2021

THE EFFECTS OF ESCALATED COCAINE INTAKE ON DECISION-MAKING DYNAMICS

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Digital Object Identifier: https://doi.org/10.13023/etd.2021.242

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THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
College of Arts & Sciences
at the University of Kentucky

By

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2021

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ABSTRACT OF THESIS

THE EFFECTS OF ESCALATED COCAINE INTAKE ON DECISION-MAKING DYNAMICS

Cocaine Use Disorder (CUD) is characterized partly by the use of cocaine at the expense of other alternatives, in other words, it is a decision-making pathology (Kalivas & Volkow, 2005). Concurrent choice tasks assess decision-making in a dynamic scenario that more closely resembles real life. Value-based decision-making is an important facet of understanding the addictive properties of drugs of abuse. In order to compare two value-based theories of addiction (habit theory and relative value theory), a concurrent choice task was run in tandem with an escalation procedure. First, animals were trained on a choice task until stable, then trained on to self-administer cocaine (0.3mg/kg to the animal's weight) using a fixed ratio 1 schedule under 1-hr access. For the escalation procedure, some animals remained on 1-hr access and others were given 6-hr access to cocaine for 21 days. Then all rats returned to 1-hr access. The animals were trained such that they performed the choice task in the morning (while not under the influence of drugs) and then after a rest in the home cage, were put back into the operant boxes for self-administration sessions.

Escalation of cocaine intake was evident in the 6-hr exposed animals but intake was stable in the 1-hr exposure animals. The choice behavior between the two groups did not differ, despite difference in intake between the groups. Indicating that despite dysregulated cocaine intake, value-based decision-making and goal-directed behavior remained intact. This supports the idea of looking beyond habit theory as the sole explanation for the change in decision-making behavior seen in CUD.

KEYWORDS: Cocaine, Escalation, Decision-Making, Habit, Relative Value

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ACKNOWLEDGMENTS

I would like to extend my gratitude to my advisor Dr. Joshua Beckmann, and to my committee members Dr. Mike Bardo and Dr. Thomas Zentall, for their guidance and support during the development of this work. I would also like to thank my lab manager, Joshua Lavy, this project would not have been possible without his organization and oversight. Additionally, I would like to thank the previous graduate students in the Beckmann lab; Dr. Jonathan Chow, Dr. Seth Batten, and Dr. Aaron Smith, for their assistance and tutelage throughout this project

Lastly, I am thankful for the support of my family and friends. Especially John and Kelly Stephens for always believing in me and fostering my dreams of becoming scientist, even when it meant putting up with experiments that inevitably turned to messes. And finally, I would like to thank my fiancé, Nate Hibbitts, for being a shoulder to lean on when experiments go awry.

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CHAPTER 1. INTRODUCTION

1.1 Cocaine

Cocaine is one of the most commonly used stimulants in Europe and the United States (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2020; Substance Abuse and Mental Health Services Administration (SAMHSA), 2020). In 2019, there were an estimated 5.5 million people, 2%, in the United States (SAMHSA, 2020) and 4.3 million people, 1.3%, in Europe who had used cocaine in the past year (EMCDDA, 2020). Of those who used cocaine in the U.S., 1 million transitioned from controlled drug use to developing Cocaine Use Disorder (CUD) (SAMHA,2020). The development of CUD causes serious negative impact on many areas of patient's lives. For example, the Substance Use Disorder (SUD) diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM–5; American Psychiatric Association, 2013) includes not only biological factors such as increased craving, tolerance, and withdrawal but also impairments in social, occupational, and recreational obligations as well as hazardous health effects. Each of these symptoms is tallied to garner a score of mild, moderate, or severe to determine how profoundly the drug-use is affecting the patient. While each patient may present with different symptomology and severity, the chronic, relapsing nature of SUDs makes it a serious detriment to patient's lives.

CUD not only has deleterious effects for those suffering from addiction but also has serious effects on society. In 2018, 14,666 Americans died of cocaine-related overdose out of more than 67,300 total drug-involved overdoses (Center for Disease Control, 2020). In addition to the loss of life, illicit drug use is thought to cost $193 billion to society annually due to crime ($61 billion), lost work productivity ($120 billion), and health care ($11 billion; National Drug Threat Assessment, 2011). Additionally, since cocaine is classified as a Schedule II drug according to the Drug Enforcement Administration (DEA), its possession and sale are criminal offenses and oftentimes associated with other crimes. According to the National Drug Threat Survey in 2010, cocaine and methamphetamine are the drugs that most often contribute to crime;

the updated 2019 assessment says the stimulant threat is worsening and becoming more widespread (Drug Enforcement Administration, 2019). Therefore, understanding and creating treatments for CUD is of significant interest to society as a whole.

1.1.1 Mechanism of Action

Cocaine, like other drugs of abuse, produces feelings of "high" or "euphoria" which patients describe as pleasurable and reinforcing. These feelings drive the initial desire to take the drug. This euphoric effect is produced by indirectly stimulating the monoamine system in the brain. Although cocaine has a structure similar to that of the endogenous catecholamine neurotransmitters dopamine (DA) and norepinephrine (NE), it cannot directly activate the neuronal receptors on the postsynaptic neurons that they bind to. Instead, it makes more of the naturally occurring neurotransmitters available by blocking their reuptake from the synapse via the transporter. Thus, allowing the DA or NE to remain in the synapse longer and continue to bind to the post-synaptic receptors. Cocaine is a potent inhibitor of the dopamine transporter (DAT) and has been shown to significantly elevate the basal DA levels in the nucleus accumbens (NAc) (Wise, 1987, 1988; Di Chiara & Imperato, 1988).

The increase in extracellular DA has been associated with both the rewarding and motoric effects of stimulants. The motoric effects include dose-dependent increases in activity in rodents, oftentimes seen as running. At higher doses, though, animals may engage in stereotypy, or repetitive actions such as head swaying, sniffing or licking. Although more common in amphetamine users, punding, or repetitive and impulsive behaviors, has also been noted in humans (Fasano et al., 2008). Punding was first noticed in patients with Parkinson's disease triggered by their DA replacement therapies (Black & Friedman, 2006). Both stimulants and DA replacement therapies increase the amount of DA in the synapse, giving further evidence that DA plays an important role in the effects of drugs of abuse. Additionally, in studies using intra-cranial self-stimulation (ICSS), it was found that humans and rats will learn to respond for direct electrical stimulation of the medial forebrain bundle (MFB); which includes dopaminergic projections from the hypothalamus to the ventral tegmental area (VTA) (Old & Milner, 1954; see Negus & Miller, 2014 for review). ICSS also has been shown to increase DA

release in the NAc and is enhanced by drugs that increase extracellular DA (Phillips, Blaha, & Fibiger,1989; Fiorino et al., 1993; You & Wise, 2001; Cheer et al., 2005; Hernandez et al., 2012). These findings, coupled with the fact that humans report that they find ICSS stimulation pleasurable, led to the linkage of these dopaminergic neurons in the midbrain with the reward circuitry. Similarly, it was found that the mesolimbic pathway, which is comprised of the VTA and projections to the ventral striatum, is critical for the rewarding effects of drugs of abuse (Wise & Rompré, 1989; Wise, 2009). Further studies with moveable-electrodes confirmed that stimulation along the mesostriatal (substantia nigra to dorsal striatum) and mesocortical (VTA to frontal cortex) pathways are also associated with drug reward and addiction (Wise, 2009; Prado-Alacá & Wise, 1984a; Prado-Alacá, Streather, & Wise, 1984). In sum, midbrain DA neurons play a vital role in producing the rewarding effects of drugs of abuse.

Midbrain DA neurons are also thought to be involved in the encoding of information about the value of rewarding events. Specifically, their firing rate is thought to encode reward prediction error (RPE) and guide decision-making in reinforcement learning models (RL; Schultz et al., 1997; Hollerman & Schultz; 1998; Nakahara et al. 2004; Bayer & Glimcher, 2005). In RL models, the value of a given outcome is updated on a trial-by-trial basis based on the differences between the expected and experienced outcomes (Rescorla & Wagner, 1972; Sutton & Barto, 1998). The set of average values of different rewards over a series of trials is called a value function. It is presumed that the set of value functions for a given environment, based on past experiences, is used to predict the likelihood of future reward or punishment. The RPE modulates those predictions by encoding how "surprising" the received outcome was, or how much it differed from the predicted outcome based on previous trials. A reward such as an infusion of a drug can vary on multiple dimensions such as its magnitude, the probability that it will be delivered, the delay to being delivered, etc. These dimensions can then be manipulated to change the value of the reward. For example, if the delivered infusion is made more valuable by a change in magnitude (e.g. the dose is higher than expected), there would be positive RPE and the firing rate of the DA neurons would increase. On the other hand, if the reward were made less valuable by increasing the delay to delivery, there would be a negative RPE and the firing rate would decrease (Schultz & Montague,

1997). If the same reward is presented over and over again with no change in any of the reward dimensions, there would be no RPE and the firing rate would decrease or stay stable at some low firing rate (Hollerman & Schultz, 1998). A study by Rutledge et al. (2009) confirmed that phasic DA activity is involved in encoding RPE in Parkinson's patients taking L-DOPA using a dynamic foraging task. With these studies, it is clear that manipulations of value via alterations in one or more reward dimensions affect the RPE and firing rate of the midbrain DA neurons. Since cocaine acts on these midbrain DA neurons that play a part in both the rewarding effects of the drug and the encoding of value, RL models that use value to predict choice behavior play an important role in understanding how the value of drug guides decision-making behaviors related to SUD.

1.2 Common Procedures in Substance Abuse Research

To study the rewarding effects of drugs and decision-making processes related to drug abuse, researchers have utilized many types of procedures that uncover different aspects of SUD. Below are some commonly used procedures, citing their benefits as well as shortcomings in order to determine which procedures would be best suited to measure relative value changes over the course of a rodent model of SUD.

1.2.1 Conditioned Place Preference

One of the earliest procedures developed to measure the effects of drugs of abuse is conditioned place preference (CPP; Spragg, 1940) where animals are exposed to experimenter administered drug as a passive measure of determining the rewarding effects of different drug or non-drug rewards (Carr et al. 1989; Calcagnetti & Schechter, 1992; Tzschentke, 1998). To pair the subjective effects of the drug (unconditioned stimulus) with that of the chamber stimulus context (e.g. particular flooring, wall patterning, or set of olfactory cues; conditioned stimulus), the animal is administered the drug and then placed in one side of a three-chamber box. The opposite side of the chamber, which has its own unique stimulus context, is then paired with saline, vehicle, or no drug. After exposure to both sides, animals are placed into the middle chamber and allowed to freely access both the drug-paired and non-drug-paired chambers. An increase in time spent on a given side of the chamber is taken to indicate that the state in which the

animal experienced that context was rewarding - i.e. more time spent on the drug-paired chamber indicates that the subjective drug effects were rewarding. CPP is a tool that can quickly be used to determine if the effects of a drug are rewarding or aversive (Tzschentke, 1998; Ettenberg et al., 1999; Tsuji et al., 1996). But due to the passive nature of the drug administration, and discordance between CPP and self-administration as reviewed in Bardo and Bevins (2000), CPP bears little face validity to the drug-taking behavior seen in human substance use disorders.

1.2.2 Self-Administration

In contrast to the passive administration of the drug in CPP, animal self-administration procedures were developed in rats (Weeks, 1962), and monkeys (Schuster & Thompson, 1969) where the administration and history of drug experience are under the control of the animal. In these procedures, the animal is implanted with an indwelling jugular catheter with which they are able to administer a drug themselves by emitting an operant response (i.e. lever press, or other response on a manipulandum), which will activate a pump connected to a syringe filled with the drug to deliver a specific dosage. In this procedure, the drug functions as a reinforcing stimulus, meaning that it increases operant responses that lead to the delivery of the drug. Many self-administration studies have demonstrated that drugs of abuse function as reinforcers (see Schuster & Thompson, 1969 for review; Weeks, 1961,1962; Pickens & Thompson, 1966). From the basic self-administration procedure, there have been a variety of offshoot procedures developed to investigate other facets of drug valuation.

1.2.3 Escalation Model

One of these is the escalation model developed by Ahmed & Koob (1998). In this model, animals are given either short (10min, 1hr) or longer (60min, 6hr, sometimes 12hr) access to self-administer drugs. The longer access sessions are thought to produce a gradual dysregulation of drug intake during self-administration, such that the animals with longer access take more drug than their shorter access counterparts and will show enhanced reinstatement (Ferrario et al., 2005; Kippin, Fuchs, & See, 2006; Knackstedt & Kalivas, 2007) or even continued self-administration despite concomitant punishment

(Pelloux, Everitt, & Dickinson, 2007; Deroche-Gamonet, Belin, & Piazza, 2004) The escalation of drug intake and resistance to punishment is thought to show a deviation from normal reward-based decision-making indicative of SUD (Edwards & Koob, 2013).

1.2.4 Progressive Ratio

Another derivation of the traditional self-administration paradigm is the progressive ratio (PR) schedule (Hodos, 1961; Richardson & Roberts, 1996) in which the number of responses required to deliver a dose of the drug increases systematically until the animal no longer completes the response requirement in a given time period. This maximum-response value is called the breakpoint, which serves as a measure of reinforcer efficacy. The PR schedule can be used to evaluate the reinforcing efficacy of drugs by comparing the breakpoints of a series of doses in a dose-response curve (Richardson & Roberts, 1996). A higher breakpoint indicates that the animal will "work harder" for a given dose and thus that dose is a more effective reinforcer. PR measures are based on the idea that the value of the reinforcer lies in how hard the animal will work to obtain it.

1.2.5 Demand Schedule

Similar to PR schedules, the reinforcing value of a drug can be determined by the extent to which it is sensitive or insensitive to changes in price. In demand analyses, price is defined as the amount of monetary expense, time, or effort required to obtain a commodity. In non-human animal studies, price is often manipulated by increasing the Fixed Ratio (FR requirement to earn a reinforcer, making these tasks look very similar to PR schedules. However, in these procedures, the manipulation of interest is unit price; here defined as the number of responses required divided by the reinforcer magnitude, or the dose of the reinforcer. Unit price can also be conceptualized as the relation of cost-benefit. The effect of changing the unit price on drug-taking behavior is approximated by the elasticity of demand, the consumption of a commodity as a function of the unit price required to acquire it (Hursh & Roma, 2016). Generally, as the unit price for a commodity is increased, the consumption of that commodity decreases. At low unit prices consumption is high and insensitive, or inelastic, meaning that changes in unit price do not easily change the consumption. Then as the unit price is increased further,

the responding reaches a point in which it becomes elastic, meaning it is very sensitive to unit price, and responding for the commodity decreases as the unit price continues to rise (Hursh & Roma, 2013). This relationship can be described by the following equation characterized by Hursh and Silberberg (2008) called the demand curve:

$$\log Q = \log Q_0 + k(e^{-\alpha Q_0 C} - 1) \quad (1)$$

where Q is consumption, Q_0 is consumption at zero cost, C is unit price, α is demand elasticity, and k is a scaling constant associated with consumption. The slope of the curve is determined by k and α, but because k is a constant, changes in elasticity are determined by α. This model not only characterizes intake of commodities when they are free (Q_0) but also how intake will change as a function of increased price (α). When graphed as a demand curve, a more elastic reinforcer will show steeper slopes compared to an inelastic one. By normalizing these plots, two reinforcers, or multiple doses of the same drug, can be shown on the same graph (Hursh & Winger, 1995; Winger et al., 2006). Although each drug is given in isolation, and therefore these graphs cannot determine preference between doses or drugs, fitting a demand model to the data may begin to uncover differences that exist in terms of reinforcing efficacy. From these values, it is possible to compare how alterations in the environment change the elasticity of drug responding and thus, the drug's reinforcing efficacy in different scenarios.

1.3 Theoretical and Pragmatic Issues with Single Schedules

All of the above approaches have their uses for answering specific questions, but because they are all quantifying the reward value of a single commodity (i.e. a single schedule), they all suffer similar theoretical issues and none can compute the relative value of the commodity as it exists in different environments.

1.3.1 Rate Measures are not dissociable From Preference

Using single schedules will often produce a bitonic dose-response curve or "inverted U-shaped" where the lowest and highest doses produce lower self-administration levels than the mid-range dose(s), leading to the conclusion that intermediate doses are the most reinforcing when given in isolation. However, when

given the choice between a low and high dose, the higher dose will be chosen almost exclusively (Iglauer & Woods, 1974; Johanson & Schuster, 1975; Beckmann, Chow, & Hutsell, 2019). This disconnect between the findings of rate-based measures of reward efficacy and that of choice measures show that single-schedule paradigms are susceptible to other effects that are independent of the value of the commodity. These independent effects are often referred to as direct effects (Katz, 1989).

1.3.1.1 Direct Effects: Satiety

One possible explanation for the decrease in responding on the descending limb of the dose-response curve is satiety. This effect is most intuitively explained through experiences with non-drug rewards. As described in Killeen and Reilly (2001), animals regulate responding for food to create a homeostatic balance, up-regulating behavior when driven by a state of hunger and down-regulating when in a state of surfeit. The threshold for increasing or decreasing responding is called satiation and is centered around the set point. For example, when hungry at the beginning of a meal we eat quickly, then slow down towards the end of the meal as we become satiated. Finally, we stop completely, until we are hungry again. The cessation of responding after surpassing the upper satiation limit is called the post-reinforcement pause (PRP). The same pattern of responding can be seen in the self-administration of drugs. It has been shown that animals will titrate their intake of cocaine to maintain a steady-state of drug level in the body (Gerber & Wise, 1989; Richardson & Roberts, 1996). Tsibulsky & Norman (1999) characterized the relationship between cocaine dose and the length of the mean inter-injection interval, or PRP, as non-linear. Human cocaine self-administration showed a similar non-linear relationship between cocaine dose and PRP (Angarita et al., 2010). When using larger doses of the drug the animal reaches the satiation point (termed "satiety threshold" by Tsibulsky & Norman (1999)) more quickly and the PRP will be long until the metabolism of the drug moves the animal back below the action threshold and it begins to respond again. Whereas when using smaller doses of the drug, the animal may never reach satiation and respond continuously. This regulation system would then imply that the differences in the rates of responding for the two doses seen in rate-dependent measures are not due to differences in value (i.e. lower doses are not better

reinforcers than higher doses), but instead the difference in rates is due to the clearance of the drug and maintenance of a steady-state.

1.3.1.2 Direct Effects: Motoric Effects

Oftentimes, the effects of the drug on the body may change the mobility of the animal, and when using a single schedule, it is impossible to disentangle the changes in mobility from changes in value. According to rate-dependent measures of value, increases in the rate of responding are taken to mean that the drug or dose has high reinforcing efficacy and low response rates are associated with low efficacy; however, this may be misleading when considering other factors that could account for changes in response rate. For example, a stimulant may increase overall activity, which may be expressed as increased operant responding, whereas an opioid may decrease overall activity and lead to a decrease in operant responding. In both cases, the direct effects of the drugs will have altered the response rates, but this change was not due to differences' in the value of the drug doses.

To combat the conflation of motoric and rewarding effects, many studies use supplementary locomotor assays to attempt to control for the motoric effects of drugs. These studies assume a 1:1 relation between locomotor activity and operant responding - i.e increased locomotion will be associated with increased operant responses. However, it has been shown that drug-induced locomotor sensitization and self-administration rates are dissociable. In a study using the escalation model of CUD, it was found that for longer-access animals the level of cocaine self-administration was not associated with an increase in psychomotor sensitization and that for the shorter-access animals the amount of sensitization was negatively correlated with levels of cocaine self-administration (Ahmed & Cador, 2006). The same finding remained even during reinstatement tests after a 14-day withdrawal period (Ben-Shahar, Ahmed, Koob, & Ettenberg, 2004). In a further study, 1 month after the last self-administration session, injections of cocaine produced increased locomotor activity relative to saline, but there was no correlation between previous self-administration experience (6-hr, 1-hr, acute cocaine) and the locomotor response produced at low doses of cocaine (Ferrario et al., 2005). Therefore,

additional locomotor assays are not enough to control for the coupling of motoric and rewarding effects when using single schedules.

1.3.2 Invocation of the Cardinal Scale

The main theoretical issue regarding single schedules is that offering a commodity via a single schedule disregards that all rewards must be viewed in context. The contextual dependency of decisions is characterized in behavioral economics (e.g., Glimcher, 2011; Kahneman & Tversky, 1979) and represents the theoretical assumption that all choices must be viewed as relative to other available commodities. By ignoring that context, single schedules assume that there is a 'True', invariant value of a commodity that can be uncovered and quantified. One common invocation of the cardinal scale is the use of essential value in economic demand models. In Equation (1), the demand equation (Hursh & Silberberg, 2008), essential value is the elasticity of a commodity (α) across the unidimensional space of unit price after normalizing the differences in maximum consumption (Q_0). The goal of essential value is to manipulate unit price to determine a single measure of reward value that can then be used to compare different commodities (e.g. Christensen, et al., 2008a; Schwartz et al. 2019; Smethells, Harris, Burroughs, Hursh, & LeSage, 2018) or characterize 'addiction-like' vulnerabilities in decision-making (e.g. Christensen, et al., 2008b; Bentzley, Jhou, & Aston-Jones, 2014; Murphy, Mackillop, Skidmore, & Pederson, 2009)

The characterization of value as an absolute, however appealing, is flawed in that it ignores that different dimensions (i.e. effort, magnitude, delay, probability, etc.) are not psychophysically scaled the same (Stevens, 1957). For example, unit price deals with cost, otherwise known as effort. If essential value does indeed represent an absolute measure then altering another dimension such as magnitude so that the unit prices are equivalent should lead to the same essential values. However, manipulating cost and magnitude produce different estimates of essential value (Smith, Rupprecht, Sved, & Donny, 2016), and subject's choices between commodities with identical unit prices but different cost or magnitude are not equivalent (Madden, Bickel, & Jacobs, 2000). Additionally, essential value can be altered by the presence of other concurrent commodities (Carroll & Rodefer, 1993; Smethells et al. 2018), meaning that value is

dependent on the decision-making context. Single schedules, by offering drugs in isolation, miss a vital facet of reward valuation that is crucial to understanding drug value; all decision contexts include some variant of choice alternatives, and valuation of any reward is only understood in reference to those alternatives.

1.4 Concurrent schedules

To combat the pragmatic and theoretical issues seen with single schedules, a choice procedure with two alternatives can be used to determine changes in relative valuation and thus decision-making processes. As opposed to a single schedule, where only one reinforcer is presented at a time, concurrent schedules make use of two options, with distinct operandi, that have consequences that the respondent can freely allocate behavior across. The options can then be manipulated in terms of delay, probability, and magnitude, or even be used to compare drug and non-drug reinforcers. This type of procedure not only has methodological advantages over single schedules of reinforcement but also is more applicable to valuation and decision-making analyses in real life(see Banks et al., 2015 for review).

The derivation of the switch from single to concurrent schedules can be visualized through the evolution of the mathematical models used to make quantitative, orderly, and theoretically-based predictions about choice behavior. The first model of decision-making behavior began with the observation that response rates appeared to be under orderly control of the relative reward rates in variable-interval schedules. This observation led to the quantification of the effect by Herrnstein (1961) as follows:

$$\frac{B_1}{B_2} = \frac{R_1}{R_2} \tag{3}$$

B1 and B2 are response rates for option 1 and option 2, R1 and R2 are the reinforcement rates for the same options. Although the prediction that relative responding rates will match that of the relative reinforcement rates works well in a variety of conditions, it needed to be further altered due to pragmatic issues regarding rate of output and the adaptation to use with single schedules. It was noted that the response rate could

not be linearly related to reward rate because organisms have a maximum motoric output for a given manipulandum, and thus the best fitting equation must allow for an asymptote in responding. Additionally, adjustments needed to be made to account for the fact that responding for the reward determined by the experimenter was not the only response available to the organism, and thus 'leisure behavior' in the case of single-schedule paradigms were included, leading to Herrnstein's hyperbola (Herrnstein, 1970):

$$\frac{B_1}{B_e \ldots + B_N} = k\frac{R_1}{R_e \ldots + R_N} \tag{4}$$

The rate of responding behavior for the two options (B_1, B_N) and that of responding for anything other than the scheduled commodity (B_e) is now a function of its rate of reinforcement (R_1) scaled by the organism's maximal rate of responding for a given operant (k), divided by the rate of reinforcement for all other concurrently-available scheduled alternatives (R_N) and all other non-scheduled alternatives (R_e). R_e was an attempt to control for non-scheduled reinforcing alternatives in single schedules, and B_e, extraneous behavior, was meant to account for some of the confounding motoric effects seen in single schedules. But these additions were not fully effective because the lack of experimental control makes R_e difficult to evaluate and B_e was not able to effectively differentiate the motoric effects from motivational effects (see Dallery & Soto, 2004 for review). However, in concurrent rather than single schedules the choice for each option must be viewed as relative to the choice for the other. Thus, allowing for increased control over the relative effects of choice between the alternatives making R_e and B_e no longer necessary. Instead, deviations from the matching law (2) were accounted for by individual biases for one alternative or by a lack of sensitivity to relative reinforcer rates, leading to Baum's generalized matching law (Baum, 1974):

$$\frac{B_1}{B_2} = b\left(\frac{R_1}{R_2}\right)^s \tag{5}$$

Equation 4 is the first in a series of more modern matching equations called power functions (McDowell, 2005). Here, again, B1 and B2 are response rates for each alternative, and R1 and R2 are the reinforcement rates for the same options. s and b are empirical constants representing the sensitivity to relative reinforcer rate and bias,

respectively. Sensitivity refers to how well the subject is able to discriminate between the differences in the reinforcer dimension. This term maps the effects of the relative differences in reinforcer rate across alternatives onto differences in choice across them. "Greater" detection occurs if s is greater than 1, "lower" detection occurs if s is less than 1, and perfect matching occurs when s is equal to 1. Bias refers to a subject's predisposition for one option over another. A bias for the first option is seen if b is greater than 1, a bias against option 1 is seen if b is less than 1, and there is no bias when b is equal to 1. Finally, Baum created a logarithmic form of the generalized matching equation to make the output linear.

$$\log\left(\frac{B_1}{B_2}\right) = s\log\left(\frac{R_1}{R_2}\right) + \log b \tag{6}$$

By adding the choices for each option and their relative reinforcement rates, a linear regression can be fit to the data such that s is the slope and b is the intercept.

As mentioned earlier, the options can be manipulated on multiple reinforcer dimensions (i.e. magnitude, probability, delay, etc.) which can affect choice behavior (Rachlin & Baum, 1969; Rachlin, 1971). To account for the effects of multiple dimensions of reward on choice behavior, the relative rates of each dimension were concatenated as follows.

$$\frac{B_1}{B_2} = b * \frac{R_1}{R_2} * \frac{M_1}{M_2} * \frac{I_1}{I_2} * \frac{\dots X_1}{\dots X_2} \tag{7}$$

In Equation 6, the relative behavior (B) is a function of the relative rates of reward (R), magnitude (M), Immediacy (the inverse of delay; I), and other extraneous dimensions between the two alternatives (X).

$$\frac{B_1}{B_2} = b\left(\frac{R_1}{R_2}\right)^{s_R} * \left(\frac{M_1}{M_2}\right)^{s_M} * \left(\frac{I_1}{I_2}\right)^{s_I} * \left(\frac{\dots X_1}{\dots X_2}\right)^{s_X} \quad (8)$$

$$\log\left(\frac{B_1}{B_2}\right) = s_R \log\left(\frac{R_1}{R_2}\right) + s_M \log\left(\frac{M_1}{M_2}\right) + s_I \log\left(\frac{I_1}{I_2}\right) + s_x \log\left(\frac{\dots X_1}{\dots X_2}\right) + \log(b) \quad (9)$$

Then each dimension was raised to its own sensitivity parameter where $s_{R, M, I, \dots X}$ represent the scaled sensitivity to changes in those dimensions. Again, a logarithmic form was created for linear analysis (8).

The use of mathematical models to analyze behavioral output allows for testable predictions of changes in behavior in different scenarios. Since the equations predict responding, deviations from the expected outcomes can describe the sensitivity to changes in one or more dimensions of reward, and by extension changes in the decision-making process. As Stout et al. (2004) put it, cognitive modeling can allow for the connection neuropsychology and behavior.

1.5 Value-Based Decision-Making in CUD

As only a relatively small fraction of total cocaine users transition from controlled drug use to developing disordered drug-taking (SAMHSA,2020), it is clear that it is not the effect of the drug itself that leads to addiction, but rather a combination of the hedonic effects of the drug combined with the drug-related changes in neurobiology and behavior that lead to CUD. Oftentimes these changes in behavior are seen as alterations in decision-making processes. For example, one of the diagnostic criteria for CUD is continued substance use despite harmful consequences (DSM-5). For example, pursuing and using addictive substances, such as cocaine, despite ill effects on health, employment, and relationships. If one chooses to use cocaine or pursue drug-related activities, they are necessarily foregoing other activities or rewards to which they could allocate their finite amounts of time and/or money. This shift in behavioral preferences to a state in which cocaine is chosen at the expense of other alternatives is indicative of the decision-making alterations seen in CUD and is thought to be an alteration in the relative value of the drug. In order to quantify and measure these changes in behavior, mathematical modeling techniques can be used to detect changes in value and value-

based decision-making. Therefore, modeling is an ideal tool to compare two opposing theories of drug addiction, habit theory and relative value theory. These theories both rely on the importance of DA, neuronal adaptation, and associative learning processes to explain the changes in the way the value of the drug is used to make decisions, but differ in how the valuation processes shift after the development of SUD.

1.5.1 Habit Theory of Addiction

In this theory the development of SUD is viewed as a transition from initial voluntary drug use, driven by the reinforcing effects of the drug, to loss of control over behavior, driven by compulsive, habitual actions (Koob & Le Moal, 1997, 2001, 2005; Lüscher, Robbins, Everitt, 2020). The actions are compulsive in the sense that the negative costs associated with the drug are discounted and do not deter the drug-seeking behavior (Hogarth, 2020) and habitual in the sense that the drug-seeking is not mediated by the value of the drug but instead by associations between the drug and the response due to training. Addictive drugs act as instrumental reinforcers, increasing the likelihood of the responses that produce them, which allows for self-administration procedures. It is thought that in these procedures, at first, the drug-seeking is goal-directed (i.e. a lever press to obtain the drug), but as training continues and the instrumental performance (i.e. lever press) is repeatedly paired with the stimuli associated with the administration of the drug, the stimulus-response (S-R) association increases and eventually dominates the behavioral output. This shift is thought to lead to habitual learning where the drug serves to strengthen the S-R association but is not the goal of the response. The instrumental response for the reinforcer is no longer goal-directed, but now automatic, whether that be through habitual or compulsive control. Therefore, devaluing the reinforcer does not affect the instrumental responding acquired by habit learning. In the habit theory of addiction, the relative value of the drug reinforcer becomes superfluous as the actions are driven by habitual responding after chronic drug use.

This changeover from voluntary to more habitual drug use is thought to represent a degradation in decision-making processes and a change of functioning in circuitries that mediate executive control. In humans with CUD, there is a loss of grey matter in regions of the anterior cortex, which may be associated with impairments in inhibitory control

(Ersche et al., 2013). These impairments are most often seen as impulsive decision-making processes as it has been demonstrated that cocaine users exhibit deficits in tasks related to impulsivity. These include deficits in response inhibition in Go/No Go tasks (Verdejo-Garcia et al. 2007a), in processing reward and punishment contingencies in the Iowa Gambling Task (IGT) (Verdejo-Garcia et al. 2007b; Bechara at al. 2002; Kjome et al. 2010; Hulka et al., 2013) and a preference for smaller sooner rewards in Delayed Discounting tasks (Kirby & Petry, 2004; Heil et al. 2006; Bickel et al. 2011). Similar patterns of behavioral changes have also been seen in rodent models of CUD. Studies have found that animals that have undergone escalation procedures have shown not only the expected increased intake of the drug but also evidence of compulsivity shown via progressive ratio schedules (Paterson & Markou, 2003; Wee, Mandyam, Lekic & Koob, 2008), increase drug-induced and stress-induced reinstatement of drug-seeking (Kippin et al 2006, Ferrario et al. 2005, Knackstedt et al. 2007), and persistent responding despite concomitant punishment (Vanderschuren & Everitt, 2004; Deroche-Gamonet el al., 2004; Pelloux, Everitt, & Dickinson, 2007). The deficits in these measures imply a change in the ability to properly evaluate and use value-based feedback to make decisions about the future. Instead, those with CUD are thought to make decisions that are impulsive and focused on gaining immediate rewards rather than choices that will allow them to obtain greater rewards or forgo future punishments. The impairment in executive control exacerbates the compulsive drug-seeking and taking; creating a cyclic effect with more years of abuse related to poorer decision-making (Bechara et al., 2001; Rogers et al., 1999; Everitt & Robbins, 2015). Therefore, understanding the decision-making processes underlying drug preference is important to improve SUD treatments (Kalivas &Volkow, 2005; Heyman 2013).

The transition from voluntary to habitual is thought to occur not only in behavior but also in neurobiology. In the initial stages of cocaine use (recreational use) the stimulant increases DA release in the ventral striatum (Boileau et al. 2006). But in habitual drug use, associated with CUD, the DA is released in response to drug-associated cues in the putamen, part of the dorsal striatum (Wong, D. et al., 2006). The habit theory of addiction is centered around the process of overriding the circuitry that uses relative value to make decisions and shifting the control to the habitual circuitry

which is not sensitive to value. This transition is used to account for the continued use of the drug despite negative consequences, one of the behavioral hallmarks of SUD.

1.5.2 Relative Value Theory of Addiction

In contrast to habit theory, where the initial drug use is based on value and the secondary effects are explained through separate non-value-based processes that override or exploit the reward system, in the relative value theory of addiction both the initial drug use as well as the secondary effects are explained by changes in value. In relative value theory, the continued choice for drug alternatives is not accounted for by a disruption of the decision-making mechanisms but instead by a shift in the subjective value of the drug, such that now it is more valuable than other alternatives. Relative value theory originates from concepts found in behavioral economics which state that all choices are rational and based on the relative value of the alternatives to determine the likelihood that either option is chosen. While subjective value cannot be measured directly, it is revealed by choice procedures where the relative price of the drug as compared to other alternatives can be established.

In human concurrent choice tasks, participants choose between a drug and a natural reinforcer. These studies have found that drug choice was significantly associated with dependence severity and drug use in experiments that used pictures (Hardy et al., 2018; Moeller et al., 2013) or actual consumption of the rewards (Stoops et al., 2012). Preferential drug choice was also associated with increased negative affective states, such as depression and anxiety (Hardy et al., 2018), which are known to be risk factors for dependence formation and relapse (Crum et al., 2013; Mathew et al., 2017; Samet et al., 2013). Importantly, studies run to compare concurrent choice behavior between self-administered cocaine and a species-specific non-drug alternative (money for humans, food for rhesus monkeys and rats) showed a similar pattern of cocaine choice across both human and non-human animals (Lile et al., 2016; Thomsen et al., 2013) such that increasing the dose of cocaine increased cocaine choice and vice versa; increasing the value of the alternative increased choice for the alternative. This shift in choices supports the idea that the concurrent choice task indexes the relative value of the drug and non-drug rewards. Since choices in concurrent choice tasks are sensitive to changes in the

magnitude of either alternative, it implies that the mechanisms for comparing or establishing the value of a reinforcer are not impaired in SUD. Thus, the continued choice of drug is not necessarily a byproduct of disrupted decision-making abilities but an increased preference for the drug caused by a shift in relative valuation.

1.6 Introduction to the Current Experiment

As mentioned above, changes in value-based decision-making are thought to underlie the behavior patterns seen in SUD but there are various types of tasks that study decision-making, ranging from simple delay discounting to more intricate gambling tasks. Each of these tasks is an example of a concurrent schedule but they differ in their complexity and in the different reinforcer dimensions they seek to manipulate in order to examine relative valuation processes. The task chosen for this experiment is a concurrent choice task that measures decision-making between two isomorphic food options with varying probabilities of reward. In this way, it is more lifelike than traditional two-option choice tasks with fixed outcome probabilities. The different probability blocks are not signaled, so the animal must constantly re-evaluate the options to determine which one has the higher probability of delivering reward at a given time. Therefore, although the animals employ the same general tactics every day, their individual choices must remain sensitive to the changes in relative value across choice options.

The goal of the present study was to investigate, directly, changes in decision-making over the course of escalation of cocaine intake. Specifically, this study aims to compare rats with assumed regulated and dysregulated intake at timepoints throughout the escalation procedure and thus to compare any changes in behavior based on the predictions of habit theory and relative value theory to determine which is more appropriate for describing CUD. To compare these two theories, a concurrent choice task was run in tandem with an escalation procedure, which was used as a rodent model for developing CUD-like behavior. After the escalation procedure, the rats that underwent longer access to cocaine (6hr) should exhibit the characteristic increase of cocaine intake over time that is associated with the assumed dysregulation of intake, whereas the rats with shorter access (1hr) should maintain regulated intake patterns and serve as a control

to account for the effects of the drug in the brain without the accompanying behavioral changes. In terms of alterations in behavioral output after escalation, habit theory would predict that the increased drug intake in the longer access animals would be accompanied by a shift in the behavior from goal-directed to habitual, which would account for the increased intake over time; further, it would predict that the shift would also lead to a disruption in decision-making abilities. Conversely, if there is not a change in decision-making after escalation of intake, this would correspond with the predictions of relative-value theory in which decision-making abilities remains intact and shifts in the relative-values of the options explains alterations in choice behavior. However, in this present experiment we are not able to assess any shifts in relative-value the cocaine as compared to food so further studies are needed to test the cocaine-food relative value shifts predicted by relative-value theory. To compare decision-making over time, the rat's behavior was compared at a baseline, throughout the 21-day escalation period, during a return to 1-hr access for all animals, and during a forced abstinence period. This week-by-week analysis will allow for the detection of changes in decision-making via escalated intake and determine if those changes, if any, are long-lasting.

CHAPTER 2. METHODS

2.1 Subjects

Fifteen male and sixteen female Sprague-Dawley Rats (Harlan Inc.; Indianapolis, IN, USA), weighing approximately 250-275 g on arrival were used. Rats were individually housed (12:12hr light:dark cycle) with ad libitum access to food and water in their home cage. During food restriction rats were maintained at approximately 85% of their free-feeding body weights. All experiments were conducted during the light phase. All experiments were conducted according to the 2010 *NIH Guide for the Care and Use of Laboratory Animals* (8th Edition) and were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

2.2 Apparatus

Experiments were conducted in operant chambers (ENV-008, MED Associates, St. Albans, VT) enclosed within sound-attenuating compartments (ENV-018M). Each chamber was connected to a personal computer (SG-502), and all chambers were operated using MED-PC. Within each chamber, a recessed food receptacle (ENV-200R2MA) outfitted with a head-entry detector (ENV (ENV-254-CB) was located on the front response panel of the chamber, two retractable response levers were mounted on either side of the food receptacle (ENV-122CM), and a white cue-light (ENV-221M) was mounted above each response lever. The back-response panel was outfitted with two nosepoke response receptacles (ENV-114BM) directly opposite to front response levers, a house-light (ENV-227M) was located at the top of the back panel between the two nosepoke response receptacles with Sonalert© tones (ENV-223 AM and ENV223-HAM) located on either side of the house-light. Food pellets (45-mg Bio-Serv Precision Pellets; Flemington, NJ) were delivered via a dispenser (ENV-203M-45). Drug infusions were delivered via a syringe pump (PHM-100) through tubing strung through a leash (PHM-120) that attached to a swivel (PHM-115) above the chamber.

2.3 Drugs

Cocaine hydrochloride, gifted from the National Institute of Drug Abuse (Bethesda, MD, USA), was mixed with sterile saline (0.9% NaCl).

2.4 Initial Training

2.4.1 Magazine Shaping

Rats were first trained to retrieve food pellets from the food receptacle for four consecutive days. Rats were placed in the operant chambers and given 25 minutes to retrieve and consume 25 food pellets, delivered on a 60-s fixed time schedule.

2.4.2 Orienting Response

Next, an orienting response was added. The start of each trial was now signaled by the illumination of the house-light. A contingent response, head-entry into the magazine, would result in the offset of the house-light and illumination of either the left or right nosepoke port. Breaking the beam in the illuminated port resulted in the delivery of a food pellet in the magazine. Each session consisted of 30 trials, 15 left- and 15 right-nosepoke port illuminations. Ports were illuminated individually and pseudo-randomly, where no more than 6 presentations of the same port would occur in a row. Trials were separated by a 10-s ITI. Rats were trained on this response chain for four days.

2.5 Concurrent Choice Task

Rats were then trained on the decision-making task. The start of the trial was signaled by the illumination of the house-light, as in training. A head-entry into the magazine resulted in the offset of the house-light and the illumination of both the left and right nosepoke ports. Rats selected either the left or right port by breaking the beam. Once a selection was made, both ports went dark and the reward was delivered or not. On rewarded trials a pellet was dispensed into the magazine, the magazine light was illuminated, and a tone was played for 5-s. On non-rewarded trials, there was a time out for 5-s. Trials were separated by a 5-s ITI regardless of reward status.

The reward was set up on either the left or right nosepoke port based on 4 probability blocks. The ratio of reward for the blocks were 6:1 (6), 2:1 (2), 1:2 (0.5), and 1:6(0.167). The block order was pseudo-randomly shuffled each session. For example, if the first block was 1:6 then the second block could be either 2:1 or 1:2. Each block consisted of 30 trials, for a total of 120 trials per session. Blocks were separated by a 2-minute blackout period. Rats were trained on this task until stable, about 30 days.

2.6 Lever-Training

To pretrain responding on the levers before surgery, rats were trained to lever press on a fixed ratio 1 (FR-1) schedule of reinforcement, where a food pellet was delivered

following each press on the active lever (counterbalanced for each side of the experimental chamber). The opposite, inactive, lever was not presented at this time. Each session consisted of 50 trials or an hour whichever came first. Training consisted of five consecutive 1-h sessions for five days preceding surgery.

2.7 Catheter Surgery and Maintenance

Rats then underwent surgery for implantation of a chronic indwelling jugular catheter. Rats were first anesthetized with a ketamine (Schein, Dublin, OH)/xylazine (Akorn, Inc., Decatur, IL)/acepromazine (Boehringer Ingelheim, St. Joseph, MO; 75/7.5/0.75 mg/kg) mixture at 0.15 ml/100 g body weight (i.p.). The female rats were anesthetized with a mixture that excluded acepromazine. Catheters were inserted into the jugular vein, extended under the skin, and exited the body through an incision on the scalp. A cannula was attached to the end of the catheter and secured to the skull using dental acrylic and four jeweler screws. Animals were given a week to recover after surgery. After each self-administration session, catheters were with 0.2ml of a gentamicin-heparin-saline solution to prevent infection and preserve patency. Catheter patency was checked periodically and at the end of the self-administration portion of the experiment by muscle tone loss following 0.2ml remifentanil administration.

2.8 Cocaine Self-Administration and Escalation

Methods were similar to those published previously (Ahmed & Koob, 1998) with minor changes. Following recovery, all rats were trained to self-administer cocaine on an FR-1 using the same active/inactive lever assignment from food training. Presses on the active lever resulted in an infusion of cocaine, retraction of both levers, and the illumination of the cue light above the active lever for 5.9-s. After 5.9-s both levers were presented and the next trial began. Presses on the inactive lever had no consequence. Acquisition of cocaine self-administration using a dose of 1 mg/kg/infusion was continued for 7 days and then the dose was reduced to 0.3 mg/kg/infusion for another 7 days of acquisition. The remainder of the self-administration sessions used a 0.3 mg/kg/infusion dose.

Animals were then assigned one of two groups. Animals assigned to the short-access group (n=16; 7 males and 9 females) continued to self-administer cocaine under the 1-hr access conditions from acquisition for an additional 21 days. Animals assigned to the long access group (n=15; 8 males and 7 females) were switched to the 6-hr access for 21 days. After this 21-day period all animals returned to the 1-hr access for an additional 7 days.

2.9 Daily/Overall Timeline

Each day the concurrent choice task was run in the morning. Once the rats had completed the task they were returned to their home cages for 1 hour before they were run in the self-administration sessions. Rats were run in different boxes for the concurrent choice and self-administration tasks to reduce the context effects. The periods of the experiment for analysis were 1-week averages as follows: “Baseline”-before catheter surgery, “Acquisition”- 0.3mg/kg/infusion training, “Escalation”- 21 days at either 1hr or 6hr, “Return to 1hr”- all rats returned to 1hr access, and “Forced Abstinence”- concurrent choice task alone with no self-administration in the afternoon.

CHAPTER 3. ANALYSIS

3.1 Self-Administration

For each period of the self-administration procedure; Acquisition, Escalation, and Return to 1hr, model-comparisons predicting the number of infusions of 0.3mg/kg of cocaine were fit to determine the best model using the following taxonomy: Model A included Subject nested within Access(1hr or 6hr) as predictors of both the intercept and the slope. The continuous timepoint variable Day was centered to make model coefficients more interpretable (Algina & Swaminathan, 2011; Enders & Tofighi, 2007). Model B was the same but included Subject nested within both Access and Sex the interaction between Sex and Access as predictors of the intercept and slope. Models were compared using ΔAIC values (the difference in Akaike Information Criterion (AIC)

values between models) and the accompanying evidence ratios (Burnham, 2002; Burnham, 2011); evidence ratios indicate goodness-of-fit of the best model relative to the second-best model. Only statistics from models with the highest evidence ratios were reported.

3.2 Concurrent Choice Task

Choice behavior was calculated as a seven-day average ratio of choices for Option A as a function of Option A's relative reward rates. To create a linear relationship, the raw ratios and probability blocks (6, 2, 0.5, 0.167) were log transformed. Molar data was analyzed using the Generalized Matching equation (described above; (4 & 5)). As mentioned above, the bias term (intercept) captures preferences for the left or right irrespective of relative reward rates between the two options. Lower values of *b* reflect a greater bias for the right, and values closer to 1 (or 0 when logged) reflect no bias. The constant *s* (slope) captures individuals' sensitivities to changes in the relative reward rates between the two options. Perfect matching between behavior and rates would create an *s* value of 1.

Hierarchical linear models predicting Log Choice for Option A were fit according to the following taxonomy: Model A included Subject as a random factor nested within Access (1hr or 6hr) as well Condition (dummy coded week by week; Before Surgery(1), After Surgery(2), Acquisition(3), Weeks 1-3 of Escalation(4-6), Return to 1hr access(7), and Forced Abstinence(8)) as predictors of both the intercept and the slope. The continuous variable Log Raw Ratio (the logged values of the probability blocks) was centered to make model coefficients more interpretable. Model B was the same but also included Sex and the interaction between Sex and Access. As before models were compared using ΔAIC and only statistics from models with the highest evidence ratios were reported.

To compare the performance of steady state behavior, hierarchical linear models predicting Log Choice for Option A during the Escalation period were fit according to the following taxonomy: Model A included Subject as a random factor nested within Access (1hr or 6hr) as predictors of both the intercept and the slope. The continuous variable Log

Raw Ratio (the logged values of the probability blocks) was centered to make model coefficients more interpretable. Model B was the same but Log Choice for Option A was now calculated as the averages of the last 10 trials of each block (rather than all 30 trials in Model A). As before models were compare using ΔAIC.

Finally, to check the form of the model, we compared the linear model described above to that of a cubic model and compared using ΔAIC.

3.3 Preference Reversal

To illustrate the changes choice for option A before and after a shift from a low to a high probability block (i.e. a preference reversal), choice behavior was calculated on a trial-by-trial basis and reported as Percent Choice for Option A. In preference reversals, the animal first encountered a block that favored Option B (i.e. 1:2; 1:6) then switched to a block that favored Option A (i.e. 2:1; 6:1). Percent Choice for Option A is a group average of the percent choices for Option A of each of the final 5 trials of the block that favors Option B and each of the 30 trials after the switch to the block that favors Option A. The trials are averaged over the 21 days of the escalation period.

Hierarchical linear models predicting Percent Choice for Option A were fit according to the following taxonomy: Model A included Subject as a random factor, nested within Access (6hr or 1hr) as predictors of both the intercept and the slope. The continuous variable Trial was centered to make model coefficients more interpretable. Model B was the same but also included Sex and the interaction between Sex and Access.

3.3.1 Preference Reversal: Endpoints

Additionally, the endpoints of the preference reversals were compared. Endpoints were calculated as averages of the choices for Option A during the last 5 trials of both the low (1:6 or 1:2) and high block (6:1 or 2:1 respectively).

Hierarchical linear models predicting Percent Choice for Option A were also fit to the endpoint analysis according to the following taxonomy: Model A included Subject as

a random factor, nested within Access (6hr or 1hr), and Magnitude of the reversal (1:6 to 6:1; large switch or 1:2 to 2:1; small switch) as predictors of both the intercept and the slope. The continuous variable Block was centered to make model coefficients more interpretable. Model B was the same but also included Sex and the interaction between Sex and Access. As before models were compared using ΔAIC and only statistics from models with the highest evidence ratios were reported.

CHAPTER 4. RESULTS

4.1 Cocaine Self-Administration

Figure 1 shows the self-administration infusions of 0.3mg/kg cocaine throughout the Acquisition, Escalation, and Return to 1hr access periods. Overall, both groups had low, stable responding during the acquisition period. Then during the escalation period, the 6-hr access group showed an escalation in drug-taking that increased over time whereas the 1-hr access group's responses remained low and stable. Finally, when 6-hr access rats were returned to the 1-hr access condition their responses became similar to those of the 1-hr access group. To quantify these changes in self-administration behavior over each time period, multilevel models were fit to the data.

4.1.1 Acquisition

In the acquisition period, Model A (Access only) was used for analysis as the evidence ratio was 330876.34, showing strong support for Model A over Model B. The model revealed no main effects of Access on cocaine intake but a significant main effect of Day [$F_{1,29.31} = 8.32$, $p = 0.0073$] with an increase of 1.51 infusion per day. The average centered intercept was estimated to be 15.82 infusions of cocaine, which is significantly different from 0 ($p = <0.0001$). In summary, there were no differences between the groups during the acquisition period and both groups self-administered a significant amount of cocaine.

4.1.2 Escalation

In the escalation period, Model B (Sex and Access) was used as the evidence ratio was 223.18, showing strong support for Model B over Model A. The model revealed no main effects of Sex, but a main effect of Access [$F_{1,27} = 33.72$, $p < 0.001$], where the intercept for the 6hr access group was significantly higher than that of the 1hr access group (79.53 and 14.91 infusions, respectively). There was also a main effect of Day [$F_{1,27.04} = 5.36$, $p = 0.0284$] and also an interaction between Access and Day [$F_{1,27.04} = 4.32$, $p = 0.047$] such that the estimate for the slope for the 6hr access group at the center of the escalation period increased significantly from 0 by 1.86 infusions per day, whereas the 1hr access group increased by 0.19 infusions per day. In summary, the 6hr access rats took more infusions and increased their taking at a faster rate than 1hr access rats over the escalation period.

4.1.3 Return to 1hr

In the Return to 1hr period, when all animals had 1hr access to cocaine, Model A (Access only) was chosen for parsimony because the evidence ratio was 1.33, showing weak support for Model B over Model A. The model found no main effects of Access or Day. The intercept was estimated to be 38.29, which was significantly different from 0 [$p <.0001$]. The average slope was estimated to be 0.72, which was not significantly different from 0 [$p = 0.34$]. In summary, there were no differences between the groups and their intake remained stable during the return to 1hr period.

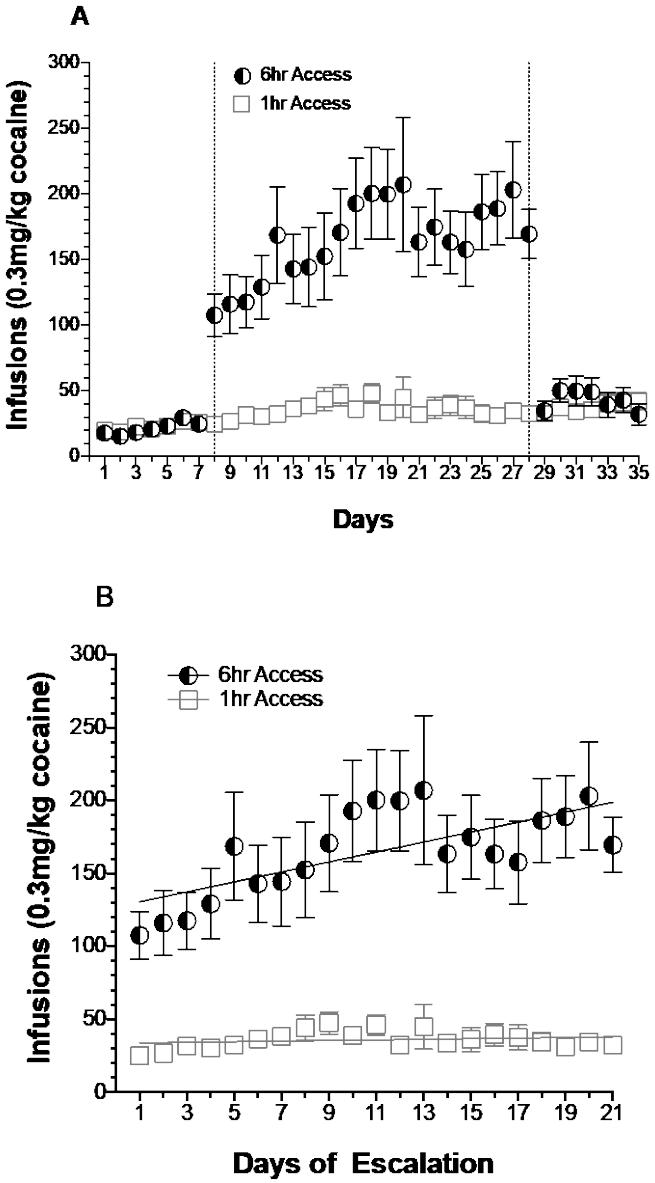

Figure 1: Cocaine Self-Administration

A) Mean (∓ SEM) infusions of 0.3mg/kg cocaine over acquisition (days 1-7), escalation period (days 8-28), and return to 1hr access (days 29-35) for both the 6hr and 1hr access rats. **B)** Mean (∓ SEM) infusions of 0.3mg/kg cocaine over the 21-day escalation period fit with a simple linear regression for each group

4.2 Concurrent Choice

Figure 2 shows the Log Raw Ratio choices for Option A as a function of the log of Option A's relative reward rates. Overall, both groups tended to prefer the option providing the greater reward odds (or the "richer" option), with preferences being stronger the more disparate the relative rates. The model chosen for analysis was Model A (Access only) as the evidence ratio was 2.6 e^{16} , indicating large support for Model A over Model B. This model revealed a main effect of Log Raw Ratio (slope) [$F_{1,29}$ = 874.89, p <.0001], such that both groups have a positive slope of 0.33. Additionally, there was an effect of the interaction between Log Probability and Condition [$F_{1,29}$ = 11.44, p = 0.0021] such that the slope positively increased with each subsequent week. In summary, both groups were sensitive to the relative probabilities of Option A, as seen by the slope, and improved their decision-making over time as seen by the interaction between Log Probability and Condition. There were no differences in decision-making due to Sex or Access.

The model chosen for the comparison of steady state during the Escalation period was Model A (all 30 trials) as the evidence ratio was 4.7 e^{43}, indicating large support for Model A over Model B. This model revealed a main effect of Log Raw Ratio (slope) [$F_{1,29}$ = 415.00 , p <.0001], such that both groups have a positive slope of 0.36. There was no main effect of Access. This model can be seen in Figure 2C. The support for Model A over Model B indicates that it is acceptable to include all 30 trials in the analysis of choice behavior rather than only the last 10 trials where the behavior is fully established.

The comparison of model form favored the cubic function with an evidence ratio of 1442.75, indicating support for the cubic model over that of the linear model. However, even though the AIC comparison favors the cubic model, the model comparison with Bayesian Information Criterion (BIC) was inconclusive. BIC penalizes model complexity more heavily than AIC and is therefore more likely to choose the more parsimonious model. When fitting models that are based on quantitative models of behavior it is also important to consider the theoretical implications of the form of the model. The current steps between the relative reward ratios are uneven. For example, a switch from 6:1 to 2:1 is larger than the switch from 2:1 to 1:2. These unequal step sizes may give the

impression of a non-linear relationship, which appears to have been picked up by the cubic form of the model. Because this cubic relation can be explained by the sampling size of the relative reward rats and the two likelihood criterion disagree, the linear model is more parsimonious and was chosen for all analyses of behavior.

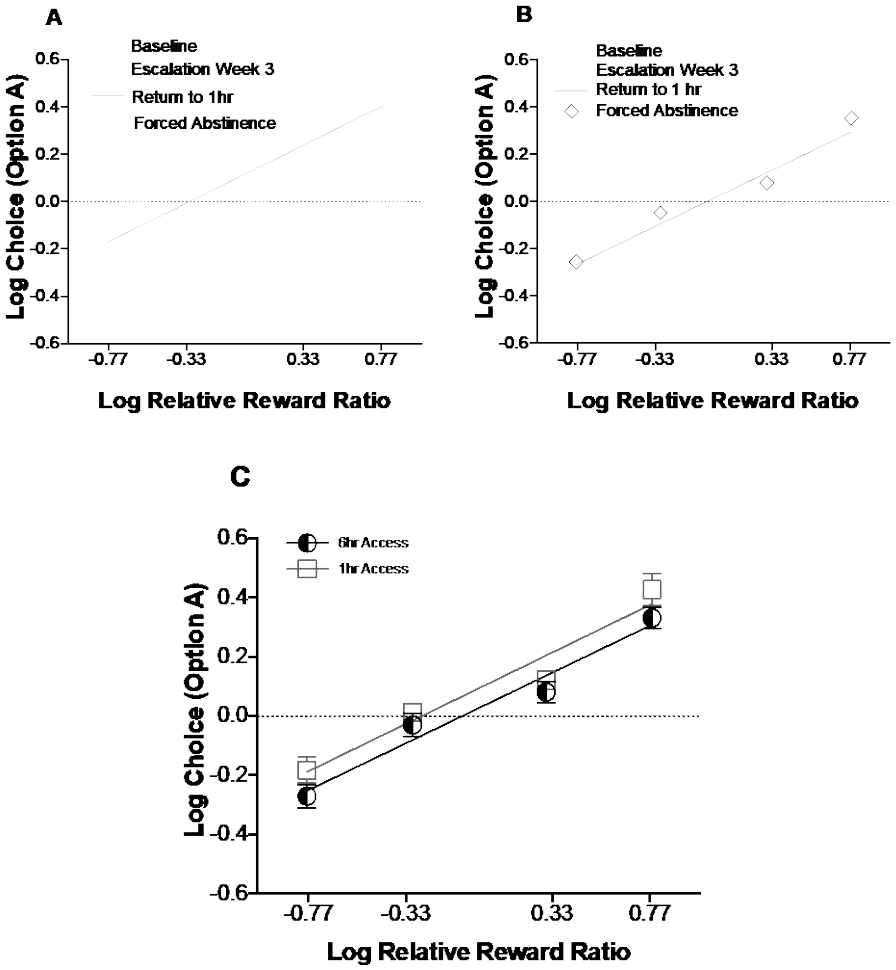

Figure 2: Concurrent Choice Task Macro Averages

A) Mean (∓ SEM) log raw ratio for choice for Option A over Option B as a function of Option A's log relative reward rate(1:6 as -0.77, 1:2 as -0.33, 2:1 as 0.33, 6:1 as 0.77) for 1-hr rats over 4 7-day averages (Baseline, Week three of the escalation period, Return to 1hr access, and Forced abstinence). B) Mean (∓ SEM) log raw ratio for choice as a function of Option A's log relative reward rate for 6-hr rats over 4 7-day averages. C) Mean (∓ SEM) log raw ratio choice a function of Option A's log relative reward rat during the third week of escalation for the 6hr and 1hr access rats.

4.3 Preference Reversal

Both 1hr and 6hr groups showed similar sensitivity to the change in relative reward rates for both 1:2 to 2:1 reversal and the 1:6 to 6:1 reversal (Figure 3). When the magnitude of the switch was large (1:6 to 6:1), the choice behavior tended to more rapidly increase for Option A compared to smaller magnitude switch (1:2 to 2:1)

For the preference reversal from the 1:6 to 6:1 block (Figure 3A), Model A (Access only) was chosen as the evidence ratio was over 11 billion, indicating strong support for Model A over Model B. This model revealed a main effect of Access [$F_{1,29}$ =7.99, p= 0.0084] such that the intercept for the 6hr animals was estimated to be 40.4 percent choice for option A and the intercept for 1hr animals was estimated to be 43.3 percent choice for Option A at trial 25. There was also a main effect of the centered continuous variable Trial [F $F_{1,29}$ =154.19, p<0.0001] such that the percent choice significantly increased over trials. But no interaction between access and day indicating that both groups similarly adjusted to the reversal of the optimal option.

For the preference reversal from 1:2 to the 2:1 block (Figure 3B), Model A (Access only) was chosen as the evidence ratio was over 3 billion, indicating support for Model A over Model B. This model revealed a main effect of Access [$F_{1,29}$ = 4.21, p= 0.049] such that the intercept for the 6hr animals was estimated to be 49.5 percent choice for option A and the intercept for 1hr animals was estimated to be 51.5% at trial 25. There was also a main effect of the centered continuous variable, Trial [$F_{1,29}$ =23.90, p<0.0001] such that the slope increased significantly over trials. But no interaction between access and day indicating that both groups similarly adjusted to the reversal of the optimal option.

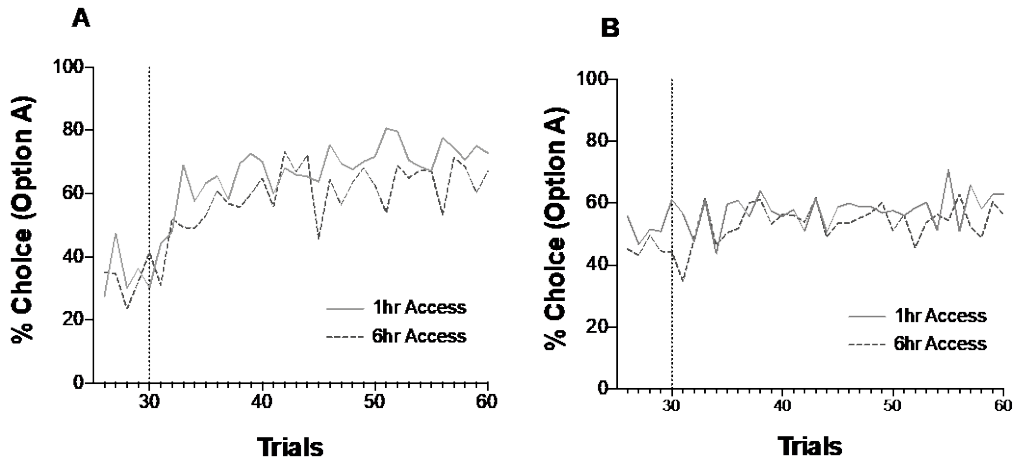

Figure 3: Preference Reversal

A,B) Percent choice of Option A (∓ SEM) during adjoining blocks in which the relative rate of reinforcement transitioned from low to high. The larger magnitude switch (1:6 to 6:1) is shown in A, and the smaller, (1:2 to 2:1) in B. Data to the left of the vertical line are the last 5 trials in the block in which the relative reinforcement rates favored Option B - 1:6 (A) and 1:2 (B). Data to the right of the vertical line are the next 30 trials for the block which the relative reinforcement rates favored Option A- 6:1 (A)and 2:1 (B). The lighter solid line represents the 1hr-access rats and the dark dashed line represents the 6hr-access rats.

4.3.1 Preference Reversal: Endpoints

Both 1hr and 6hr groups showed similar sensitivity to the change in relative reward rates for both large and small magnitude reversals (Figure4). As above, the larger magnitude reversal showed more rapid increases in the choices for Option A than the smaller reversal. There appears to be a difference in intercept, but not slopes seen between the groups. Indicating that although the groups may have had different starting points before the reversal, they adjusted similarly to the change in optimal option.

For the comparison of the endpoints for the two preference reversals (Figure 4), Model A (Access only) was chosen as the evidence ratio was $6.3e^{16}$, indicating support for Model A over Model B. This model revealed a main effect of Access [$F_{1,13.35} = 9.38$, $p = 0.0088$] such that the pooled intercept for the 1hr access group was 22.3 percent choice for Option A and the 6hr access group was 19.4 percent choice for Option A. There was also a main effect of the centered continuous variable, Block, [$F_{1,34.68} = 139.48$, $p<.001$] such that there was a positive slope from the transition from the low to the high probability block. Additionally, there was an interaction between the Magnitude of the reversal (1:6 to 6:1; large switch or 1:2 to 2:1; smaller switch) and the Block [$F_{1,34.68} = 49.87$, $p= p<.001$] such that the slope of the preference reversal was steeper for the large magnitude switch than the smaller magnitude switch. There was no interaction between Access and Block, therefore both groups similarly adjusted to the reversal of the optimal option despite the differences in starting points.

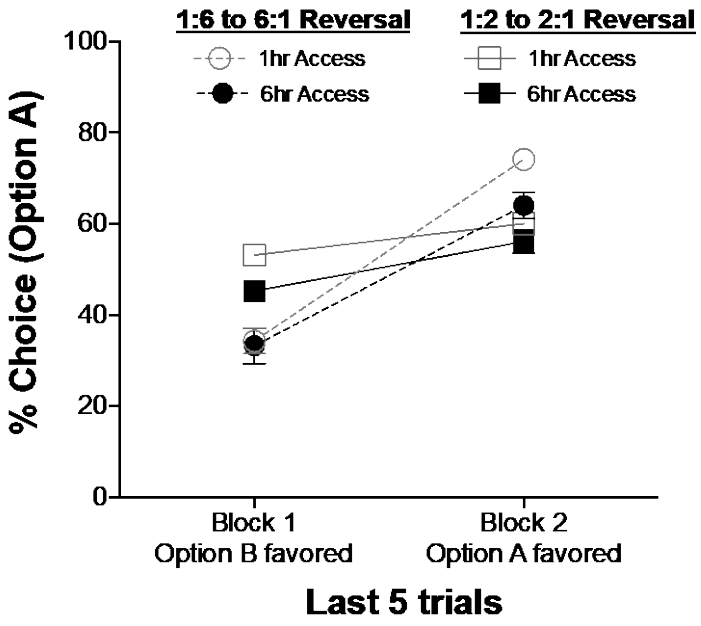

Figure 4: Preference Reversal: Endpoints

Percent choice of Option A (∓ SEM) averaged for the last 5 trials of the two adjoining blocks. Block 1 in which the relative reinforcement rate favors Option B and Block 2 which favors Option A. The circles represent the larger reversal, 1:6 to 6:1, and the squares represent the smaller reversal, 1:2 to 2:1. The open, gray symbols represent the 1hr access rats and the filled, black filled symbols represent the 6hr access rats.

CHAPTER 5. DISCUSSION

5.1 Discussion

The discussion of SUDs in the preclinical literature is largely centered around the brain disease model of addiction. In this model, SUD is considered a chronic relapsing disease, in which there are repeated cycles of binge/intoxication, withdrawal/negative affect, and preoccupation/craving. These cycles are accompanied by neurobiological changes in the mesocorticolimbic system related to drug usage that are thought to change the propensity of an individual to make subsequent choices for drugs (Koob & Volkow, 2016; Volkow, Koob, & McLellan, 2016). The correlation between neural and behavioral changes after chronic drug administration has led to theories centered around insensitivity to consequences and devaluation of rewards. Additionally, many of the theories posit that these insensitivities are linked to aberrant and maladaptive habit-based learning (Robbins & Everitt, 1999). For example, habit theory posits that initial drug-taking is driven by the rewarding effects of the drug, but after repeated use, the hedonic effects diminish as tolerance mechanisms increase the dosage required to obtain the rewarding effects of the drug and avoid withdrawal. In turn, these alterations are thought to lead to suboptimal or disordered decision-making, in which a person with SUD will choose the drug over other alternatives. Given the chronic nature of SUD in the disease model of addiction alongside the proposed impairments in decision-making mechanisms, this theory predicts that global decision-making would be altered after chronic substance use and that these impairments would be long-lasting.

The brain disease model of addiction is largely supported by animal models using single schedules of reward. But given the theoretical problems that rate-dependent models face (as discussed above), it is improper to use these schedules to determine the real-world implications of the effects of drugs on decision-making. To correct this inaccuracy and to compare two theories of addiction, this study measured decision-making over the course of chronic cocaine self-administration. The escalation of drug intake paradigm was used as an animal model of CUD and combined with a daily

concurrent choice task as well as a behavioral economic framework for analysis. The present experiment has shown that despite drastic differences in escalated cocaine intake, there were no differences in decision-making between the two groups. Choice behavior was viewed in light of Herrnstein's (1970) matching law (3), emphasizing that over time the relative rate of choice for a particular option will approximate the rate of reward for that option. Models using the generalized matching equation (Baum, 1974; Rachlin, 1971; (4 & 5) provided good descriptions of molar data for the choice task, indicating that the animals showed sensitivity to relative reward rates and allocated their decisions appropriately, similar to monkeys (Lau & Glimcher, 2005) and humans (Rutledge et al., 2009). Both the longer (6-hr) and shorter (1-hr) access rats favored Option A when the relative reward rates also favored Option A and gradually shifted their preferences to Option B when relative reward rates also switched, as seen in the analysis of preference reversal, indicating that despite the "disordered" intake after cocaine escalation, the rats showed no change in sensitivity to the reward ratios. Similar results have been found in laboratory decision-making procedures with substance-using populations who have shown sensitivity to relative reward magnitude, price, and delay (Moeller & Stoops, 2015; Jones & Comer, 2013; Griffiths, Rush, & Puhala, 1996). The sustained sensitivity to these manipulations implies that value-based decision-making remains intact in both rodent models and those with SUD. The retention of sensitivity to value manipulations is inconsistent with the predictions of habit theory, which posits that after chronic cocaine use the decision-making mechanisms used to evaluate the relative values of two alternatives become somehow impaired. Yet, since we see no changes in task performance, another theory might be considered to explain the changes in behavior seen in CUD.

There are several reviews urging the addiction research field to broaden its understanding of SUD and look beyond the brain disease model of addiction, arguing that it has not been as well-supported or as effective in creating new treatments as many had hoped (Hall, Carter, & Forlini, 2015; Kalant, 2010). As an alternate theory, a growing literature is accounting for addiction by using value-based mechanisms. From a behavioral economic viewpoint, the development of addiction is a reinforcement pathology, specifically a distortion in the valuation process seen through hyperbolic

discounting of rewards (Bickel et al., 1999; Madden et al., 1999; Myerson & Green, 1995). Discounting is a decrease in the value of a given reward that is proportional to the delay (i.e. initially a steep decline in the value when the delay is short, then the decreases in value become shallower as the delay increases; Ainslie & Haslam, 1992). Hyperbolic discounting can also be described by the common phrase "smaller, sooner and larger, later", describing the scenario in which a subject chooses a smaller reward that is delivered in a short time rather than a larger reward delivered at a delay. Delay discounting procedures that alter the magnitude and delay of rewards have often been linked with the construct of impulsivity, which has then been associated with the habit theory of addiction. However, studies that focus only on the change in relative value and not additional behavioral constructs show greater support for relative value theories. For example, one study found that SUD symptom severity is associated with greater relative value of the drug to a food alternative, but not greater discounting of opportunity or delay costs associated with the drug (Hogarth & Hardy, 2018). Other behavioral economic review papers have concluded that results from both demand and discounting procedures indicate an increase in the relative value of the drug after continued use (Bickel et al. 2014; MacKillop 2016).

In addition to the increased value of the drug, there is evidence to suggest that those with SUD show inhibited responses and attention towards non-drug reinforcers (Lubman et al., 2009). Similarly, increased drug-taking behavior was associated with diminished engagement in alternative, future-oriented activities (Meshesha et al., 2018). Both of these studies hint at a reduction in responses to non-drug rewards after chronic substance use. If so, not only is there an increase in the relative value of the drug after the development of SUD, but also perhaps a simultaneous decrease in the relative value of the non-drug alternatives. If indeed there is a shift in relative values such that the drug increase as alternatives decrease, this proposed distortion explains how there could be a continued choice for drug, yet the mechanisms for making value-based decisions could remain intact and functional. In this scenario, when faced with a choice between a drug and non-drug reward, hyperbolic discounting increases the relative value of the drug leading to its immediate use (Bickel et al., 2014). If discounting occurs and the relative value of the drug is greater than that of the non-drug alternative(s), the continued choice

for drugs can be explained not as a disruption in decision-making mechanisms, but as a product of a shift in the relative-value scale. This discounting behavior can also be viewed in light of the principles of Baum's generalized matching law (4) by using time-allocation instead of behavior as shown in Rachlin (2006).

$$\frac{T_1}{T_2} = b\left(\frac{R_1}{R_2}\right)^s \tag{10}$$

Given two activities to which time is allocated (T_1 and T_2), the proportion of time allocated to one of them equals the proportion of obtained reinforcers on that option. The proportions are then scaled by sensitivity, s, and bias, b, as before. Equation 9 implies that the time allocated to each activity is discounted by reinforcement contingent on the other activity. When viewed in this way, the hyperbolic discounting that leads to the use of drugs can be said to follow the stipulations of matching in that the option with the higher relative value (drug) is chosen more often. Based on this definition, decision-making abilities remain intact despite the choice for a reward that may have negative consequences in the future. In other words, the individual choices for drugs are maximizing local utility (i.e. at the present moment or trial-by-trial; Herrnstein & Prelec, 1992; Heyman, 2013; Rachlin, 1997) by choosing the more valuable option on each trial even though in the long run, these choices seem as if the decisions are controlled by habit or compulsion.

Given the lack of behavioral differences seen in longer and shorter access animals in this study, it seems that decision-making as a whole was not disrupted by chronic cocaine self-administration, suggesting that habit learning may not be the underlying cause of addiction. Instead, the data support relative value theories that posit that chronic exposure to the drug leads to a differential weighting of drug as compared to non-drug reinforcers. The transition from viewing SUD through the lens of habit theory to that of relative value theory is also supported by meta-analysis performed by Hogarth & Field (2020). They found that in human studies of SUD, dependence severity was not associated with insensitivity to the devaluation of the drug, contradicting the expectations of habit theory. In contrast, they found support for behavioral-economic-based theories that focus on the relative valuation of drug and non-drug alternatives. In relative value

theory vulnerability to drug dependence is driven by individuals attributing greater value to drug rewards, which can be exacerbated by negative affective states such as stress or sadness, in which users report using drugs as a coping mechanism. These findings suggest that instead of an impairment in valuation processes or habitual S-R relationships, the drug-seeking/taking behavior remains goal-directed even after chronic exposure.

5.2 Limitations

Although there was no change in global decision making, as measured by the molar averages of concurrent choice task behavior, there were significant differences found between the 1-hr and 6-hr access groups in the analysis of the preference reversal. One possible explanation for the differences between the access groups in the preference reversal analysis but not the molar choice analysis is that there were slight differences in the biases of the groups during the escalation period in which the analysis occurs (seen but not significantly different in the intercepts of figure 2C). Due to limitations in the number of animals that could be run at one time, groups were run at different time points and therefore could have had different biases from initial training. However, since the shifts in slopes are parallel between the two groups, they responded similarly to changes in valuation despite differences in individual biases which is the main outcome of the manipulation. In the future, groups will be counterbalanced and run concurrently to avoid group bias differences. Additionally, perhaps with a larger sample size for each group, it would be possible to negate those biases.

It is important to note that there have been contradictions in studies investigating changes in decision-making following chronic cocaine self-administration. For example, one study found deleterious changes in decision-making after cocaine exposure in the rat Gambling Task (rGT) (Cocker et al., 2019). However, the Iowa Gambling Task (IGT)(Bechara et al., 1994), and thus it's rodent counterpart, rGT, are known to have high inter-study and inter-individual variability (Steingroever et al., 2013; see Bull, Tippet, & Addis, 2015 for further review). This inconsistency may be due to the use of a wide number of procedural variables that differ between laboratories in both the IGT

(Areais et al., 2013) and the rGT (Visser et al., 2011). Additionally, as mentioned in a review of IGT, typically all 100 trials are included in the analysis instead of reaching a predefined criterion of performance before beginning the analysis. The inclusion of all trials means that healthy individuals with a slower learning rate are not flagged as a false-positive for impairments. (Bull, Tippett, & Addis, 2015). Therefore, it is possible that if the rats did not reach a stable baseline for behavior, the deleterious effects are sample variability in the task rather than negative effects of the drug exposure. In the current choice study, rats reached a stable baseline before the drug was introduced to avoid differences in learning rate and focus only on changes in decision-making relevant to the onset of drug self-administration.

5.3 Further Studies

More studies are needed to investigate manipulations of the various reinforcer dimensions of drug and non-drug reinforcers in CUD to determine the interplay between different rewards, the environment, and choice behavior. The inclusion of the effect of environment, specifically through the use of concurrent choice tasks, is crucial to the study of relative value as value is defined by the decision-making context in which the reinforcer is made available (Hursh & Roma, 2016). For example, procedures that 'devalue' the drug reward through satiation or increase the choice for the non-drug reward after inducing a rodent model of CUD would allow us to examine how the relative value of both rewards shift over time. Relative value theories would predict that after chronic use the relative value between alternatives would be shifted toward the drug such that manipulations that favor the drug option would lead to increased drug choice, whereas those that favor the alternative could either decrease the drug choice or increase the choice for the alternative. The sensitivity to these changes could determine how drastically and how long-lasting the shift in relative value for the drug is; important factors for a clearer understanding of how relative value shifts associated with CUD affect behavior.

Another area of interest is the simulation of opportunity costs, such that increased drug choice leads to an environment with a lack of reward alternatives. This progression

follows the anecdotal experience of humans with CUD, as their drug-use becomes more severe they begin to lose out on opportunities to engage with other alternatives, such as a job, interactions with loved ones, or other resources. By simulating the decrease in available rewards, it is possible to investigate how the relative value of drugs changes with reductions in access to alternative activities/reinforcers. In animal models, differences in the environment has been simulated by environmental enrichment studies in which one group of animals is reared in a novel social environment (enriched condition, EC) and another is reared in isolation (isolated condition, IC; Bardo, Neiswander, & Kelly 2013; Simpson & Kelly, 2011). The condition of the IC rats is likened to that of the human experience of CUD since they have few alternative rewards to engage in their daily life. For the rats, one of the few rewards available to them is the drug during their self-administration sessions. This difference in environment between the EC and IC rats is associated with changes in drug-taking such that EC rats show decreased self-administration of cocaine compared to their isolated counterparts (Puhl et al. 2012). EC rats also show increased demand elasticity (α; (1)) for both stimulants and non-drug reinforcers as compared to IC rats. Yet when the IC rats are switched to the enriched environment their α levels become similar to that of the EC rats (Yates, Bardo, & Beckmann, 2017). The restoration of α levels by adjusting the environment may indicate that the novel environment and social interaction given in the enriched condition increases the number of reward alternatives available in the home cage and thus decreases the demand for reinforcers outside of the home cage (i.e. drug). If so, the availability of other non-drug alternatives may account for the decrease in self-administration and the increased elasticity seen after the IC rats experience environmental change. If this concept of differential environments is extended to humans using socioeconomic status as a proxy for the degree of enrichment, similar patterns emerge. Drug-use is correlated with socioeconomic status, with those in the lowest annual income groups reporting more substance-use-related problems (Baptiste-Roberts & Hossain, 2018). In addition, unemployed persons are more likely to use and abuse drugs (Bali, Raisch, Moffett, & Khan, 2013; Henkel, 2010). In both of these scenarios, there is a paucity of other alternatives available due to a lack of resources. In those situations, the relative value of the drug may continue to increase as the number of other alternatives

available decrease. This shift in relative values over time is supported by models of consumption which show that as the relative value and availability of the alternative reward decreases, the relative value and consumption of the drug option will increase until it reaches a point where the drug is chosen exclusively (Rachlin, 1997). Since these alterations happen over time, our current study may not have detected shifts in behavior because it was only able to access decision-making at a local utility level, even when using the macro-level analysis of choice, because the consequences were not far enough out into the future. Therefore, even though there does not appear to be changes in maximizing local utility (i.e. the present moment) there may be changes in global utility as it deals with consequences further in the future such as loss of rewards, job loss, social isolation, etc. Studies that manipulate opportunity costs and loss of alternatives could be useful in extending the predictions of relative value theory as it relates to long-term choice for the drug.

CHAPTER 6. FUTURE DIRECTIONS FOR TREATMENT

Using a relative value framework to explain drug-taking behavior may also have implications for the treatment of SUD. One popular treatment plan has been the token economy developed in the 1960s for use with psychiatric patients (Ayllon & Azrin 1965, 1968) and classrooms or other populations (O'Leary & Drabman, 1971). In these original procedures, the aim was to increase positive behaviors through the presentation of a second-order conditioned reinforcer, a token that could be later exchanged for a reward. The extension of this concept to the treatment of SUDs is called contingency management. In these treatment plans, "choices" to abstain from drugs, verified by negative urine screens, are rewarded with money, vouchers, or tokens that can be exchanged for goods or services. Contingency management appears to alter the relative value of drug rewards by providing a salient alternative to the drug. Contingency management has been shown to effectively increase rates of abstinence for stimulants, alcohol, opioids, and tobacco (see review by Stitzer & Petry, 2006). Additionally, one offshoot of the contingency management model called the Therapeutic Workplace, in which patients with SUD abstain from drug or adhere to addiction medications to gain

access to a working environment, has shown long-lasting effects in patient abstinence (Silverman et al., 2012; Silverman, Holtyn, & Morrison, 2016). These therapies appear to be shifting the relative value of the drug and non-drug alternatives to produce their abstinence effects as one study found that ratings of non-drug activities were graded amongst CUD patients receiving contingency management treatment, such that the highest scores for non-drug activities corresponded with the highest levels of abstinence (Rogers et al., 2008).

Other examples of treatment plans focusing on shifting the relative value of the drug are motivational interventions such as mindfulness technique training (Mindfulness-Oriented Recovery Enhancement (MORE; see review by Garland et al., 2019; Garland, Froeliger & Howard, 2014) and Mindfulness-Based Relapse Prevention (MBRP; see review by Witkiewtiz, Lustyk, & Bowen, 2013) that work to train the cultivation of positive thoughts that "savor" experiences associated with drug-free states and teach patients to learn to better cope with uncomfortable or challenging situations. These mindfulness studies have been effective in reducing reports of craving, especially in response to negative affect (Garland et al., 2016; Bowen et al., 2009). Additionally, in a recent meta-analysis, various mindfulness-related therapies were found to promote abstinence better than other control conditions (treatment as usual; Cavicchioli, Movalli, & Maffei, 2018).

An existing, first-line treatment method that can be explained from a relative value perspective is maintenance therapy, also known as pharmacotherapy. In these treatments, the drug of abuse is replaced by another drug that mimics the effects of the original drug but has a lower abuse liability and/or is less likely to lead to overdose if misused. For example, methadone, used for Opioid Use Disorder (OUD), is a potent agonist at the mu opioid receptor but absorbs slowly and does not generate an intense "high." Maintenance therapies are clinically effective in reducing mortality rates among people with OUD (National Academies of Science, Engineering, & Medicine, 2019.). When viewing these therapies from a holistic perspective, it appears that they might also cause a shift in the relative value of the drug much the same as the therapies discussed above. By administering a drug that has similar mechanisms of action to the drug of abuse,

maintenance therapies can stave off craving and withdrawal symptoms allowing the patient some relief from the need to take the drug to avoid the negative withdrawal symptoms. The removal of the need to use/pursue the drug, allows the patient to use time and/or resources towards other alternatives that may not have been available previously (Bart, 2012). The maintenance drugs function as a substitute for the drug of abuse, just like money did in contingency management, and thus reduces the relative value of the drug.

The combination of contingency management and maintenance therapy has been very effective in reducing positive urinalysis, and thus abstinence outcomes (Griffith et al., 2000). Contingency management combined with methadone maintenance performed better than cognitive behavioral therapy, methadone maintenance alone, and contingency management combined with cognitive behavioral therapy (Rawson, et al., 2002). Additionally, patients who received contingency management as well as methadone had significantly longer periods of abstinence from opioids and cocaine relative to either treatment alone (Schottenfeld et al., 2005). The combination of two therapies that reduce the relative value of the drug appears to have an additive effect, further reducing the relative value of the drug and producing higher rates of long-term abstinence than either therapy alone. The effectiveness of these types of treatments gives credence to the idea that the decision-making mechanisms involved in valuation process are not irrevocably impaired by chronic drug use and that choice for drug reinforcers is sensitive to manipulations in relative value through a change in environmental contingencies. Studies focused on behavioral and environmental changes, alongside pharmacological interventions may prove useful in reducing the harm done by SUD.

CHAPTER 7. CONCLUSION

Given that addiction is seen as a behavioral disorder with an increasingly complex interplay between individual use, environment, and an ever-evolving understanding of neurobiological mechanisms, addiction researchers must remain open to the influences of other fields, such as economics, sociology, psychology, and political science to create the

most robust theories of addiction and reduce the harm caused by SUD and drug misuse. As posited by Redish, Jensen, and Johnson (2008), many of the theories of addiction have been noted to be incomplete and unable to explain the full spectrum of behavior seen in SUD, but when combined they may lead to a richer understanding and explanation. In order to combine portions of theories it is vital to determine the merits and flaws of the many different theories of addiction. Based on the results this of experiment, habit theory alone is not the most appropriate theory to account for changes in value-based decision-making of the course of developing CUD. Instead, theories that focus on relative value changes are better able to account for the behavior.

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PUBLICATIONS

Stephens, M.J., Daniels, C.W., Romero, K., Hewitt, L.T., Nishimura, K.J., Olive, M.F., Newbern, J. and Sanabria, F. Response Topography Modulates Response-Inhibition Capacity of Mice in Two Response-Withholding Tasks. [In progress]

Gupta, T.A., Daniels, C.W., Ortiz, J.B., **Stephens, M.J**., Overby, P., Romero, K., Conrad, C.D., and Sanabria, F. The Differential Role of the Dorsal Hippocampus in Initiating and Terminating Timed Responses: A Lesion Study Using the Switch-Timing Task. Behavioural Brain Research. 2019.

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