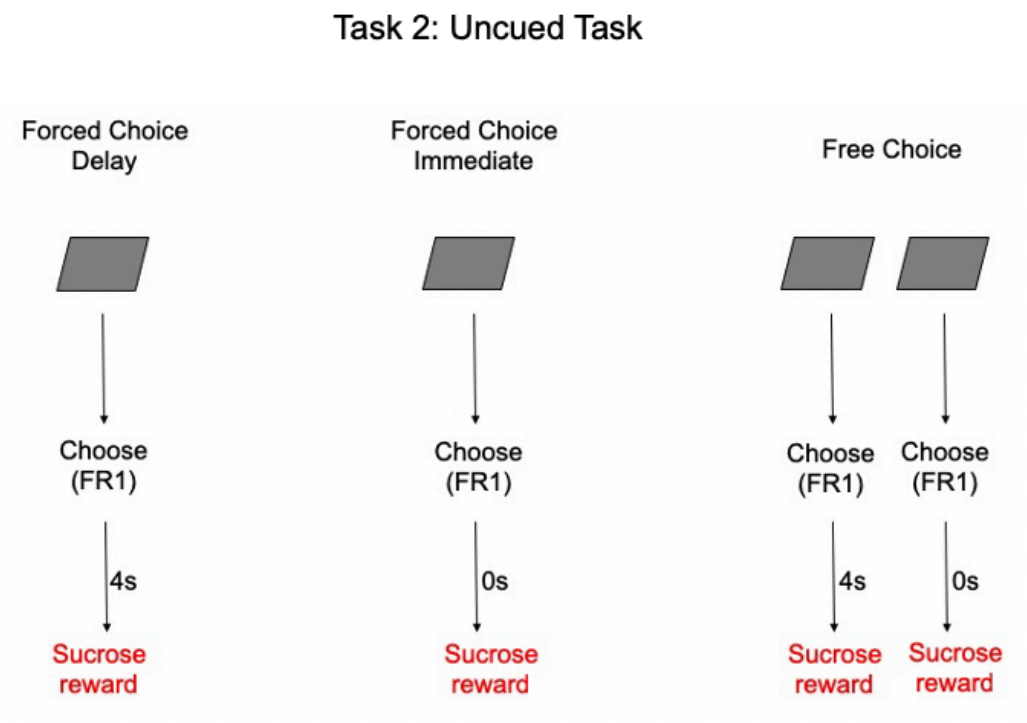

Figure 3. Schematic diagram of task 2: Uncued delay based decision making task **Left:** During forced choice delay trials, one lever was extended into the behavioral chamber. Presses on the extended lever resulted in a reward delivery of 1 sucrose pellet after a 4s delay. **Middle:** During forced choice immediate trials, one lever was extended into the behavioral chamber. Presses on the extended lever resulted in a reward delivery of 1 sucrose pellet immediately. **Right:** During free choice trials levers were extended into the chamber. Responses were rewarded based on the contingency of the lever chosen. See text for additional details.

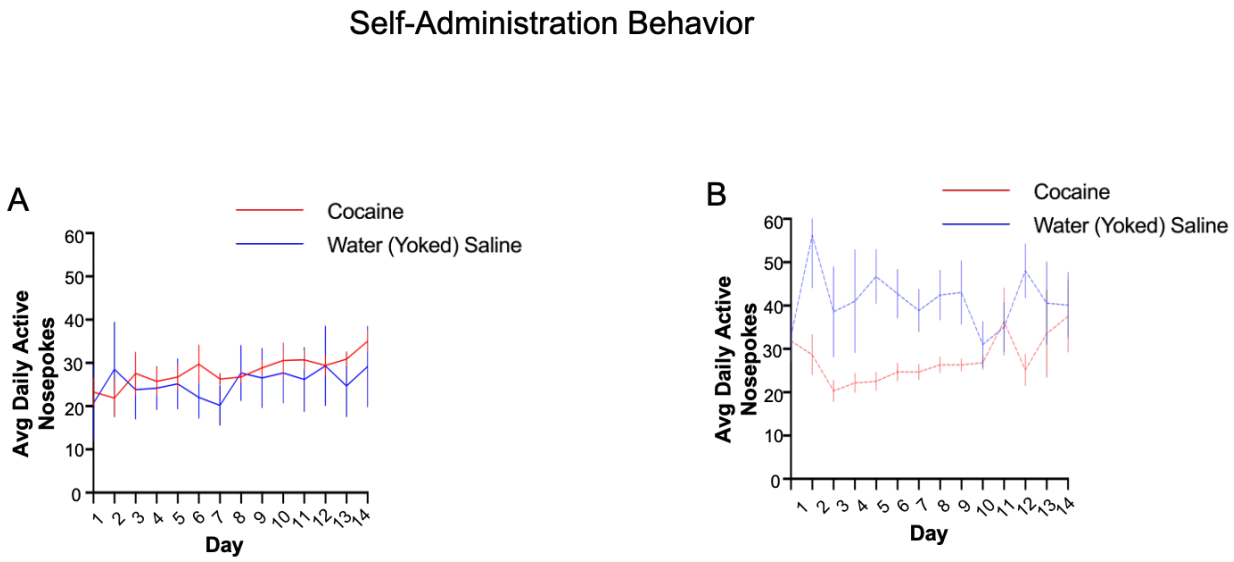

Figure 4. Self-administration behavior. **A.** Average total daily nosepokes for Cued Task cocaine and water self-administration animals. **B.** Average total daily nosepokes for Uncued Task cocaine and water self-administration animals.

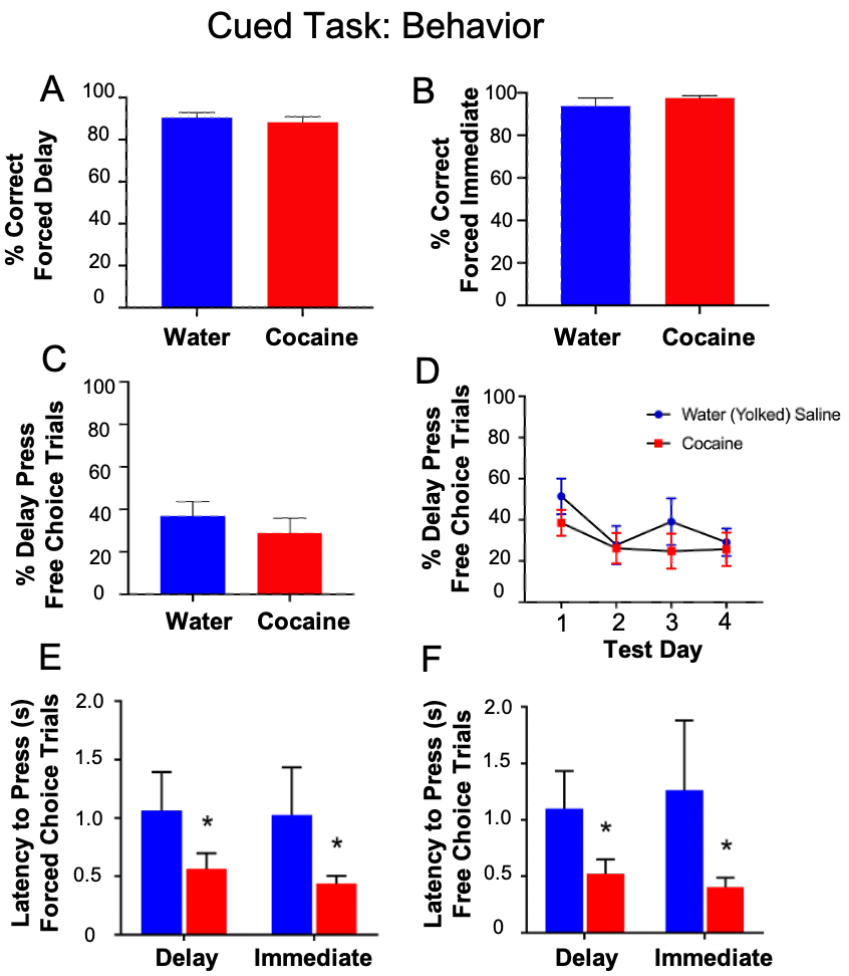

Figure 5. Behavior during cued delay-based decision making task. **A.** Percentage of correct reinforced responses during forced choice delay trials. **B.** Percentage of correct reinforced responses during forced choice immediate trials. **C.** Percentage of delay lever responses during free choice trials averaged across all test days for each group. **D.** Percentage of presses on the delay lever during free choice for each group across each test day. **E.** Response time to lever press during forced choice trials. Animals with a history of cocaine were faster to press for reward ($p < 0.05$). **F.** Response time to lever press during free choice trials. Animals with a history of cocaine were faster to press for reward ($p < 0.05$).

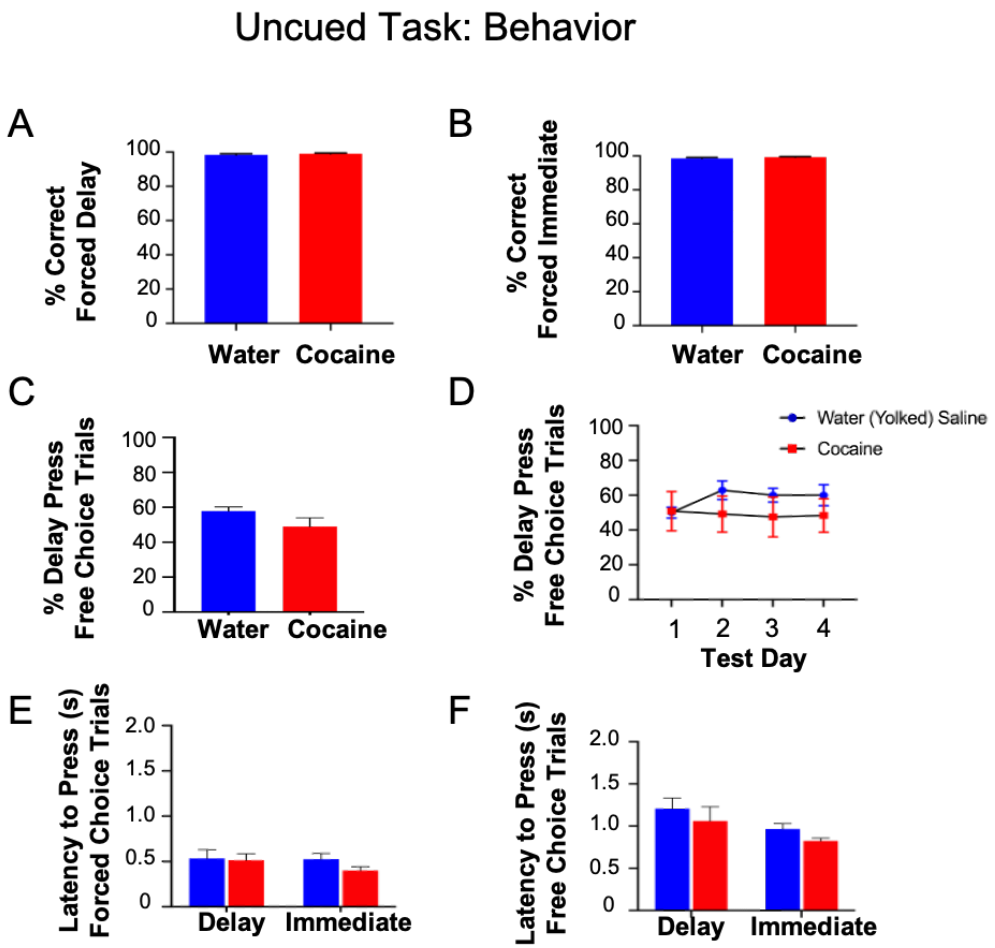

Figure 6. Behavior during uncued delay-based decision making task. **A.** Percentage of correct reinforced responses during forced choice delay trials. **B.** Percentage of correct reinforced responses during forced choice immediate trials. **C.** Percentage of delay lever responses during free choice trials averaged across all test days for each group. **D.** Percentage of presses on the delay lever during free choice for each group across each test day. **E.** Response time to lever press during forced choice trials. **F.** Response time to lever press during free choice trials.

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