2023

The Effects of Extended Fructose Access on Relative Value and Demand for Fructose, Saccharin, and Ventral Tegmental Stimulation

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Digital Object Identifier: https://doi.org/10.13023/etd.2023.288

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THE EFFECTS OF EXTENDED FRUCTOSE ACCESS ON RELATIVE VALUE AND DEMAND FOR FRUCTOSE, SACCHARIN, AND VENTRAL TEGMENTAL SELF-STIMULATION

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences
at the University of Kentucky

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ABSTRACT OF DISSERTATION

THE EFFECTS OF EXTENDED FRUCTOSE ACCESS ON RELATIVE VALUE AND DEMAND FOR FRUCTOSE, SACCHARIN, AND VENTRAL TEGMENTAL SELF-STIMULATION

Globally, food addiction (FA) is a growing area of research and is largely attributed to the availability of foods that are both energy dense and high in fats and sugars. Further, it has been suggested, that sugar and fat, when consumed frequently, have properties similar to drugs of abuse. While the validity of FA is questioned, researchers have drawn parallels between substance use disorder (SUD) and FA. For example, sugar binge models emphasize craving, withdrawal and binging as primary components of FA, which are also hallmarks of SUD. Additionally, both natural rewards, like sugars, and drug rewards act on the dopamine (DA) system, which is implicated in SUD. Currently, research on FA has largely focused on demonstrating the similarities between FA and SUD, but few studies have assessed preclinical decision-making processes when animals are exposed to extended sugar access. Substance abuse research has highlighted the importance of including non-drug alternatives to mimic real-world scenarios in which many competing alternatives are available, but similar experiments have not been implemented for FA. The current experiment implemented a controlled reinforcement ratio (CRR) task in which rats were presented with the choice between fructose and another non-drug alternative, intracranial self-stimulation (ICSS), to assess choice behavior following a fructose self-administration paradigm. Additionally, the use of ICSS in this manner challenges the rate-dependent threshold procedure that currently dominates the literature. Baseline measures of exchange rate for both fructose and saccharin as well as measures for fructose and ICSS threshold were compared to measures following fructose self-administration. Rats were assigned to a short-access (1-hr) fructose condition or long-access (6-hr) fructose condition. While 6-hr rats did not show escalation of intake, results showed that both groups exhibited a decrease in demand intensity for fructose and an increase for ICSS following fructose self-administration. Additionally, the 6-hr group exhibited an increase in ICSS demand elasticity following self-administration, but the same was not noted for the 1-hr group. Finally, a global parameter for both fructose and saccharin exchange rate provided the best model fit for these data meaning there was no difference between pre- and post- self-administration or between access groups. These results provide

support for relative value theory and highlight the importance of using concurrent choice models as opposed to single schedule models when conducting SUD and FA studies.

KEYWORDS: [Food Addiction, Relative Value, Intracranial Self-Stimulation, Choice, Demand Analysis, Ventral Tegmental Area]

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05/24/2023

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ACKNOWLEDGMENTS

First, I would like to express my appreciation to my supervisor, Josh Beckmann, for taking me on midway through my graduate school career as well as your support when I've proposed new (and costly) methodologies. Your unwavering trust in my ability to add additional courses, finish certificates, and meet impractical (but self-imposed) deadlines have been invaluable in shaping this dissertation and finishing my doctorate.

I am profoundly thankful to my committee members, Mike Bardo, Mark Prendergast, and Jill Turner, for their valuable insights, constructive criticism, and thoughtful suggestions that have greatly enhanced the quality of this dissertation. Their expertise and dedication have been instrumental in shaping my research and pushing me to achieve the highest standards.

Additionally, Josh Lavy, McAllister Stephens, and Trinity Shaver — thank you for making research enjoyable with all our chats about music, fun lab decorations, and office snacks. I would not have been able to complete this project without your flexibility and hard work.

To my family — thank you for instilling such an appreciation for education and learning from a young age. You've always supported my choices, even if you didn't necessarily agree with them. Thank you to my sisters for pushing me to be the third doctor in the family. I'm content knowing that I at least attended the most years of school.

To my friends and rugby team — thank you for providing an outlet to vent and commiserate. To those of you who spent hours in a coffeeshop working on our respective project, I would not have found the motivation without your support. To those of you who I played alongside, rugby gave me a reprieve from school and allowed me to maintain my mental health throughout school. It was an honor to serve on the executive board over the last five years.

To my wife — you kept me sane throughout all of my research projects, even during the long distance. Thank you for keeping me fed, maintaining the house, and managing your own schoolwork during my busiest and most stressful moments. You supported my wild deadlines while making sure we made time for fun. I love you.

Finally, to the rats — my least favorite part of animal research is knowing their lives will only be given to science. I am incredibly grateful for the opportunity to conduct research and acknowledge the rats that made this dissertation possible.

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CHAPTER 1. INTRODUCTION

Introduction to Reward Neurocircuitry

The mesolimbic pathway, often referred to as the reward pathway, consists of dopaminergic neurons projecting from the ventral tegmental area (VTA) in the midbrain to the nucleus accumbens (NAc) in the ventral striatum and is most commonly associated with motivation and reward (Alcaro, 2007). In simple terms, activity in this pathway is thought to determine the strength of a stimulus and whether it should be sought out or avoided. Further, it helps inform which stimuli should be prioritized above others, and this can result in behavioral changes (Lewis et al., 2021).

Dopamine (DA), a neurotransmitter released from the VTA in the mesolimbic pathway, has historically been implicated in the feelings of pleasure associated with rewarding stimuli (Bressan & Crippa, 2005) however, more recent research has shown increases in DA even upon anticipation of a rewarding stimulus (Phillips et al., 1993; Linnet, 2014; Weiland et al., 2014). Additionally, DA is implicated in motivation and learning (Beninger, 1983, Hamid et al., 2016, Mohebi et al., 2019). Therefore, the many roles of DA are continuing to be elucidated. Despite this, research has shown a clear connection between DA and the processing of, motivation for, and continued use of rewarding stimuli, whether natural or otherwise.

Role of Dopamine in Natural and Drug Rewards

DA receptors are generally classified as either D1-like DA receptors (D1R), including D1 and D5, or D2-like DA receptors (D2R), including D2, D3, and D4 (Baik, 2013). D1R tend to be described as excitatory, while D2R tend to be inhibitory (Keeler et al., 2014). Further, evidence has shown that DA neurons fire in both a tonic mode, which is stable and low frequency, and a phasic mode, which is brief and high frequency (Keeler et al., 2014). It is hypothesized that tonic firing acts on D2R, which have a higher affinity for DA, while phasic firing acts on D1R, which have a lower affinity for DA and therefore require the resulting high

extracellular concentrations of DA (Volkow et al., 2017). This “burst” of DA associated with phasic firing has been implicated in the processing of both natural and drug rewards (Alcaro, 2007).

Research regarding the rewarding properties of DA and drugs of abuse, and therefore the theories associated with addiction, have relied heavily on experiments first done with natural rewards, like food (Kelley & Berridge, 2002). Research has shown that natural rewards as well as drugs of abuse increase extracellular DA in the NAc (Hernandez & Hoebel, 1988; Spanagel & Weiss, 1999), with early preclinical research suggesting that natural rewards only increase DA if an animal is deprived or the reward is novel (Wilson et al., 1995; Bassareo & Di Chiara, 1997). However, as mentioned previously, more recent research suggests DA release occurs in anticipation of a natural reward (Kiyatkin & Gratton, 1994; Richardson & Gratton, 1996) as well as drug reward (Kiyatkin et al., 1993; Kiyatkin & Stein, 1996; Di Ciano et al., 1998), which implies a learned relationship as opposed to novelty. Additionally, in a preclinical rat study, researchers found that rats who self-administered cocaine had greater levels of extracellular DA as compared to rats on a yoked schedule of reinforcement (Hemby et al., 1997). Taken together, these data suggest that several factors influence the release of DA and therefore the rewarding value of a stimulus.

One of the first DA theories of reward, the anhedonia hypothesis, was introduced by Wise (1982) and suggested that DA mediates the pleasure of rewards like food, sex, and drugs of abuse. This theory implies that blocking DA receptors eliminates the ability to derive pleasure from normally rewarding stimuli. With widespread acceptance of this theory, researchers noted the importance of DA in the reinforcing process associated with natural rewards and drugs of abuse, particularly in the anhedonia associated with drug withdrawal (Weiss et al., 1992; Koob et al., 1997).

In the 1990s, neuroimaging techniques became more advanced, allowing for the imaging of DA receptors. A series of experiments showed that the administration of certain drugs, like stimulants (Laruelle et al., 1995; Volkow et al., 1999) alcohol (Boileu et al., 2003; Urban et al., 2010), ketamine (Vollenweider,

2000), and nicotine (Barrett et al., 2004) increased DA release, and this increase was correlated to the “high” felt by the drug. Through these experiments, the DA theory of drug addiction was widely adopted by the field. This theory posited that non-addictive drugs do not induce a DA release, while addictive drugs do (Nutt et al., 2015). These discoveries, taken together, helped to inform the Habit Theory of Addiction.

Habit Theory of Addiction

The Habit Theory of Addiction is used to describe the transition from voluntary (i.e. controlled) drug use to compulsive drug use resulting in substance use disorder (SUD). It highlights three main components of the addiction cycle: preoccupation-anticipation, binge-intoxication, and withdrawal-negative affect (Koob & Le Moal, 1997). This theory posits that individuals, and animals in preclinical models, initially use drugs for the positive, reinforcing effects. In this way, the behavior is goal-directed, whereby obtaining a drug reward is the objective and a response, like a lever press, will be completed to obtain the reward (ie. response-outcome association). Over time, the drug reward is continually paired with an operant response, leading to a strong stimulus-response association. With continued, chronic stimulus-response pairings, it is thought that habit formation occurs, and an operant response is made automatically, transitioning from goal-directed drug intake to compulsive drug intake (Koob & Le Moal, 1997, 2001, 2005; Lüscher et al., 2020).

This theory closely aligns with the criteria set forth for substance use disorders and continues to be one of the dominant theories in the literature. Notably, while drug research initially relied on experimental evidence from natural rewards, now drug research and the implications of addiction are being used to inform other addictions, namely non-substance addictions like food, sex, and gambling.

Substance vs. Non-Substance Addiction

Drug addiction was initially recognized clinically in the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1952. Over the course of several revisions, the nomenclature changed from drug addiction to substance use disorder in an attempt to reduce stigma and encompass both dependence and uncontrolled use (Robinson & Adinoff, 2016). SUD is a disorder defined as a loss of control over substance use accompanied with compulsive seeking and taking of the drug despite negative consequences. Formal diagnosis of an SUD typically relies on the diagnostic criteria set forth by the DSM-5. In general, these criteria fall into one of four categories: 1. Impaired control, 2. Social impairment, 3. Risky use, and 4. Pharmacological criteria (Zou et al., 2017).

Impaired control emphasizes the uses of larger amounts of the substance for a longer duration than planned, unsuccessful attempts to quit or reduce use, significant time spent seeking, using, and recovering from the substance, and craving. Social impairment includes failure to fulfill major obligations, continued use despite recurrent social or interpersonal issues and reduction of activities and hobbies due to substance use. Risky use comprises use in dangerous or hazardous conditions and continued use despite physical or psychological ailments and finally, pharmacological criteria include withdrawal and tolerance (American Psychiatric Association, 2013). Most drugs of abuse fit these overarching criteria for SUD, but individual differences in diagnostic criteria exist amongst substances.

Other addictive disorders have also been proposed that emulate the criteria of SUDs. Importantly, these typically involve behaviors (ie. gambling, internet, sex) rather than substances. Non-substance addictions have been shown to involve the same reward circuitry as SUDs (Zou et al, 2017; Olsen, 2011). Despite this, gambling addiction, previously called pathological gambling and considered an impulse control disorder (Grant & Chamberlain, 2016), is currently the only non-substance addiction recognized by the DSM-5 and is characterized by gambling with increased amounts of money, inability to cut back, preoccupation with gambling, attempts to even out losses (i.e. “chasing” one’s losses), deceit

surrounding activity, loss of meaningful personal opportunities (i.e. relationships, job) and financial dependence on others' due to loss gambling. Due to these overlapping criteria with SUD, gambling addiction was deemed a more appropriate fit for the "addiction" category rather than the "impulse control" category in the DSM-5 (Grant & Chamberlain, 2016). Further, other addiction-like disorders, like internet gaming disorder and caffeine use disorder, have been included in the DSM as "Conditions for Further Study" (American Psychiatric Association, 2013; Vasiliu, 2021) due to their similarities to SUD and gambling addiction, but other potential addictions, like sex or food, have been excluded.

Collectively, the above highlights the need to examine the ways in which addiction is determined and what constitutes sufficient evidence to classify a substance or behavior as addictive versus a lack of impulse control.

Introduction to Food Addiction

Food addiction (FA), first mentioned by Randolph (1956), has been widely debated over the decades. At its core, it comprises the loss of control of intake of hyperpalatable foods, like sugars, fats, and salts (Vella et al., 2017), mirroring the accepted definition for SUD. Though, significant controversy still surrounds FA due to conceptual and definitional difficulties (Zou et al., 2017).

Opponents of FA emphasize the biological importance of food and imply that an individual cannot be addicted to a compound that is required for survival (Ziauddeen et al., 2012). Additionally, there is a lack of consensus surrounding the definition and presentation of FA clinically and therefore difficulty producing research that supports FA as a theory (Finlayson et al., 2017). Finally, in studying FA, it is challenging to determine if the supposed addiction is to food ("food addiction") or to the behavior ("eating addiction"), which further complicates the interpretation of current research (Hebebrand et al., 2014; Vella et al., 2017).

On the other hand, supporters of FA highlight the correlation between the availability of hyperpalatable foods and the rise in obesity and metabolic diseases since the 1970s (Ifland et al., 2009), with some studies estimating a 1240% increase in high fructose corn syrup and nearly 220% increase in carbonated soft

drink consumption per capita from 1970-1997 (Putnam & Allshouse, 1999). Additionally, the population as a whole has struggled to implement weight-loss strategies that are effective and long-lasting despite the known health risks associated with obesity. This suggests the presence of a separate underlying issue, which could be explained by addictive processes (Gearhardt et al., 2009). However, until relatively recently, the FA construct could not be uniformly studied in humans due to a lack of established, universal diagnostic criteria.

The Yale Food Addiction Scale (YFAS) was first introduced and validated as a 25-item questionnaire in 2009 and was largely derived from the DSM criteria for SUD and an updated 35-item questionnaire, YFAS 2.0, was developed following the release of the DSM-5 (Gearhardt et al., 2009; Gearhardt et al., 2016). The survey highlights key factors of addiction like overconsumption, inability to reduce intake, craving, etc. and has been the primary methodological tool to operationalize FA in the contemporary literature.

Prevalence of total population FA, determined by the YFAS and based on a meta-analysis, is 20%, with a greater prevalence for individuals who are overweight (24%) or obese (28%) compared to normal weight (17%). Further, FA has been shown to be more prevalent in males (27%) rather than females (24%; Praxedes et al., 2022). Research also shows a correlation between a “diagnosis” of FA and the overconsumption of ultra-processed foods (Filgueiras et al., 2019; Whatnall et al., 2022) indicating further support for the association of FA and the rising availability of hyperpalatable foods. Importantly, many of these studies, as well as preclinical models, focus on specific substances, like refined sugars, as potential drivers of FA.

Metabolism of Sugars

The most commonly available sugars include fructose, often found naturally in fruits and prevalent now as added sugars in processed foods (i.e. high fructose corn syrup), glucose, the dominant circulating sugar in animals, and sucrose, a disaccharide made up of one unit of fructose and one unit of glucose. While both

fructose and glucose are monosaccharides, they are metabolized quite differently upon ingestion.

Glucose is absorbed into the bloodstream through the lining of the small intestine. Specifically, it is transported from the small intestine via a sodium-glucose transport protein (SGLT1) and into the bloodstream by glucose transporter 2 (GLUT2). Fructose is also absorbed through the small intestine but is transported via glucose transporter 5 (GLUT5; Hannou et al., 2018; Merino et al., 2019). Notably, fructose does not induce insulin secretion like glucose. Further, fructose is primarily metabolized by the liver (Lowette et al., 2015) and, unlike glucose, bypasses a phosphorylation step by phosphofructokinase (PFK-1). The PFK-1 step in glucose metabolism is highly regulated and is typically activated during a state of energy depletion and inhibited by a state of energy surplus. In skipping the PFK-1 step, fructose can alter normal lipid metabolism in the liver which stimulates a rapid influx of pyruvate into the Krebs Cycle and increases the formation of acetyl coenzyme a (acetyl-CoA) leading to the development of fatty acids (Campbell et al., 2014, Merino et al., 2019) and implicating fructose in the development of obesity.

In addition to differences in metabolism, glucose and fructose differ in their promotion of satiety hormones. Glucose, as mentioned previously, promotes the secretion of insulin. Further, there is an increase in leptin, a hormone involved in signaling satiety, and decreases ghrelin, which is involved in stimulating hunger. In contrast, fructose produces a markedly lower secretion of leptin and repression of ghrelin thereby promoting less satiety than glucose and leading to increased food intake (Cha et al., 2008; Merino et al., 2019).

Differences also exist between glucose and fructose neurologically and in decision-making tasks. Neuroimaging research suggests that glucose decreases cerebral blood flow in regions of the brain that are involved in appetite signaling, like the hypothalamus, but fructose induces a moderate increase in activity, potentially leading to overeating (Page et al., 2013). Additionally, Luo and colleagues (2015) found that participants were more willing to give up delayed monetary rewards in favor of immediate high-calorie foods after ingesting fructose,

but not glucose. Taken together, this further supports the hypothesis that fructose promotes, rather than attenuates, feeding behavior and implicates fructose as a central player in disordered eating and food addiction.

Comparing Food Addiction & Binge Eating Disorder

As mentioned previously, FA is associated with a loss of control regarding the consumption of hyperpalatable foods. Because of this, there is significant overlap in the clinical hallmarks of Binge Eating Disorder (BED) and FA which adds to the debate surrounding the clinical significance of FA. BED is classified in the DSM-5 as a feeding and eating disorder and its diagnostic criteria includes bingeing large portions within a discrete period of time and feeling a lack of control regarding eating behavior. Importantly, these binges often result in rapid eating, eating until uncomfortably full, eating larger portions despite lack of hunger, eating in isolation due to embarrassment, feelings of guilt following binge, and a lack of purging/vomiting. Additionally, individuals with BED can be either normal weight or overweight/obese and typically feel distress surrounding this behavior (American Psychiatric Association, 2013).

While these criteria appear to fit the proposed diagnostic criteria for FA, studies have shown that while related, there is not perfect overlay for these disorders. One study found that in a sample of obese patients who met the criteria for BED only 57% met the criteria for FA as determined by the YFAS (Gearhardt et al., 2012). However, they noted that the subset that met the classification for FA also reported higher levels of emotional dysregulation and lower self-esteem, theorizing that FA points to a more disturbed variant of BED. Contrary to this hypothesis, Davis and colleagues (2011) found that in a sample of obese patients, 30% of those that met criteria for FA did not meet the criteria for BED, implying that FA is not a more extreme subset of BED. In addition to differences in clinically relevant diagnoses, data suggests that the motivation behind each of these conditions differs. While not a formal diagnostic criterion, patients with BED often report a sense of concern surrounding their weight or body shape (Grilo et al.,

2010), which is not a defining feature of FA. These results taken together support the theory that while similar, BED and FA are distinct disorders.

Food Addiction & Substance Use Disorder Parallels

Since food addiction cannot be completely described by the criteria of BED, parallels have been drawn between FA and SUD, as evidenced by the development of the YFAS. Both disorders are characterized by the cycle of craving, bingeing, and withdrawal and further defined by the exhibition of tolerance and continued use despite apparent negative consequences (Hone-Blanchet & Fecteau, 2014; Rogers, 2017).

Historically, substances of abuse existed in a natural, less concentrated form than what is currently available. These substances were originally used medicinally (Saah, 2005; Crocq, 2007) but over time have become more concentrated, and faster routes of administration have been developed, driving the increase in SUD (Courtwright, 2012). Similarly, sugars and fats were found intermittently amongst our ancestors' food sources in low concentrations, but now are highly processed increasing the concentration. Further, due to the low availability of these compounds historically, humans have evolved to consume them in high quantities when the opportunity arises. Unfortunately, highly processed, high calorie foods are now widely available in many forms (Armelagos, 2010) leading to overconsumption. This has led many researchers to compare models of SUD to FA.

Preclinical Models of Addiction

SUDs have long been modeled preclinically with a long-access (LgA) self-administration procedure where animals are allowed to self-administer drug over an extended time interval, typically 6 hrs. (Ahmed & Koob, 1998). As compared to short access (ShA) self-administration, where self-administration access is limited to 1 hr, LgA is marked by a distinct escalation of intake (i.e. increased consumption) of drug across subsequent sessions (Ahmed & Koob, 1998; Ahmed

at al., 2000; Kitamura et al., 2006), increased intake within the first hour of a given session (Ahmed & Koob, 1999; Ahmed et al, 2002; Kitamura et al, 2006) as well as an increase in breakpoint, defined as the maximum work an animal will exert for a given dose of drug (Walker & Koob, 2007; Wee et al 2008; Hao et al, 2010). Further, somatic withdrawal symptoms, like teeth chattering and “wet dog” shakes, have been reported after a challenge with opioid-antagonist naloxone (Ayoub et al., 2021) as well as spontaneously following a period of abstinence (Martin et al., 1963).

Similarly, FA, particularly addiction to highly palatable foods like sugar, has been commonly assessed using a sugar-binge model. It consists of a 12-hr food deprivation period followed by 12-hr access to a sugar solution (typically sucrose) as well as normal chow (Avena, 2006). Like drug escalation paradigms, sugar-binge models show evidence of bingeing during the first hour of sugar access (Goeders et al, 2009; Avena et al, 2008) and increased daily intake (Corwin et al, 2011) as well as increased motivation for sugar following a period of abstinence (Avena et al, 2005). Further, studies show signs of withdrawal upon administration of naloxone to sugar-bingeing rats (Colantuoni et al, 2002) and spontaneous withdrawal symptoms with 24-hr abstinence (Avena et al, 2008, Colantuoni, 2002).

Parallels in Neurocircuitry

In addition, there is evidence to suggest that extended access to both drugs of abuse and palatable foods affect neurotransmitter systems in a similar manner. Research has shown that individuals with cocaine dependence (Volkow et al., 1997; Martinez et al., 2007) or alcohol dependence (Martinez et al., 2005) experience blunted extracellular DA release in the striatum upon delivery of amphetamine as compared to non-users. Likewise, obese individuals with a history of food overconsumption, have lower DA levels as compared to their normal-weight counterparts upon palatable food intake (Stice et al., 2008). This effect has also been shown in preclinical models (Geiger et al., 2009). The apparent decrease in DA transmission is often interpreted as a deficient hedonic response triggering those with SUD or FA to overconsume to compensate for the

comparative reduction in DA. Further, with repeated use, there is a switch from DA release upon delivery of a substance to DA release when a cue associated with the substance is present for both drugs (Volkow et al., 2006; Wong et al., 2006) and food (Jastreboff et al, 2013).

Moreover, there is increased binding of D_1 receptors (drug: Unterwald et al., 1996; food: Colantuoni et al., 2001) and decreased D_2 receptor binding (drug: Volkow et al., 2001; Nader et al., 2006; Thanos et al., 2007; food: Colantuoni et al., 2001; Wang et al, 2001; Johnson & Kenny, 2010) in the NAc evident in both SUD and FA models. It has been hypothesized that decreased D_2 receptor binding is implicated in increased impulsivity and therefore contributes to loss of control. This is supported by delay discounting research that indicates that people with SUD or those who overconsume food are more likely than healthy subjects to choose a smaller immediate reward over a larger delayed reward, especially if the immediate reward is drug (in SUD) or food (in FA) related (Bickel et al., 2007; Weller et al., 2008; Brogan et al., 2010). Finally, research shows increased mu-opioid receptor binding, another receptor important in reward processing, in both food and drug paradigms (Zubieta et al, 1996; Yuferov, et al 1999; Colantuoni et al., 2001; Colantunoi et al., 2002).

With similar preclinical models and neurotransmitter adaptations, there are also parallels in the activation of brain regions during neuroimaging studies when comparing SUD and FA. Evidence shows that individuals with SUD, in response to drug cues, have greater activation in brain regions that are associated with encoding reward value including the orbitofrontal cortex (OFC), amygdala, anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (Maas, et al., 1998; Liu et al., 2021). Similar studies in obese individuals and those with FA have shown comparable activation in these regions in response to food cues (Rothemund et al., 2007; Stoeckel et al., 2008; Gearhardt et al., 2011). Importantly, this increase in activation is specific to cues whereas a reduction in activation, compared to healthy controls, is observed upon receipt of reward (Martinez et al., 2005; Stice et al, 2009). Taken together, these data suggest a common underlying mechanism

between SUD and FA, which may be assessed quantitatively using Intracranial Self-Stimulation.

Intracranial Self-Stimulation

Intracranial Self-Stimulation (ICSS) is an operant behavior paradigm that allows for the self- administration of reinforcing electrical stimulation via an implanted electrode, typically along the mesolimbic pathway. Olds and Milner (1954) first discovered the reinforcing nature of ICSS when they found that rats will return to the same area of an operant chamber in which they were given an electrical brain stimulation. This discovery was a critical breakthrough for researchers studying the areas of reward. Notably, with further investigation, it was determined that rats could be trained to complete an operant response to self-stimulate with an electrical stimulation, leading to the development of various experimental paradigms utilizing ICSS.

ICSS Experimental Models

Several parameters, both manipulable and constant, are central to the ICSS paradigm regardless of the experimental model being used. These parameters include: 1. current intensity, 2. frequency, and 3. pulse duration. Current intensity, measured as amplitude (μA), quantifies “how much” of the brain is being stimulated (i.e., the population of neurons being stimulated). In other words, it is the radius around the electrode that receives stimulation. Frequency is measured in Hz and indicates “how often” the brain is stimulated. Finally, duration, measured in milliseconds (ms), is the length of a given stimulation. Typically, either current intensity or frequency is manipulated within an experimental procedure, while duration remains constant (Vlachou & Markou, 2011). Several experimental models using ICSS exist in the literature, but the two most common models are the rate-frequency curve-shift model and the discrete-trial current intensity model.

The rate-frequency curve-shift model, uses rate of responding to a specific manipulandum (i.e., lever pressing, nosepoking, wheel turning, etc.) across

increasing or decreasing frequency magnitudes to develop a frequency-response function. Response rates are magnitude-dependent, with lower response rates occurring at lower frequency magnitudes and higher response rates at higher frequency magnitudes. Eventually, animals reach a maximal response rate, whereby additional increases in magnitude do not increase rates of responding (Carlezon & Chartoff, 2007; Vlachou & Markou, 2011). ICSS is typically used in this model to assess how a manipulation, like drug or withdrawal, shifts response rates, and therefore reward threshold, at a given frequency (Kenny, 2007). A leftward curve shift from baseline is interpreted as facilitation of reward, while a rightward curve shift is interpreted as attenuation of reward (Stratmann & Craft, 1997; Carlezon & Chartoff, 2007; Vlachou & Markou, 2011). Importantly, two measures — M_{50} and Θ_0— are commonly used to infer reward threshold. M_{50} is a measure of the level of stimulation necessary to maintain half of the maximum response rate (Yeomans et al., 2000; Konkle et al., 2001; Bossert & Franklin, 2003) typically calculated using a sigmoid growth model (Coulombe & Miliaressis, 1987), while Θ_0 measures the minimum level of stimulation necessary to induce responding (Wise & Munn, 1993; Elmer et al., 2005; Carlezon & Chartoff, 2007). It has been argued that Θ_0 is a superior measure for threshold because it is not sensitive to changes in rate of responding, while M_{50} is extremely sensitive to changes in rate of responding (Miliaressis et al., 1986).

The discrete-trial current intensity model is also designed to measure reward threshold but implements discrete trials to provide a rate-independent measure of threshold. This model utilizes four blocks of descending and ascending current intensities, beginning with descending amplitude levels. In each trial, the animal initially receives a noncontingent stimulation and is given a discrete time interval to complete a contingent operant response to administer an identical stimulation. If a response is made, the trial is considered positive, but if no response is made, the trial is considered negative. A series of 3-5 trials is administered at each amplitude level until three negative responses (in descending blocks) or three positive responses (in ascending blocks) are made on two consecutive amplitude levels. In this model, threshold is defined as the midpoint

between the amplitude level in which 2 or more positive responses were made and the amplitude level in which less than 2 positive responses were made. The threshold level for each of the four blocks (2 descending, 2 ascending) is averaged to determine the mean reward threshold (Markou & Koob, 1992; Vlachou & Markou, 2011).

Like the rate-frequency curve-shift model, the discrete-trial current intensity model assesses the effects of drug manipulations or withdrawal on reward threshold, with decreases in threshold equated with facilitation of reward and increases equated with attenuation of reward. In both paradigms, researchers have shown decreases in reward threshold upon administration of cocaine (Kornetsky & Esposito, 1981; Frank et al., 1988; Gill et al., 2004), amphetamines (Schaefer & Holtzman, 1979; Franklin & Robertson; 1982; Paterson et al., 2000), opiates (Nazzaro et al., 1981; van Wolfswinkel & van Ree, 1985; Hubner & Kornetsky, 1992), nicotine (Panagis et al., 2000; Harrison et al., 2002; Kenny & Markou, 2006) and MDMA (Hubner et al., 1988) and increases in reward threshold upon withdrawal from these substances (Epping-Jordan et al., 1998; Baldo et al., 1999; Harrison et al., 2001; Easterling & Holtzman, 2004). Researchers have thus suggested that changes in reward threshold are indicative of abuse potential (Vlachou & Markou, 2011). However, administration of other substances, like ethanol (Carlson & Lydic, 1976; Schaefer & Michael, 1987; Moolten & Kornetsky, 1990) and cannabinoids (Kucharski et al., 1983; Lepore et al., 1996; Vlachou et al., 2007) have shown decreases in reward threshold in some studies, but no effect or increases in reward threshold in others, suggesting that not all drugs of abuse affect ICSS paradigms in the same way. Further, it implies that subjective value of a given substance cannot be elucidated using reward threshold alone.

Strengths and Weaknesses of ICSS Models

The use of ICSS in operant paradigms has several strengths. One of its greatest strengths is the lack of satiation. Other types of reinforcers, like food, sex, and drugs, are all bound by the limits of satiety, whereas animals will continue to respond to brain stimulation endlessly (Carlezon & Chartoff, 2007). Remarkably,

there is evidence to suggest that rats choose ICSS over both food (Routtenberg & Lindy, 1965) and heat (Carlisle & Snyder, 1970), even when food deprived or in freezing environments, demonstrating the potent reinforcing effect of ICSS. Additionally, ICSS has been shown to be effective in several different areas of the brain including: the medial forebrain bundle (MFB), substantia nigra, VTA, amygdala, NAc and others, making it a versatile form of reinforcement (Vlachou & Markou, 2011). With this versatility, it can be used as a tool to determine if certain brain regions are associated with reward. Further, due to the nature of ICSS, it results in the rapid acquisition of operant responding since there is no delay between completing a response requirement and receiving stimulation. Finally, using ICSS bypasses other potentially interfering, input (i.e., signals to the brain upon consuming food) that could affect data interpretation, due to the direct stimulation of the reward pathway (Vlachou & Markou, 2011). However, despite their strengths, these ICSS paradigms are not without their weaknesses.

First, they rely on a single schedule of reinforcement, meaning with both paradigms only one reinforcement option, electrical self-stimulation, is available. When a concurrent choice model is not used, it is difficult to discern between reward value and performance capacity (Valenstein, 1964). For example, in the discrete-trial model, a lack of response to a noncontingent stimulus can be interpreted as an increased threshold for reward, but it can also be interpreted as diminished ability to complete a response (Liebman, 1983).

The curve-shift model, specifically, is a threshold procedure that is rate-dependent which, when interpreting the data, forces the assumption that rate of responding is proportional to reward value. This may stem from the idea that an increase in the rate of responding is due to an increase in motivation (Ornstein, 1979; Liebman, 1983). However, when using a choice model, instead of single-schedule, preference is not correlated with rate of responding (Ross, 1973). One study found that when given a concurrent choice between stimulating an electrode in the septal area, which supports low rates of responding and one in the hypothalamus, which supports high rates of responding, rats prefer stimulating the septal area (Hodos & Valenstein, 1962). Further, with all rate-dependent

procedures, there is a ceiling effect whereby a maximum number of responses can be completed within a given time limit, so changes in rate can no longer be assessed past a certain stimulation magnitude.

Moreover, certain brain regions, as mentioned previously, do not support high rates of responding due to aversive consequences, like seizures. Therefore, animals will engage in a pacing technique to avoid negative outcomes, while still receiving rewarding stimulation (Valenstein, 1964). Finally, it is assumed that a manipulation's effect (like drug or withdrawal effects) on response rates reflects changes in reward due to that manipulation. Indeed, there are many drug effects, unrelated to reward, that can cause changes in rate of responding, like sedation, changes in locomotor activity, and attentional deficits (Liebman, 1983)

Taken together, these findings indicate that rate of responding is not a reliable measure of reward value and studies have shown that rate-dependent ICSS procedures do not correlate to preference in choice procedures, so clear insight on reward value cannot be elucidated using a rate-dependent method. In one study, researchers utilized a threshold procedure that simultaneously measured both rate-dependent and rate-independent aspects of ICSS. Their data suggested that response rates were not correlated with rate-independent measures of threshold (Zarevics & Setler, 1979). Specifically, at high levels of stimulation, response rates are not associated with choice preferences.

In addition to rate-dependence issues, when manipulating frequency within an experiment, magnitude of reward is commonly reported using the frequency level (Hz). Since ICSS is delivered as a waveform, using Hz is misleading and it is challenging to compare values across experiments. Instead, number of stimulations, calculated as frequency multiplied by duration (in seconds), accounts for differing duration across experiments even when the same Hz magnitude is used. By determining number of stimulations as an objective measure of magnitude, it allows for comparison across experiments with differing duration parameters and provides an accurate interpretation of the level of stimulation. In this way, number of stimulations, combined with an appropriate experimental

model, may provide a quantitative measure of neural value that can be compared across different reinforcers.

Encoding Value: Theories from Economics

All decision-making and therefore reward valuation, from addiction to economic models, have roots in the 1654 philosophies of Blaise Pascal. In thinking about how humans make decisions in the face of uncertainty, he developed a model of decision-making based on expected value. He posited that when individuals are given a choice, choosing the option with the highest expected value, defined as the probability of "winning" multiplied by the amount to be won, is always the *correct* choice (Glimcher, 2011; Glimcher et al., 2013). For example, should someone choose to buy a $30 lottery ticket with a 10% probability of winning $500? Based on Pascal's model, the expected value of buying the lottery ticket is $50 (EV= 500 * 0.10), so the *correct* choice would be to buy the ticket (i.e., the expected value, $50, is greater than the associated cost, $30). Importantly, expected value designates how an individual *should* choose, insinuating each choice has a correct and incorrect option.

Utility

While Pascal provided a foundational theory integral to the study of valuation, it was clear that other factors, aside from probability and size of gains (or losses), contributed to decision-making. Bernoulli (1738/1954) hypothesized that each individual makes (economic) decisions based on their starting wealth as well as a "hidden" variable that came to be named utility. For simplicity, utility is loosely defined as subjective value, but importantly, cannot be measured directly.

As an example, he illustrates a scenario where a beggar happens upon a lottery ticket which has a 50% probability of winning 20,000 florins, but a wealthy man offers him 7,000 florins for the ticket. Using Pascal's model of expected value, the beggar *should* choose to keep the lottery ticket (10,000 florins expected value vs. 7,000 florins). However, Bernoulli suggests that changes in value are not linear

and instead takes the logarithmic value of the gain multiplied by the probability of that gain (log (20,000) * 0.50 = 2.15 utils; log (7,000) = 3.8 utils) to determine expected utility. In this model, the option with the highest expected utility is the optimal choice and therefore the beggar should choose to sell the ticket. A certain 7,000 florins has a greater subjective value, for the beggar, than an uncertain 20,000 florins. This model has been found to account for human choice more accurately than the expected value model alone (Glimcher, 2011).

Importantly, as the school of economic thought grew, choice behavior was being used as a proxy for utility, since utility is an immeasurable, hidden variable. However, choice paradigms can, at best, provide a utility ranking of the commodities included in a given context. For example, if a person is asked to give their preference of apples, oranges, and bananas, they may choose bananas over apples and apples over oranges. In this case, we would assign bananas a utility of 3, apples a utility of 2 and oranges a utility of 1. However, if grapes and peaches are added to the context, the new utilities may be bananas: 5, peaches: 4, apples: 3, oranges: 2, and grapes:1. In this way, utility describes ordinal rankings of options and do not operate on the cardinal scale of numerical value (Pareto, 1906/1971; Glimcher, 2011). To expand on this, Pareto further suggested that while utility can describe the preference of one commodity over another, it cannot describe the magnitude of that preference (i.e., a utility value of 2 does not indicate a commodity is twice as good as a commodity with a utility of value of 1).

Demand Theory

Despite issues surrounding interpretation of utility, the concept has helped to inform other economic theories, like demand theory. In its basic form, demand measures the willingness to pay for a given commodity over a variety of prices. Using this simple definition, it suggests that as price increases, the willingness to pay, or consumption of, that commodity decreases (Gilroy et al., 2019).

This theory has been adopted by researchers studying a variety of paradigms including SUD (Bickel, 2014), obesity (Batten et al., 2020), ICSS (Bauer et al., 2013) and environmental enrichment (Yates et al., 2017). Hursh and

Silberberg (2008) proposed a more complex equation of demand, the exponential demand equation (Equation 1) given as follows:

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

In this equation *Q* represents consumption, Q_0 is consumption when cost is equal to zero, *C* is unit price (i.e., cost), *k* is a scaling factor, and α is demand elasticity. This model was further expanded to allow for the incorporation of zero values (Koffarnus et al., 2015), which is common when assessing consumption data at high unit prices (Equation 2).

$$Q = Q_0 * 10^{k(e^{-\alpha Q_0 C} - 1)} \quad (2)$$

In either model, both theoretical demand intensity (Q_0) and demand elasticity can be ascertained. Demand elasticity provides a quantification of how sharply consumption decreases as price increases, with larger values indicating greater elasticity (i.e., greater sensitivity to price increases) and smaller values indicating greater inelasticity (i.e., greater insensitivity to price changes).

In demand analysis experiments, the measure of elasticity is often called *essential value* and it is used to compare commodities (larger demand elasticity values are equated with lower value; Foster, 2009) across similar experimental paradigms. However, demand analyses are typically conducted using a single-schedule of reinforcement and several theoretical issues surround the interpretation of single-schedule measures.

Theoretical Issues with Single-Schedule Paradigms

Research regarding food addiction has emphasized drawing parallels to SUD, but like ICSS methodologies, many of these paradigms rely on single-schedule measurements to ascertain value. Like ICSS paradigms, many issues in

interpretation arise when using single schedules in both SUD and FA studies (Perkins & Freeman, 2018).

Rate Measures and Preference

As mentioned with rate-dependent ICSS paradigms, single-schedule measurements force the assumption that rate of responding at a particular magnitude is indicative of reward value. Similarly, in SUD studies utilizing rate measures, there is the assumption that response rate at a given dose of the drug is a measure of utility (Banks & Negus, 2012). However, it has been shown in several studies that preference in choice models is dissociable from rate of responding in single-schedule models. The most notable example of this dissociation, shown across many classes of drugs, is the production of a bitonic (i.e., “Inverted U-shape”) dose-response curve in single-schedule paradigms, in which the lowest and highest drug doses result in the lowest rates of responding, while at intermediate doses, the highest rate of responding is observed (Katz, 1989; Mello & Negus, 1996). This would lead to the conclusion that intermediate doses are preferred, and therefore have more value, over other doses. However, when given a choice in concurrent choice models between intermediate and high doses, the high dose is often preferred (Johanson & Schuster, 1975; Negus, 2006; Beckmann et al., 2019). Similarly, Townsend (2019) found that in a single-schedule self-administration paradigm, female rats exhibited higher rates of responding as compared to male rats for fentanyl. This would, if rate is synonymous with value, logically lead to the conclusion that female rats prefer fentanyl over male rats. However, when placed on a concurrent choice procedure (fentanyl vs. food), male rats showed a higher preference for fentanyl as compared to females, suggesting that rates of responding do not correlate with preferences in a choice procedure, but instead are context dependent. Collectively, this suggests response rates are susceptible to other mitigating factors unrelated to reward value, often termed direct effects (Katz, 1989).

Direct Effects

Two central direct effects, distinguishable from preference, are linked to changes in rates of responding in both SUD and FA studies, and to a lesser degree in ICSS research: satiety and motoric effects.

In single-schedule SUD paradigms, it has been hypothesized that at higher doses of drug, fewer drug infusions are required to reach a desired level of "high," implying that satiation can be reached at a higher dose through lower rates of responding as compared to intermediate doses (Tsibulsky & Norman, 1999; Lynch & Carroll, 2001). In this way, animals titrate their drug intake to maintain a steady-state level (Gerber & Wise, 1989; Richardson & Roberts, 1996). In fact, when reporting data from these experiments as total drug consumption (determined by multiplying rate of responding by drug dose), total consumption is relatively constant at high and intermediate doses, supporting the theory that satiety, or optimal steady state, plays a critical role in rate of responding (Oleson & Roberts, 2009). Similarly, in studies using food reinforcers, higher volumes or magnitudes of a given reinforcer will produce satiety with fewer responses than smaller magnitudes (Killeen & Reilly, 2001). Conversely, ICSS is unique, as discussed above, in that it does not produce satiation, even after hours or days of continuous stimulation (Carlezon & Chartoff, 2007).

Like satiety, motoric effects can have a significant impact on rate of responding. This is particularly evident when comparing stimulants and sedatives. With stimulants, there is an increase in activity, which could inherently increase the rate of responding through locomotor activity alone (Antoniou et al., 1998; Witkin, 1993). Conversely, sedatives are likely to decrease activity and therefore may decrease rate of responding (Wadenberg, 2003; Smith et al., 2009). Since rate-dependent measures are fundamentally affected by an individual's ability to complete an operant response, motor effects are confounded with the inference of reward value. This further translates to ICSS paradigms, in which baseline threshold measures are compared to threshold measures after a drug challenge. Motoric deficits may overemphasize an increase in threshold (decreased rates of responding), while increases in locomotor activity may inflate decreases in

threshold (increased rate of responding). In FA studies, there are no reported motoric effects in the literature via acute or chronic administration of sugars, but studies have shown that chronic sugar administration results in locomotor cross-sensitization with drugs of abuse (Avena & Hoebel, 2003; Singer et al., 2012), so motoric effects may prove to be problematic for future single-schedule FA studies.

Revisiting Essential Value

Finally, single schedules inherently disregard the contextual nature of value by studying commodities in isolation, despite evidence to suggest decision-making relies on the current context (Kahneman & Tversky, 1979; Glimcher, 2011). This is best illustrated by revisiting the concept of essential value from demand theory.

As mentioned previously, essential value is often used to compare two or more commodities across similar experimental conditions (Christensen et al., 2008; Smethells et al., 2018; Schwartz et. al., 2019) this is particularly evident when assessing substances of abuse and are used to describe 'addiction-like" vulnerabilities in decision-making (Murphy et al., 2009; Bentzly et al., 2014) In using elasticity as a measure by which commodities can be compared, it implies that every commodity has one "true" reward value that can be described by essential value. However, this theory fails to account for the many dimensions of reward that have been shown to influence preference in choice models (magnitude, delay to reinforcement, probability, etc.), which are typically not scaled the same (i.e., a one unit increase in magnitude is not equal to a one unit increase in delay; Stevens, 1957). Importantly, when essential value is challenged using concurrent choice models, it has been shown to be different than essential value of one commodity in isolation (Carroll & Rodefer, 1993; Smethells et al., 2018). Taken together, the theoretical problems underpinning single-schedule reinforcement paradigms point to the necessity of conducting concurrent choice models, particularly when studying disorders theorized to be a transition from voluntary intake to compulsive use (i.e., SUD and FA).

Concurrent Choice Models

Given the theoretical issues of single-schedule models outlined above, choice models have been utilized to determine context-dependent preference when choosing between commodities of the same type (isomorphic choice) as well as commodities of different types (allomorphic choice). In SUD choice models, where drug is presented concurrently with a non-drug alternative, the allocation of choice behavior can be assessed as opposed to the rate of responding (Negus & Banks, 2018; Perkins & Freeman, 2018). In these models, a variety of dimensions of reward, for either reinforcer type, can be modified including magnitude, cost, probability of reinforcement, and delay to reinforcement, and these modifications create a new context in which value can be elucidated. Furthermore, choice procedures more closely mimic a real-life scenario in which humans have many competing alternatives, both drug and non-drug, therefore providing a more translational experimental paradigm (Lynch, 2018). Importantly, despite the parallels drawn between drug self-administration models and sugar self-administration models, there is a lack of concurrent choice models associated with FA in the literature, thereby only assessing similarities as they relate to single-schedule models.

Matching Law

With the transition from single-schedule models to concurrent choice models in operant research came the evolution of mathematical matching models to describe allocation behavior. The first instance of matching arose when Herrnstein (1961) observed that pigeons' response rates for two different reinforcers could be described by the relative reward rates of those reinforcers as determined by a variable-interval schedule of reinforcement (Equation 3).

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

In this equation, *B* is defined as the behavior allocation (i.e., rate of responding) for each of two options and *R* is defined as the rate of reinforcement for each of the options. Since this matching model relies on rate of responding, it is afflicted with the same theoretical issues that surround single-schedule models. Further, as mentioned with ICSS, ceiling effects related to response rate were noted and scaling factors were introduced to accommodate for an upper asymptote reflecting maximal responding. Moreover, in concurrent choice models there are two experimental options for which subjects can allocate their time, but there is also the option of engaging in other behaviors, not associated with an operant response, within the experimental paradigm (i.e., grooming, exploring the operant chamber, etc.). This so-named "leisure" option was therefore considered an additional choice (Herrnstein, 1970) and included in an extended version of the matching model (Equation 4).

$$\frac{B_1}{B_e \ldots + \ B_N} = \frac{kR_1}{R_e \ \ldots + \ R_N} \tag{4}$$

This extension insinuates that behavior allocation ($B_1, B_2 \ldots B_N$) can be described as a function of rate of reinforcement ($R_1, R_2 \ldots R_N$) scaled using a subject's maximal rate of responding for a given option (k) and taking into account other extraneous behaviors (B_e) as well as rate of extraneous reinforcement (R_e). While this began to address the issues associated with single-schedule and rate measures by incorporating a scaling constant as well as extraneous choice options, using rate still posed the same confounding concerns as discussed previously.

More modern versions of the matching law began to emerge with the development of power models (McDowell, 2005) and Baum (1974) proposed the generalized matching law (Equation 5).

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

This model suggests that behavior (*B*) can be described as a function of reinforcement rate (*R*) scaled by a sensitivity parameter (*s*) and multiplied by a bias parameter (*b*). The sensitivity parameter serves as a measure of the sensitivity to changes in reinforcement rate and the bias parameter is a measure of bias for one option over the other.

Further expanding on the generalized matching law, two new equations (Equation 6 and Equation 7) were proposed to incorporate the many dimensions of reinforcement that impact behavior (Baum & Rachlin, 1969; Rachlin, 1971).

$$\frac{B_1}{B_2} = b * \frac{R_1}{R_2} * \frac{M_1}{M_2} * \frac{I_1}{I_2} * \frac{\dots X_1}{\dots X_2} \tag{6}$$

$$\frac{B_1}{B_2} = b * \left(\frac{R_1}{R_2}\right)^{S_R} * \left(\frac{M_1}{M_2}\right)^{S_M} * \left(\frac{I_1}{I_2}\right)^{S_I} * \left(\frac{\dots X_1}{\dots X_2}\right)^{S_x} \tag{7}$$

In each equation, behavior (*B*) is expressed as a function of a variety of dimensions including rate of reinforcement (*R*), magnitude of reinforcement (*M*) and immediacy of reinforcement (*I*), while *X* denotes any other additional dimensions of reinforcement. Equation 4 expands the model by including a sensitivity parameter (*S*) for each dimension of reinforcement. Using the expanded models of matching, it is possible to encompass many facets of reward and assess changes in behavior as a function of changes in one or more of those dimensions. This ultimately leads to the hypothesis that allocation of choice behavior is a function of relative value of a reinforcer (affected by all dimensions of that reinforcer). Further, with this evolution of modeling choice behavior through matching and as concurrent choice models have become more prevalent in studying SUD, new theories of addiction have emerged.

Relative Value Theory

The Relative Value Theory of Addiction is proposed as an alternate theory to Habit Theory. In Habit Theory, it is hypothesized that with chronic substance use, there is a transition from voluntary to compulsive drug intake. As described previously, initial drug use is assumed to occur due to the rewarding properties of the drug (i.e., outcome-response association) and therefore is a value-based decision. However, as a stimulus is paired with drug use (i.e., stimulus-response association), habitual responding to the stimulus occurs and drug use transitions to compulsive use and is no longer value-based (Koob & Le Moal, 1997, 2001, 2005; Lüscher et al., 2020).

However, in Relative Value Theory, it is hypothesized that both initial and continued drug used is due to value-based decision-making and individuals with SUD continue to choose drug because their subjective, relative value has increased as compared to other available choices. Heyman (2013b) posited that three principles of decision-making can be applied to SUD. First, preferences are dynamic meaning that choices change as a function of time as well as previous choice history. Second, individuals always choose the best option, however the best option will vary from person to person and context to context. Third, options can be framed in different ways in that decisions may be made on a choice-by-choice basis (i.e., considering the best option only in terms of the current moment) or on a global basis (i.e., considering how the current decision will affect future outcomes). Supporting this framework, data shows that most individuals with SUD are in remission by age 30, reach remission without treatment, and highlight the importance of other non-drug alternatives (being a better parent, maintaining a job, etc.) as reasons for staying in remission which highlights the element of value-based decision-making in SUD (Heyman 2013a, 2013b). If habit was responsible for driving addiction, non-drug alternatives would be unable to provide a “cure.”

In further support of this theory, it has been shown that when given concurrent choices between a drug and non-drug alternative, preference can be switched from drug to non-drug by increasing the value of the non-drug alternative (or decreasing the value of drug), in both human and non-human SUD studies

(Thomsen et al., 2013; Lile et al., 2016). If substance use was instead habitual, individuals should continue to choose drug regardless of changes to the non-drug alternative, suggesting that decision-making is a result of contextual relative value as opposed to habit. This poses the question: On what internal scale are non-similar commodities compared so that value-based decisions can be made?

A Common Neural Signal: Revisiting Utility

Borrowing again from economics, there is an assumption that all individuals are rational consumers, meaning that given the choice between two alternatives, the option with higher value (in that moment) will be chosen over the option with lower value (Shizgal & Conover, 1996; Glimcher, 2011). Decision-making, therefore, at its core must assume that all available alternatives, from one context to the next, must be transduced to a common neural signal or common dimension (i.e., a common currency) to be compared (Levy & Glimcher, 2012).

Shizgal & Conover (1996) propose three separate decision-making scenarios to illustrate this point. First, individuals are tasked with choosing to spend $2.00 for 1kg of potatoes or 10 French francs for 1kg of potatoes, second, $10.00 for 1kg of cheese or $10.00 for 1kg of ham, and finally, $2.50 for a cheese sandwich or $3.00 for a ham and cheese sandwich. In the first scenario, a decision cannot be reached without converting at least one of the two prices into an equivalent currency to choose the potatoes with the lowest price. In the second scenario, two very different commodities are presented, making this problem more challenging to solve. Each consumer's choice will therefore be influenced by current physiological state and past experience, as well as other underlying factors (i.e., Are they making burgers tonight and desperately need cheese?). Finally, the third scenario involves determining the value of one commodity alone (cheese) with the combined value (ham & cheese) while also deciding if the cost increase reflects the increase in combined value. These scenarios lead back to the original idea of utility, or subjective value, and hypothesizes that utility is the basis for all choices. However, as discussed previously, it is an immeasurable, hidden variable that can only be inferred from contextual choices. Therefore, until a direct measure of utility can be

elucidated, it is essential to continue assessing choice models to better understand the facets of value and decision-making.

Theoretical Issues with Concurrent Choice

While concurrent choice models help to mitigate the myriad issues associated with single-schedule models, there are also concerns associated with the interpretation of traditional concurrent choice procedures. Namely, these procedures do not consider the effect of obtained reinforcer ratio on reinforcement value. Studies have shown that if one alternative has a higher rate of reinforcement, the relative value for that option will increase and thereby the preference for that option (Johnstone & Alsop, 2000; Beckmann et al, 2019). In concurrent choice, with uncontrolled ratios of reinforcement, the reinforcement ratio of the given alternatives is largely affected by a subject's performance (Stubbs & Plinskoff, 1969). Therefore, obtained reinforcement rate must be controlled so that there is an equal number of delivered reinforcements for each alternative in order to prevent uncontrolled differential reinforcement rates across options from affecting choice (McCarthy & Davison, 1984; Johnstone & Alsop, 2000; Beckmann et al, 2019). Therefore, to mitigate the limitations of a single-schedule models as well as uncontrolled concurrent choice procedures, a controlled reinforcement ratio (CRR) schedule can be implemented.

Controlled Reinforcement Ratio

In CRR (Stubbs & Pliskoff, 1969; McCarthy & Davison, 1984; Beckmann et al., 2019), animals are presented with the choice between two competing reinforcers (ie. stimulation vs. food). However, on any given trial, the option that will result in reinforcement is fixed so that an animal must collect that trial's reinforcement before moving to the next trial. In this way, an animal earns the same ratio of reinforcement from each available reinforcer, but preferred choice can still be elucidated (through choices on an option when it is not scheduled for reinforcement). This procedure ensures that neither available option increases in

value by function of increased reinforcement history and therefore preference can be determined without the confound of number of earned reinforcers.

Summary and Aims of Current Dissertation

In summary, it has been suggested that sugar and fat, when consumed frequently, have properties similar to drugs of abuse. While the validity of FA is questioned, researchers have drawn parallels between SUD and FA. For example, sugar binge models emphasize craving, withdrawal and binging as primary components of FA, which are also hallmarks of SUD. Additionally, both natural rewards and drug rewards act on the mesolimbic pathway, which is implicated in both SUD and FA. Currently, research on FA has largely focused on demonstrating the similarities between FA and SUD, but few studies have assessed preclinical decision-making processes when animals are exposed to extended sugar access. Substance abuse research has highlighted the importance of including non-drug alternatives to mimic real-world scenarios in which many competing alternatives are available, but similar experiments have not been implemented for FA. The current experiment utilizes a controlled reinforcement ratio task in which rats are presented with the choice between fructose and another non-drug alternative, intracranial self-stimulation (ICSS), to assess choice behavior following a fructose self-administration paradigm, which mimics the escalation paradigm in substance use research.

Because ICSS involves delivering an electrical stimulation to the reward system, in this case to the ventral tegmental area (VTA), it is a potent reinforcer. Further, it allows for the investigation that all rewards, both natural and otherwise, must be transduced to a common neural currency to assign value, allocate choice, and ultimately make decisions. By using a paradigm that utilizes fructose vs. ICSS, a common scale can be used to assess and compare choice behavior for a variety of reinforcers. Additionally, the use of ICSS in this manner challenges the rate-dependent threshold procedure that currently dominates the literature. This experiment aimed to assess the effect of extended fructose access on choice

behavior while also examining the validity of threshold procedures as they relate to ICSS.

By using a controlled reinforcement ratio schedule with a choice between fructose and ICSS, this study's goals included: 1. Further investigating the connection between FA and SUD by presenting fructose with a non-drug, non-food alternative to resemble real-life availability of many choice alternatives, 2. Controlling for interpretation challenges related to both rate-dependent measures and rate of reinforcement differences between alternatives, and 3. Determining discrepancies related to the comparison of threshold and choice models.

The overall hypothesis for this experiment was that long-access self-administration of 20% fructose would result in an increase in preference for fructose in the CRR procedure as compared to short-access self-administration. Additionally, no or small correlations between ICSS threshold and preference measures, either before or after self-administration were expected.

CHAPTER 2. METHODS

Materials

Animals

Eighteen (8 male, 10 female) adult Sprague-Dawley rats (Harlan, Inc.; Indianapolis, IN, USA) weighing approximately 250-300 g were used for the study. Rats were single-housed in standard cages on a 12:12 h light:dark cycle. Rats were given *ad libitum* access to water and standard rat chow throughout the duration of the experiment. All experimental protocols were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

Apparatus

Experimental sessions were conducted in a sound-attenuating operant conditioning chamber (ENV-008CT, ENV-018MD; Med Associates). Each operant chamber was connected to a computer running MED-PC and equipped with two retractable levers (ENV-122CM) on the left and right side of the front panel. Within a recessed food receptacle (ENV-202R2MA), a liquid food receptacle was situated in the bottom center between the levers and the food receptacle was equipped with a head entry detector (ENV-254-CB). One white cue light (ENV-221M) was positioned above each of the two levers. On the back panel of the operant chamber, two nosepoke response receptacles (ENV-114BM) were mounted on the left and right sides directly opposite the retractable levers and a house light (ENV-227M) was positioned in the top center of the back panel. Two distinct Sonalert tones (ENV-223AM, ENV-223HAM) were located above the nosepoke receptacles. Liquid food reinforcers were delivered to the food receptacle via a syringe pump (PHM-100) attached to the outside of the operant chamber. Stimulations were delivered via a leash attached to both an implanted electrode as well as a commutator (PHY-015-2) Each commutator was connected to an ICSS stimulator (PHM-152), and each stimulator was connected to the computer via a daisy-chain.

Liquid Reinforcers

Fructose (VWR Chemicals; Solon, OH) was dissolved in distilled water to create a 20% fructose solution. Saccharin (Thermo Fisher Scientific; Ward Hill, MA) was dissolved in distilled water to create a 0.2% saccharin solution.

Electrode Preparation

10mm stainless steel electrodes with 0.28mm diameter (MS303/1-AIU/SPC; Plastics One) were used to deliver electrical stimulation to the VTA. Electrodes were inspected microscopically to assess the condition of the tip of each electrode ensuring a flat as opposed to pointed surface. Electrodes with a pointed tip were made flat using sandpaper. Prior to surgery, electrodes were sterilized using 70% ethanol.

Establishing Procedures

Magazine Training

Rats were initially trained to consume 20% fructose solution from the liquid food receptacle over 2-3 days. Rats were placed in the operant chamber and 0.1mL of fructose was delivered on a 120-s fixed-time schedule. Upon reinforcement delivery, the magazine light illuminated and was paired with a 5-s pulsating tone cue (0.5-s on, 0.5-s off). Rats obtained 10 fructose reinforcements during each training session for at least 2 sessions (see Figure 2.1 for experimental timeline).

Lever Training

Following magazine training, rats were trained to lever press on a fixed-ratio 1 (FR1) schedule for a minimum of 2 days. During each session, levers were presented pseudo-randomly (no more than 3 of one side in succession) across left and right sides and upon completing the response requirement, a 0.18 mL fructose reward was delivered, and the lever retracted. The 5-s pulsating (1 Hz) tone cue was paired with fructose delivery, and the cue light above the lever was illuminated

for the duration of the reinforcement delivery. A new trial began with the illumination of the house light and upon completing a head entry in the magazine on the front panel the house light extinguished, and a lever was extended. Each session consisted of 30 trials (15 left, 15 right).

Nosepoke Training

Rats were then trained to nosepoke on an FR schedule. Like lever training, nosepokes were presented individually and pseudo-randomly. Upon completion of a head entry requirement, one nosepoke light would illuminate and completion of the response requirement resulted in the delivery of 0.18 mL fructose reinforcement. Again, the delivery was paired with a pulsating tone, and the magazine light illuminated for the duration of delivery. The cue lights above the levers did not illuminate during nosepoke delivery. Rats were initially trained on an FR1 schedule of reinforcement, which was incrementally increased to an FR5 schedule over 5-7 days.

Surgery

Following pretraining, surgery was performed to place unipolar electrodes into the left ventral tegmental area (VTA). Animals were anesthetized using 2-4% isoflurane in a stereotaxic frame and maintained at 37^{o} Celsius using a circulating water bath attached to a heating pad. A craniotomy was performed to expose the left VTA (AP: -5.04 (males), -4.99 (females), ML: -0.6 relative to bregma, DV: -8.6 from skull; Paxinos & Watson, 2007, Rincón-Cortés & Grace, 2017) and a small burr hole was created. A unipolar electrode was implanted into the burr hole and secured using dental acrylic. Animals were given three days of recovery.

Amplitude Threshold

To determine optimal amplitude measures for each rat, a threshold test was conducted. Within each session, descending amplitude magnitudes were presented over a series of 1-min blocks. At the beginning of each session, one

lever extended, counterbalanced on the right and left side across animals. Upon completion of an FR1 schedule, a VTA stimulation reward corresponding to the magnitude level of the current block was delivered, a single tone (0.5-sec) was sound —distinct from the tone associated with fructose reinforcement— and the cue light above the lever illuminated. There was no timeout between trials, meaning the animal was able to administer successive VTA stimulations without delay. After each 1-min block, the lever retracted, and a two-min timeout period began. A total of ten blocks, and therefore amplitude magnitudes (130, 117, 104, 91, 78, 65, 52, 39, 26, and 13 μA), were presented within each session. One rat required a higher amplitude range within this procedure (169, 156, 143, 130, 117, 104, 91, 78, 65, and 52) to determine optimal parameters.

Response rates for each block were recorded, and for each individual rat the raw rate of responding was normalized to a maximum control rate (MCR) for each session. MCR is defined as the maximum rate observed in a given session. Using the MCR, a %MCR value was determined for each block within an individual session: (response rate on a given block)/(MCR) x 100 (Bauer et al, 2012). An exponentiated demand curve (see Equation 2) was fit for each rat using %MCR. The optimal amplitude parameter was defined as P_{max}, the point in the demand curve in which demand changes from inelastic to elastic (Gilroy et al, 2019; Hursch & Silberberg, 2008), and determined using Kaplan and Reed's (2014) Excel calculator. P_{max} was calculated individually for each rat and used as the amplitude value for all subsequent procedures (Figure 2.2). Rats were run for a minimum of 10 days until stability— defined as no linear trend over 3 days —was observed (Figure 2.3).

Experiment Proper

For this experiment, order of procedure was counterbalanced so that half of the rats began with frequency and fructose threshold while the other half began with CRR to control for order effects.

Frequency Threshold

Using the individual established amplitude parameters, the frequency threshold procedure followed the same protocol as the amplitude threshold. However, in this paradigm, instead of decreasing amplitude, stimulation frequency (Hz) decreased in magnitude with each subsequent component within a given session, thereby successively decreasing the number of ICSS stimulations over 10 components (630, 561, 492, 423, 354, 285, 216, 147, 78, and 5 Hz). Total stimulation consumption (number of stimulations/second) was calculated by multiplying the number of reinforcers earned in a given component by 0.2s and multiplying the result by the number of stimulations in that component. The procedure was continued for a minimum of 10 days until stability was reached, based on %MCR as described above (Figure 2.4), and an exponentiated demand curve of consumption was fit (Equation 2).

Fructose Threshold

Following each daily frequency threshold session, a threshold procedure using a 20% fructose solution was conducted. Unlike amplitude and frequency threshold, the volume of the reinforcer decreased across sessions as opposed to within sessions thereby increasing unit price (Unit Price: 1, 1.67, 3.33, 5, 10, 16.67, 33.33, 50, 100, 166.67 responses/0.3mL) with each subsequent session (Yates et al, 2017). Each unit price was presented in one 10 min session, with sessions occurring once per day and rates of responding at each magnitude recorded. Total fructose consumption (mL) was calculated by multiplying the number of reinforcers earned in a session by the volume magnitude of that session. An exponentiated demand curve for fructose consumption was fit.

Controlled Reinforcement Ratio

Rats were placed on a CRR schedule (Stubbs & Pliskoff, 1969; McCarthy & Davison, 1984; Beckmann et al, 2019) for ICSS vs. fructose choice to establish baseline choice behavior (Figure 2.5). Sessions were split into 5 blocks of 6 trials

so that rats received an equal number of food and ICSS reinforcers in each block. Rats started on an FR1 schedule and moved progressively to an FR4 schedule over 7 days. The terminal FR requirement for each rat ranged from FR2-FR4. Trials began with an orienting response into the magazine centered on the front panel, which illuminated the right and left nosepoke response receptacles. Each trial had one available, randomly assigned, reinforcer in that animals were required to complete the FR schedule and earn the reinforcer programmed on the present trial (i.e., forced trials) before progressing to the next trial. Responses from forced trials for each reinforcer were not used to calculate preference. Upon completion of the FR schedule, the programmed reinforcer was delivered and the nosepoke lights turned off. Additionally, a fructose reinforcement was paired with the 5-s pulsating tone and a VTA stimulation reinforcement was paired with a single distinct tone as described previously. Importantly, the FR requirement reset if an animal chose to switch response nosepokes before completing the FR schedule.

Throughout a session, the volume of fructose reinforcement (0.18mL) remained constant while the number of VTA stimulations (1, 6.2, 12.6, 31.6, 63) increased with each consecutive block. Each block was paired with a distinctive pattern of alternating tones to indicate which block an animal was in (Table 2.1). A block ended with the completion of all six trials, which initiated a 2-minute blackout, and each session ended with the completion of all five blocks (30 trials). This procedure was also completed using ICSS vs. 0.2% saccharin to establish baseline choice behavior for a non-caloric reinforcer. This allowed for better disassociation of hedonic from homeostatic motivation following the self-administration phase. Animals continued to run on the CRR schedule for at least two weeks (at least 7 days per reinforcer type) until stability—defined as no linear trend over four sessions—was observed for both fructose and saccharin.

Fructose Acquisition

After completing frequency threshold, fructose threshold, and stable choice in CRR for both fructose and saccharin, rats began a one-week fructose acquisition period. Each rat completed a one-hour self-administration session per day in which

they could freely administer a 20% fructose solution via an FR1 schedule. The session began with the extension of both the right and left response levers. One lever, counter-balanced across rats, corresponded to fructose reinforcement, while the other lever was inactive. Upon completion of the FR requirement on the active lever, both levers retracted and 0.18mL of 20% fructose was delivered and paired with a cue light and the 5-s pulsating tone. Following delivery, the left and right responses levers extended. Importantly, rats completed acquisition in a different operant chamber than threshold and CRR to create a distinct context for each paradigm.

Fructose Self-Administration

Following acquisition, rats were matched on fructose acquisition, demand parameters, and choice parameters for fructose and saccharin and assigned to the short access (ShA) or long access (LgA) self-administration condition. Both conditions operated on an FR1 schedule as described in acquisition. The ShA condition was identical to acquisition while the LgA condition had six-hour unrestricted access to the self-administration paradigm. All animals completed one self-administration session per day for 38 days.

Testing:CRR

Throughout fructose acquisition and self-administration, animals continued the CRR schedule as described above completing one CRR session per day before completing the self-administration session. Rats spent at least 30 minutes in their home cage, without access to food, prior to starting self-administration each day. To evaluate changes in fructose and saccharin choice behavior associated with fructose self-administration, rats alternated reinforcement availability each day. For example, one day rats completed ICSS vs. fructose CRR followed by fructose self-administration and the next day completed ICSS vs. saccharin CRR followed by fructose self-administration. The reinforcement order was counterbalanced across rats (ie. half completed fructose CRR on self-administration Day 1).

Testing: Threshold

Following 28 days of self-administration, rats completed one day of lever training as described above. Then rats were tested on both the frequency threshold and fructose threshold procedures as described above to assess changes associated with fructose self-administration. Threshold testing continued for a minimum of 10 days. The self-administration sessions continued throughout threshold testing.

Assessing VTA Placement

Following the experiment, all subjects were humanely euthanized, and their brains were extracted and frozen at -80°C until analysis. Brains were sliced in 40µm sections using a cryostat and stained with Cresyl Violet (Sigma-Aldrich). Following staining, brains were imaged to ensure proper electrode placement in the VTA (Figure 2.6).

Data Analysis

Controlled Reinforcement Ratio

Percent choice for ICSS was calculated from the CRR procedure, averaged over the last four sessions for each reinforcer type, as total number of preferred ICSS responses (responses on the ICSS lever when it is not the available reinforcer) divided by the total number of preferred responses (preferred ICSS responses plus responses on the food lever when it is not the available reinforcer; Figure 2.5). Furthermore, a version of generalized matching (Baum & Rachlin, 1969; Killeen, 1972) was used to model the CRR data:

$$\frac{B_i}{B_i + B_f} = \frac{100}{1 + \left(a/x\right)^s} \tag{8}$$

where *B* is equal to the number of preferred responses for a given reinforcer (*i* = ICSS, *f* = food) when that reinforcer is unavailable, *x* is the number of stimulations available, *a* is a free parameter that represents the exchange rate between ICSS and food (i.e. the number of stimulations equal to one magnitude unit of food reinforcer) and *s* represents the sensitivity to changes in the relative magnitude between ICSS and food reinforcers. Importantly, *x* is reported as number of stimulations as opposed to Hz level as discussed previously (Figure 2.7).

In this model, increases in exchange rate would indicate increased value for the food reinforcer (i.e. one unit of food is equal to a greater number of stimulations) while decreases would indicate decreased value. Further, when *s* is equal to 1, there is perfect sensitivity to relative magnitude changes. Values greater than 1 indicate increased sensitivity to relative magnitude changes, while values less than one indicate decreased sensitivity to relative magnitude changes (Figure 2.8).

Threshold

Consumption during ICSS threshold was calculated as number of stimulations per second as described above averaged over the last three sessions. Fructose consumption was calculated as described previously. Both ICSS and fructose consumption data were fit using the exponentiated demand equation (Equation 2). As explained, this equation includes parameters for demand intensity, the theoretical consumption when cost is zero, and demand elasticity (α), which quantifies how sharply consumption decreases in response to increasing cost. Commodities with greater inelasticity (consumption is more insensitive to price changes) have smaller demand elasticity and are therefore interpreted as having greater value, whereas commodities with greater elasticity (consumption is more sensitive to price changes; Figure 2.9).

Statistical Analysis

Both choice data and threshold data were analyzed using non-linear mixed effects (NLME) modeling in the NLME package in R using their respective equations. For all models, subject was included as a nominal random factor. Model comparisons were conducted with Access (1 hr. vs 6 hr.), Self-Administration Phase (baseline vs. post self-administration), and Access*Self-Administration Phase as nominal fixed factors. Akaike Information Criterion (AIC) was used to determine the best-fitting model in which smaller AIC values indicate better model fit. Further, an evidence ratio, based on AIC, was calculated for each model comparison as described by (Burnham et al., 2011):

$$ER = {}^{1}\!/_{e^{-0.5\Delta AIC}} \tag{9}$$

In this model the change in AIC between two models is used to determine the evidence ratio, which represents how much stronger one model is over another. For example, a ΔAIC value of 11 would result in an evidence ratio of approximately 245. This indicates that the better model is 245 times stronger than the alternative model.

Finally, demand parameters for both ICSS and fructose (Q0, consumption at lowest experimental unit price, and demand elasticity), CRR parameters for both fructose and saccharin (exchange rate and sensitivity) and total fructose consumption during self-administration were correlated between pre self-administration (i.e. pre-self-administration ICSS demand elasticity correlated with pre-self-administration fructose demand elasticity), pre and post self-administration (i.e., pre-self-administration ICSS demand elasticity correlated with post-self-administration fructose demand elasticity), and post self-administration (i.e., post-self-administration ICSS demand elasticity correlated with post-self-administration fructose demand elasticity). Spearman's r correlation was determined using Prism Graphpad.

Table 2.1: CRR Alternating Tone Pattern
Distinct pattern of alternating tones within each CRR session to differentiate each experimental block.

Block	Tone 1	Tone 2
1	continuous	—
2	1.6-s	0.4-s
3	1.0-s	1.0-s
4	0.4-s	1.6-s
5	—	continuous

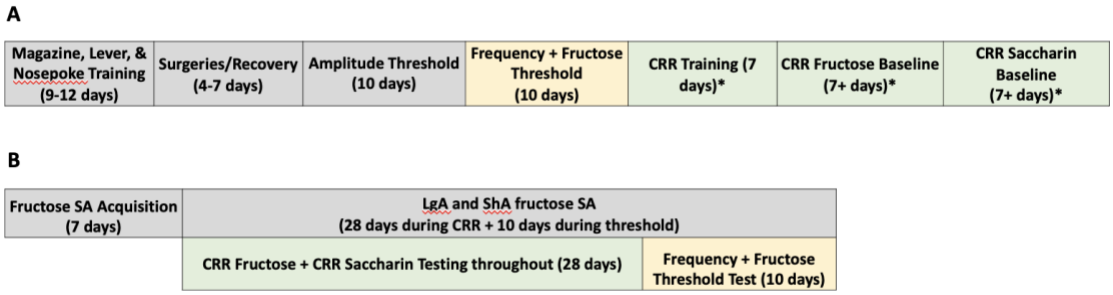

Figure 2.1 Experimental Timeline

(a) Pre-training and baseline measurement timeline, *the order of CRR Training and CRR Fructose and Saccharin baseline measurements were counterbalanced with Frequency + Fructose threshold. (b)Timeline for fructose self-administration and testing following establishing procedures and baseline training.

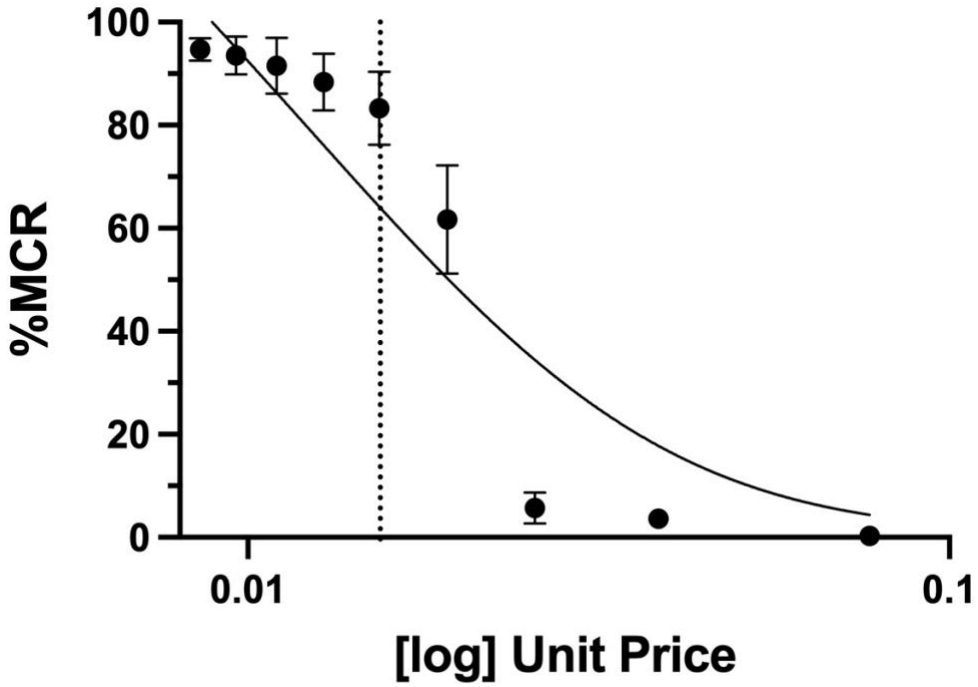

Figure 2.2: Representative Amplitude Threshold
Representative amplitude threshold demand for a single rat averaged over the last three sessions. Mean (±SEM) percent maximum control rate (%MCR) as a function of [log] Unit Price where Unit Price is 1/available amplitude level. The dotted line represents p_{max} defined as the point where demand switches from inelastic to elastic and set as the amplitude value for this individual rat for all subsequent procedures.

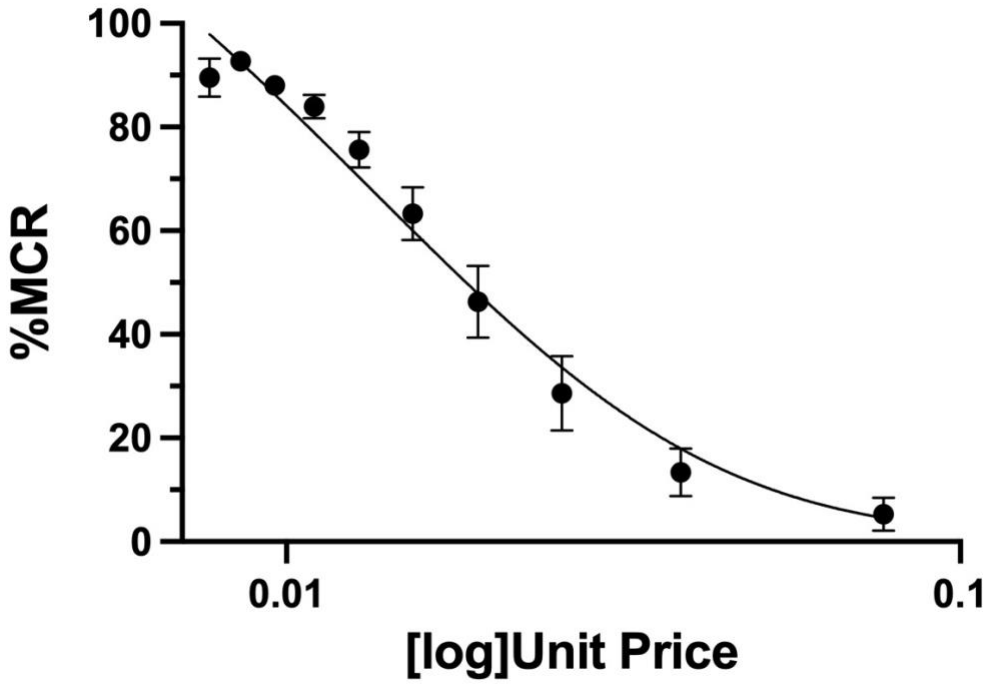

Figure 2.3: Average Amplitude Threshold
Amplitude threshold demand averaged over last three sessions. Mean (±SEM) Percent maximum control rate (%MCR) as a function of [log] Unit Price where Unit Price is 1/available amplitude level.

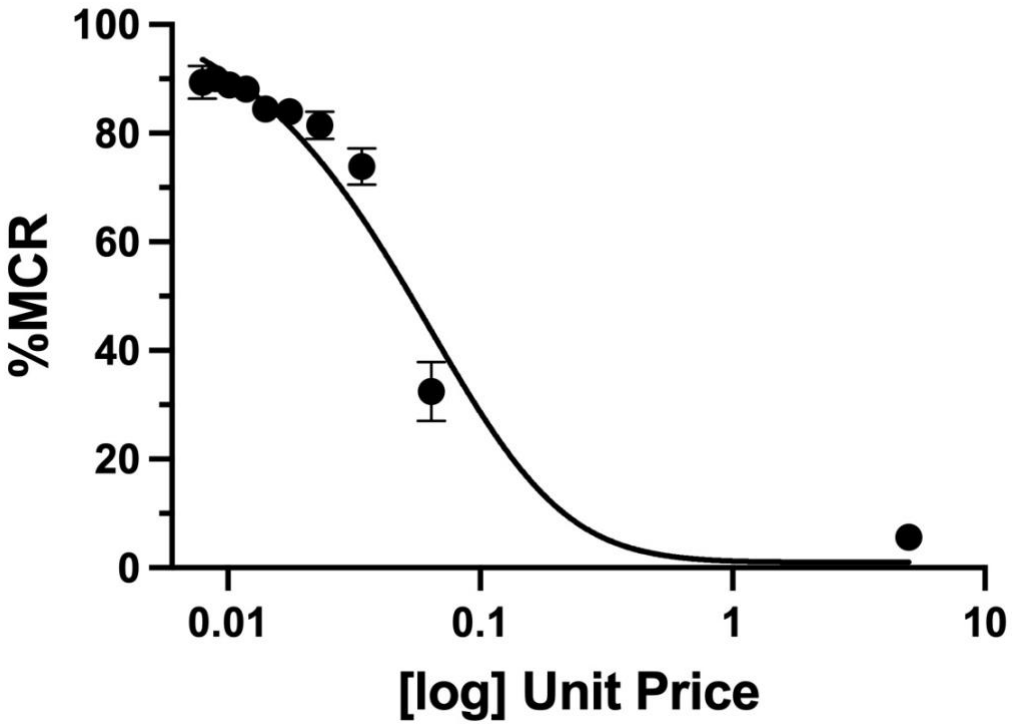

Figure 2.4: Average Frequency Threshold
Average frequency threshold demand averaged over last three sessions to assess stability. Mean (±SEM) percent maximum control rate (%MCR) as a function of [log] Unit Price where Unit Price is 1/available number of stimulations.

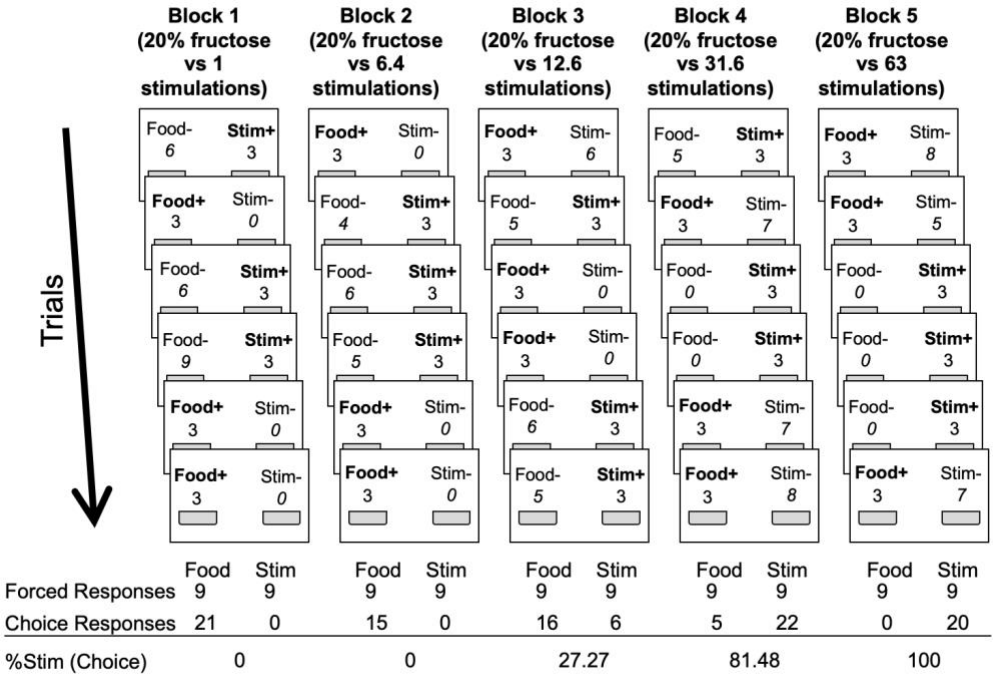

Figure 2.5: Controlled Reinforcement Ratio Example
Theoretical example of a single FR3 session under the controlled reinforcement ratio paradigm. Trial-by-trial (rows) and block-by-block (columns) breakdown where the left option is associated with food and the right option is associated with stimulation (stim). In each trial, only one option is randomly scheduled to produce reinforcement, indicated by the bolded (+) sign. The number below each food/stim label illustrates the number of responses made on each option, with numbers under (+) sign options representing forced responses and numbers under (–) sign options representing choice responses. %Choice for ICSS is calculated by dividing the total number of ICSS choice responses by the total number of choice responses (ICSS + food) within a given block.

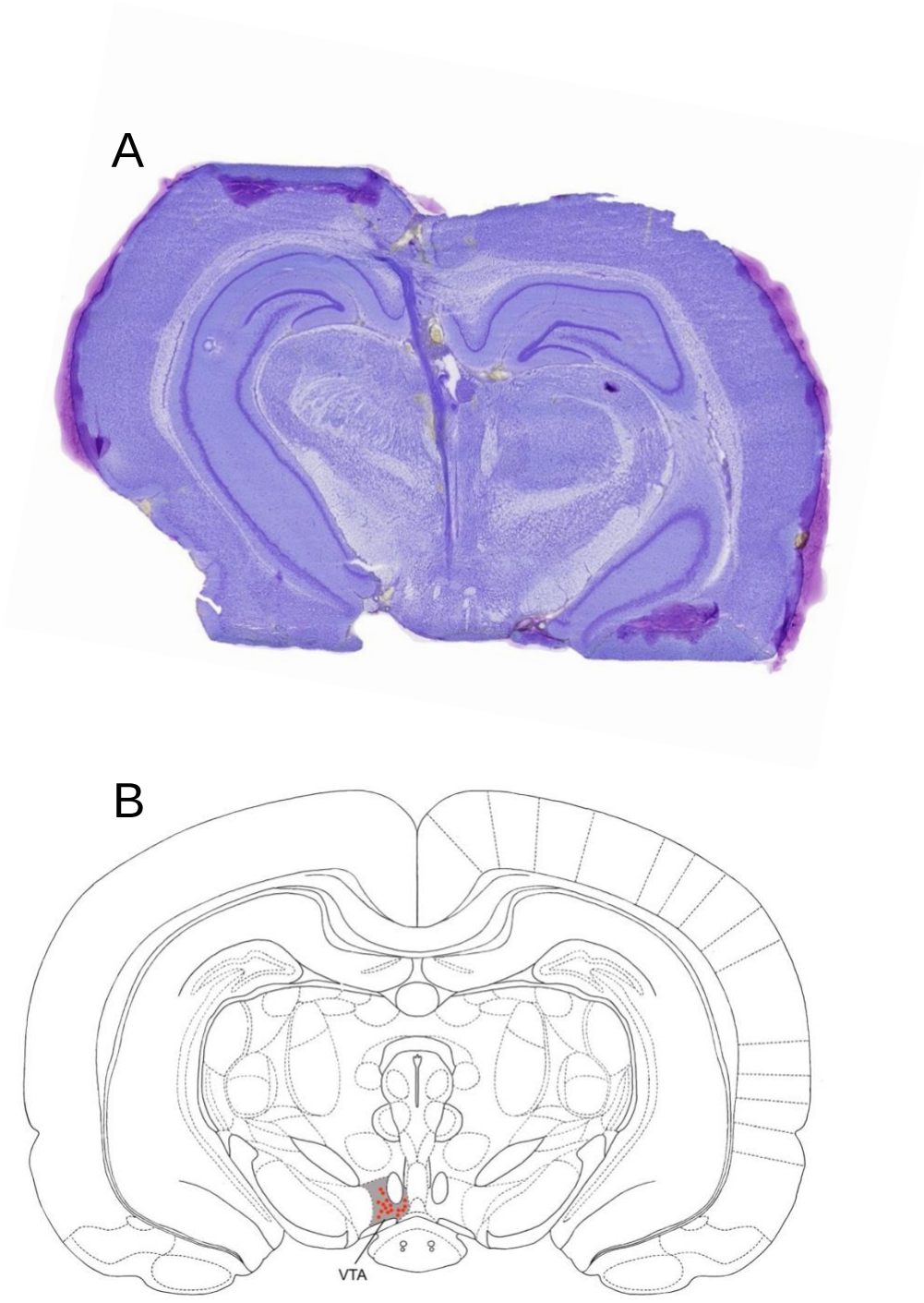

Figure 2.6: VTA Electrode Placement
(a) Representative brain slice image stained with Cresyl Violet. (b) Schematic depicting placement of N=16 electrodes.

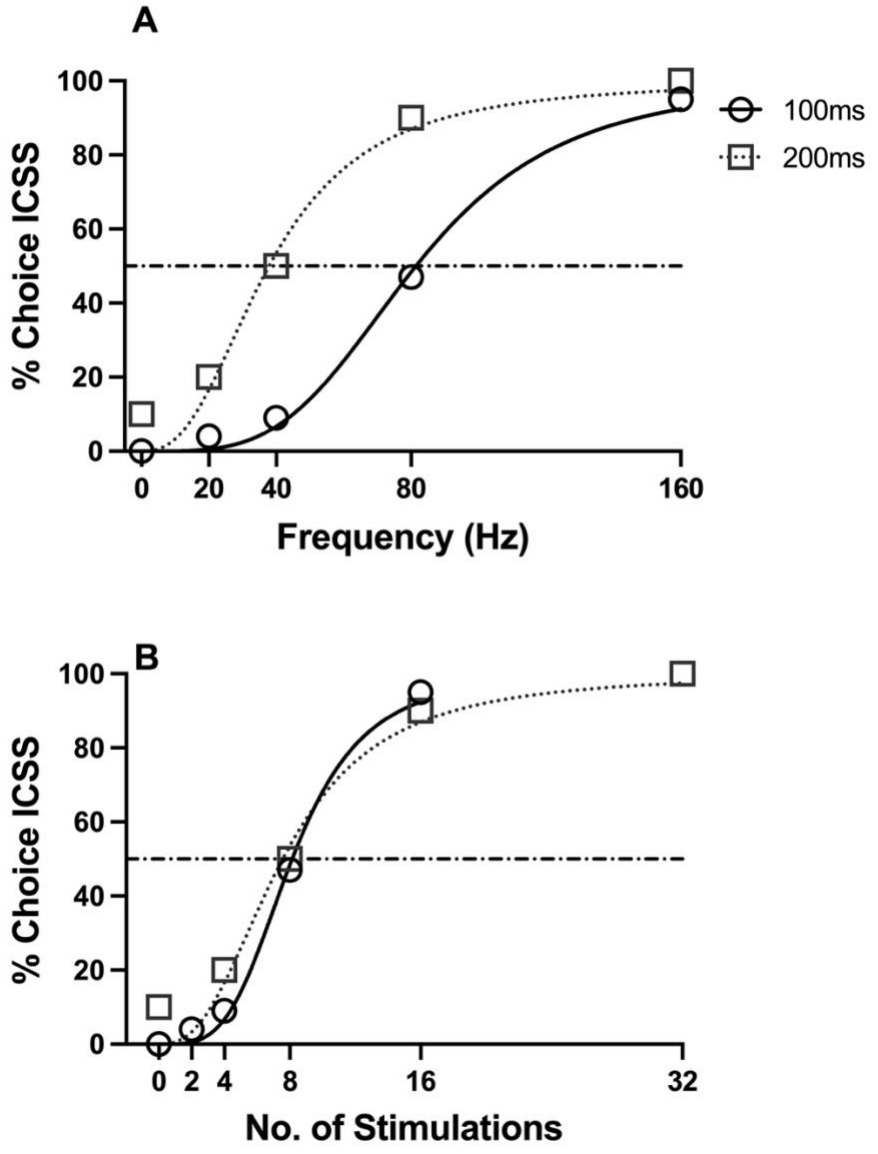

Figure 2.7: Frequency vs. Number of Stimulations in Choice
Example of the same choice data displayed as a function of frequency (a) and as a function of number of stimulations (b). This figure illustrates how using frequency without incorporating duration of stimulation can lead to misleading comparisons.

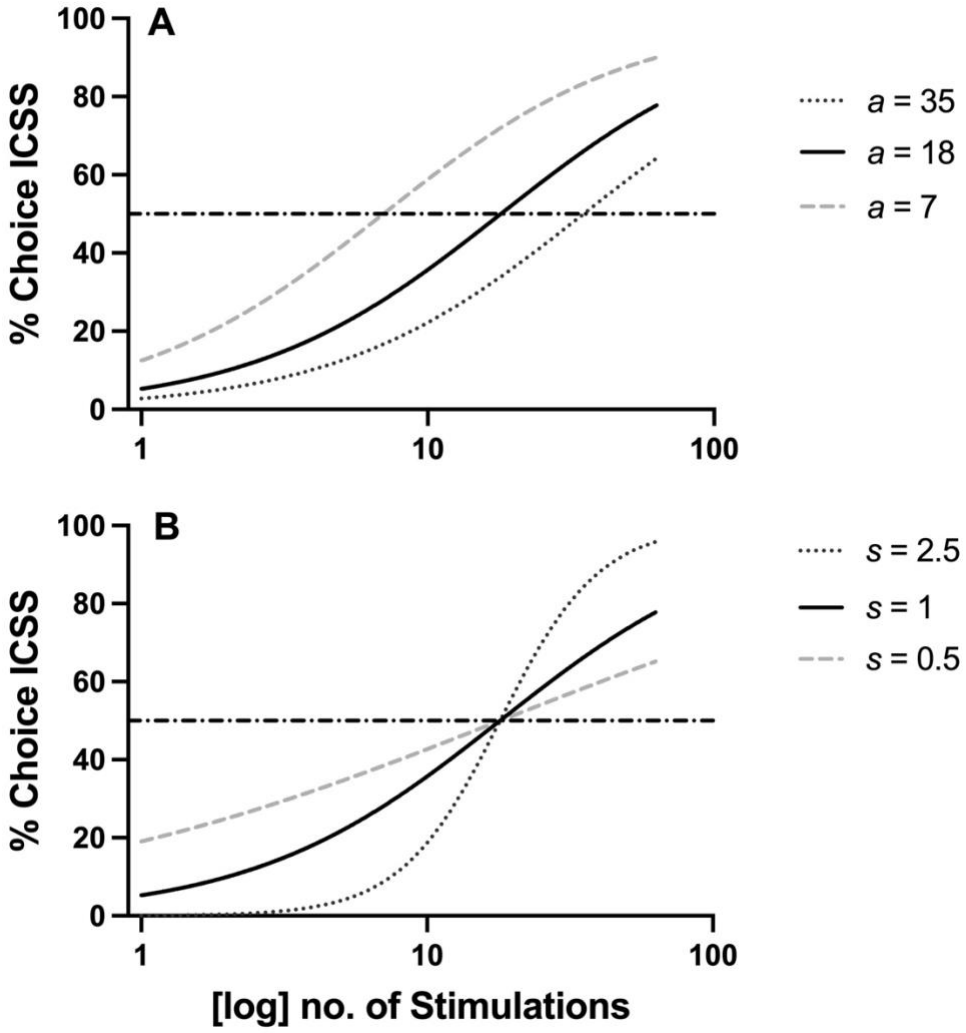

Figure 2.8: CRR Exchange Rate and Sensitivity Simulation
(a) Illustration of curve shift when the exchange rate within the CRR paradigm increases or decreases while sensitivity remains constant (s = 1). (b) Illustration of curve shift when sensitivity increases or decreases while exchange rate remains constant (a = 18).

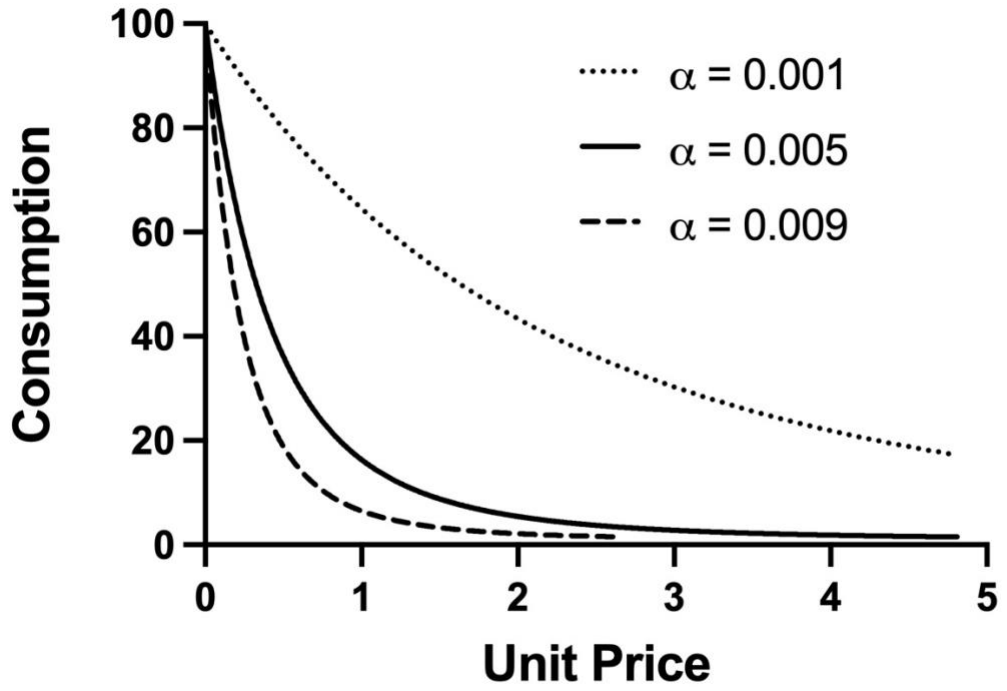

Figure 2.9: Demand Analysis Simulation
A simulation of the change in demand analysis as a function of changing demand elasticity (in this example Q_0 and *k* are constant across all three demand fits). This illustrates how a larger demand elasticity results in a sharper decline in consumption (i.e., increasing unit price) while a smaller demand elasticity results in a less sharp decline, therefore interpreted as greater value.

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CHAPTER 3. RESULTS

Self-Administration

Acquisition

During the 1-week acquisition period (Figure 3.1A) there were no differences in intake between the 1-hr and 6-hr access conditions (F (1,16) = 0.158, p = 0.696). Additionally, there was no effect of session (F (1,16) = 0.21, p = 0.653). This shows that animals were appropriately matched when assigning 1-hr and 6-hr conditions.

Extended Access

A linear mixed-effects model comparison of intake (Table 3.1) was performed, and Model B (Session, Access, and Session*Access as fixed effects) was determined to be the best model fit for self-administration data as compared to Model A (Session as fixed effect) with a reported evidence ratio of 2213.87. This model revealed a main effect of access (F (1,16) = 24.27, p = 0.0002) with the 6-hr access group having greater overall fructose intake as well as a main effect of session (F (1,16) = 5.55, p = 0.03) indicating a decrease in fructose intake as a function of session. There was no significant interaction between access and session (Figure 3.1B).

Threshold

Frequency Threshold

Figure 3.2 illustrates consumption of ICSS (stimulations/sec) as a function of [log] unit price modeled using Equation 2. Overall, ICSS consumption decreased as unit price increases. Model comparisons (Table 3.2) revealed that Model D, which included phase (pre- vs post- self-administration), access condition (1-hr vs 6-hr) and phase x access interaction as fixed factors, was the best model, as compared to the next-best fitting model (Model C). This model reported an evidence ratio of approximately 14.8 million, indicating strong support for this model. This model revealed a main effect of self-administration phase (F (1, 335)

= 43.51, $p < 0.001$) on ICSS demand intensity where demand intensity increased after self-administration ($Q_0 = 49.47, SE = 1.98$) as compared to baseline ($Q_0 = 39.63, SE = 6.01$).There were no main effects of access on ICSS demand intensity nor was there a significant interaction effect. Additionally, there were no main effects of phase or access on ICSS demand elasticity. However, there was an interaction effect on demand elasticity (F (1,335) = 29.024, $p < 0.001$) where the 6-hr access group had an increase in demand elasticity following self-administration (a = 1.64, SE = 0.035) as compared to pre-self-administration (a = 1.32, SE = 0.027), but the 1-hr group had no change from pre- to post-self-administration.

Fructose Threshold

Fructose demand threshold is depicted in Figure 3.3 as fructose consumption (mL) as a function of [log] Unit Price. Overall, fructose consumption decreased as unit price increases. Model comparisons (Table 3.3) revealed that Model C, which included phase as a nominal fixed effect was the best model with an evidence ratio of 5.35 as compared to the next best-fitting model, Model D (phase x access condition interaction). This model revealed a main effect (F (1,339) = 30.57, $p<.001$) of phase on fructose demand intensity, Q_0 in which demand intensity decreased after self-administration ($Q_0 = 0.042, SE = 0.0039$) as compared to pre-escalation ($Q_0 = 0.057, SE = 0.004$) regardless of access group. There was no effect of self-administration phase on fructose demand elasticity.

Controlled Reinforcement Ratio

Fructose CRR

Figure 3.4 shows the percent choice for ICSS during fructose CRR as a function of [log] number of stimulations. Additionally, it shows the inverse percent choice of fructose as a function of [log] number of stimulations. Overall, both the 1-hr and 6-hr access groups had a greater preference for fructose when fewer stimulations were available and a greater preference for ICSS when a greater

number of stimulations was available. When comparing models (Table 3.4), the best-fitting model was Model A (a global model with subject as a random factor) as the evidence ratio was 4.3 compared to the next best-fitting model (Model B). This model revealed that a global exchange rate (*a* = 10.83, *SE* = 0.698) and global sensitivity parameter (*s* = 1.45, *SE* = 0.173) best described the data. This indicates that during fructose CRR, one unit of fructose can be exchanged at a rate of 10.83 stimulations and that overall, sensitivity was greater than one indicating that sensitivity to changes in magnitude were steeper than "perfect" sensitivity.

Saccharin CRR

Like fructose CRR, during saccharin CRR animals showed a preference for saccharin when fewer number of stimulations were available and switched to a preference for ICSS when a greater number of stimulations was available as can be seen in Figure 3.5. Model comparisons (Table 3.5) illustrated that the best model was again Model A, the model with global parameter estimates for both the exchange rate (*a* = 10.8, *SE* = 1.43) and the sensitivity parameter (*s* = 1.71, *SE* = 0.14). Further, the evidence ratio as compared to the next best model (Model B) was 4.44, suggesting strong support for a global parameter model as compared to a model that includes access condition (i.e., 1-hr vs. 6-hr fructose access).

Fructose and Saccharin CRR

Since model comparisons for both fructose CRR and saccharin CRR indicated a global parameter best model fit, a model comparison was performed to determine best model fit in reference to reinforcer type (Table 3.6). Model B (reinforcer type as a fixed factor) was the best model fit as compared to a global parameter model (Model A) with an evidence ratio of 8.74 e^{26}. This model revealed a main effect of reinforcer type on exchange rate in CRR (F (1,339) = 8.25, p = 0.004). Figure 3.6 illustrates percent choice for ICSS as a function of [log] number of stimulations and highlights the difference in exchange rate between fructose CRR (a = 13.0, SE = 1.74) and saccharin CRR (a = 11.4, SE = 1.73).

Correlations

Correlations were computed for all parameters described previously; however, unless otherwise stated, only significant correlations are included in the following sections.

Fructose Demand Elasticity

Figure 3.7 illustrates a significant correlation between pre-self-Administration (Pre-SA) fructose demand elasticity (α) and pre-SA fructose exchange rate in CRR (Spearman's r = -0.678, p = 0.002). When assessing correlations between pre-SA fructose demand elasticity and post-self-administration (post-SA), there was a significant correlation between pre-SA fructose demand elasticity and post-SA fructose demand elasticity (Spearman's r = 0.519, p = 0.027). Significant correlations were also noted between pre-SA fructose demand elasticity and post-SA fructose consumption at the lowest unit price (LUP; Spearman's r = 0.565, p = 0.015) as seen in Figure 3.8. Finally, Figure 3.9 shows post-SA fructose demand elasticity was found to be correlated with post-SA fructose exchange rate in CRR (Spearman's r = -0.746, p = 0.0004) and post-SA saccharin exchange rate in CRR (Spearman's r = -0.645, p = 0.004).

ICSS Demand Elasticity

Figure 3.10 depicts the correlation between pre-SA ICSS demand elasticity and post-SA ICSS demand elasticity (Spearman's r = 0.515, p = 0.023) as well as correlations with post-SA ICSS consumption at LUP (Spearman's r = -0.479, p = 0.04), post-SA fructose exchange rate in CRR (Spearman's r = 0.618, p = 0.006), and post-SA saccharin exchange rate in CRR (Spearman's r = 0.645, p = 0.004). Additionally, Figure 3.11 illustrates the correlations between post-SA ICSS demand elasticity and total fructose consumption during self-administration, calculated by multiplying the total number of responses across all 38 self-administration days by the fructose reinforcer volume, 0.18mL (Spearman's r = 0.631, p = 0.005) and post-SA fructose exchange rate in CRR (Spearman's r =

0.598, p = 0.009). Notably, the correlation between ICSS demand elasticity and total fructose consumption during self-administration remains significant even when assessing the 6-hr and 1-hr groups separately.

Fructose Consumption at Lowest Unit Price

The correlations between pre-SA fructose consumption at LUP and pre-SA ICSS consumption at LUP (Spearman's r = -0.507, p = 0.032) as well as pre-SA fructose exchange rate in CRR (Spearman's r = 0.503, p = 0.034) and pre-SA sensitivity during fructose CRR (Spearman's r = -0.514, p = 0.029) are depicted in Figure 3.12. Additionally, Figure 3.13 illustrates the correlations between pre-SA and post-SA fructose consumption at LUP (Spearman's r = 0.838, p < 0.0001) and between pre-SA fructose consumption at LUP and post fructose demand elasticity (Spearman's r = -0.534, p = 0.023).

ICSS Consumption at Lowest Unit Price

Figure 3.14 illustrates the correlations between pre-SA ICSS consumption at LUP and post-SA ICSS consumption at LUP (Spearman's r = 0.513, p = 0.029), post-SA fructose exchange rate in CRR (Spearman's r = -0.609, p = 0.007), post-SA saccharin exchange rate in CRR (Spearman's r = -0.558, p = 0.016) and post-SA ICSS demand elasticity (Spearman's r = -0.472, p = 0.048).

Sensitivity in Fructose CRR

The correlations between pre-SA sensitivity in fructose CRR and post-SA fructose consumption at LUP (Spearman's r = -0.656, p = 0.003) as well as post-SA saccharin exchange rate in CRR (Spearman's r = -0.476, p = 0.046) are illustrated in Figure 3.15.

Notable Uncorrelated Parameters

Interestingly, as shown in Figures 3.16 and 3.17 there were several like parameters that did not have significant correlations when comparing pre-SA and

post-SA. When comparing pre-SA and post-SA ICSS demand intensity (Q_0) there was no significant correlation (Spearman's r = 0.319, p = 0.197). Similarly, there was no correlation between pre- and post- SA fructose demand intensity (Spearman's r = 0.201, p = 0.423). For choice parameters no correlations were noted for pre- and post-SA fructose exchange rate in CRR (Spearman's r = 0.245, p = 0.328), sensitivity in fructose CRR (Spearman's r = -0.061, p = 0.81), saccharin exchange rate in CRR (Spearman's r = 0.296, p = 0.233), or sensitivity in saccharin CRR (Spearman's r = 0.377, p = 0.123).

Table 3.1: Self-administration model comparison
Model comparison for self-administration where Model A includes subject(random) and session (fixed) as factors and Model B includes subject (random), session (fixed), access (fixed) and session x access as factors. The model with the best fit is bolded.

Model	Factors	AIC	ΔAIC	Evidence ratio
Model A	Subject, Session	5612.65	—	—
Model B	**Subject, Session, Access, Access*Session**	**5597.245**	**15.405**	**2213.88**

Table 3.2: ICSS consumption model omparison
Model comparison for ICSS consumption threshold where Model A includes subject as a random factor, Model B includes subject (random) and access (fixed), Model C includes subject (random) and phase (fixed) and Model D includes subject(random), access (fixed, phase (fixed), and access*phase interaction (fixed). Models are shown in descending order of AIC values. ΔAIC calculations and evidence ratios are in reference to the previously best-fitting model. The model with the best fit is in bold.

Model	Factors	AIC	ΔAIC	Evidence ratio
Model A	Subject	5266.29	—	—
Model B	Subject, Access	5253.389	12.901	633.02
Model C	Subject, Phase	5231.721	21.668	50 716.16
Model D	**Subject, Access, Phase, Access*Phase**	**5198.698**	**33.023**	**~14.8 million**

Table 3.3: Fructose threshold model comparison
Model comparison for fructose consumption threshold where Model A includes subject as a random factor, Model B includes subject (random) and access (fixed), where access is a nominal grouping variable for 1-hr vs. 6-hr fructose access, Model C includes subject (random) and phase (fixed) where phase is a nominal grouping variable for pre-self-administration vs. post- and Model D includes subject(random) and access*phase interaction (fixed). Both the ΔAIC and evidence ratios are in comparison to the best model fit. The model with the best fit is bolded.

Model	Factors	AIC	ΔAIC*	Evidence ratio*
Model A	Subject	1133.312	-34.632	~33 million
Model B	Subject, Access	1135.593	-36.913	~103 million
Model C	**Subject, Phase**	**1098.68**	**—**	**—**
Model D	Subject, Access, Phase, Access*Phase	1102.028	-3.348	5.35

Table 3.4: Fructose CRR model comparison
Model comparison for fructose CRR where Model A includes subject as a random factor, Model B includes subject (random) and access (fixed), where access is a nominal grouping variable for 1-hr vs. 6-hr fructose access, Model C includes subject (random) and phase (fixed) where phase is a nominal grouping variable for pre-self-administration vs. post- and Model D includes subject(random) and access*phase interaction (fixed). Both the ΔAIC* and evidence ratios are in comparison to the best model fit. The model with the best fit is bolded.

Model	Factors	AIC	ΔAIC*	Evidence ratio*
Model A	**Subject**	**1616.917**	**—**	**—**
Model B	Subject, Access	1620.064	−3.147	4.83
Model C	Subject, Phase	1620.173	−3.256	5.10
Model D	Subject, Access, Phase, Access*Phase	1623.618	−6.701	28.57

Table 3.5: Saccharin CRR model comparison
Model comparison for saccharin CRR where Model A includes subject as a random factor, Model B includes subject (random) and access (fixed), where access is a nominal grouping variable for 1-hr vs. 6-hr fructose access, Model C includes subject (random) and phase (fixed) where phase is a nominal grouping variable for pre-self-administration vs. post- and Model D includes subject(random) and access*phase interaction (fixed). Both the ΔAIC* and evidence ratios are in comparison to the best model fit. The model with the best fit is bolded.

Model	Factors	AIC	ΔAIC*	Evidence ratio*
Model A	**Subject**	**1550.383**	**—**	**—**
Model B	Subject, Access	1553.365	−2.982	4.44
Model C	Subject, Phase	1554.096	−3.713	6.41
Model D	Subject, Access, Phase, Access*Phase	1557.432	−7.049	34.48

Table 3.6: Fructose & saccharin CRR model comparison
Model comparison for fructose and saccharin CRR where Model A includes subject as a random factor and Model B includes subject (random) and reinforcer (fixed), where reinforcer is a nominal grouping variable for fructose vs. saccharin reinforcer type. The model with the best fit is bolded.

Model	Factors	AIC	ΔAIC	Evidence ratio
Model A	Subject	3197.449	—	—
Model B	**Subject, Reinforcer**	**3073.242**	**124.207**	**8.74 e^{26}**

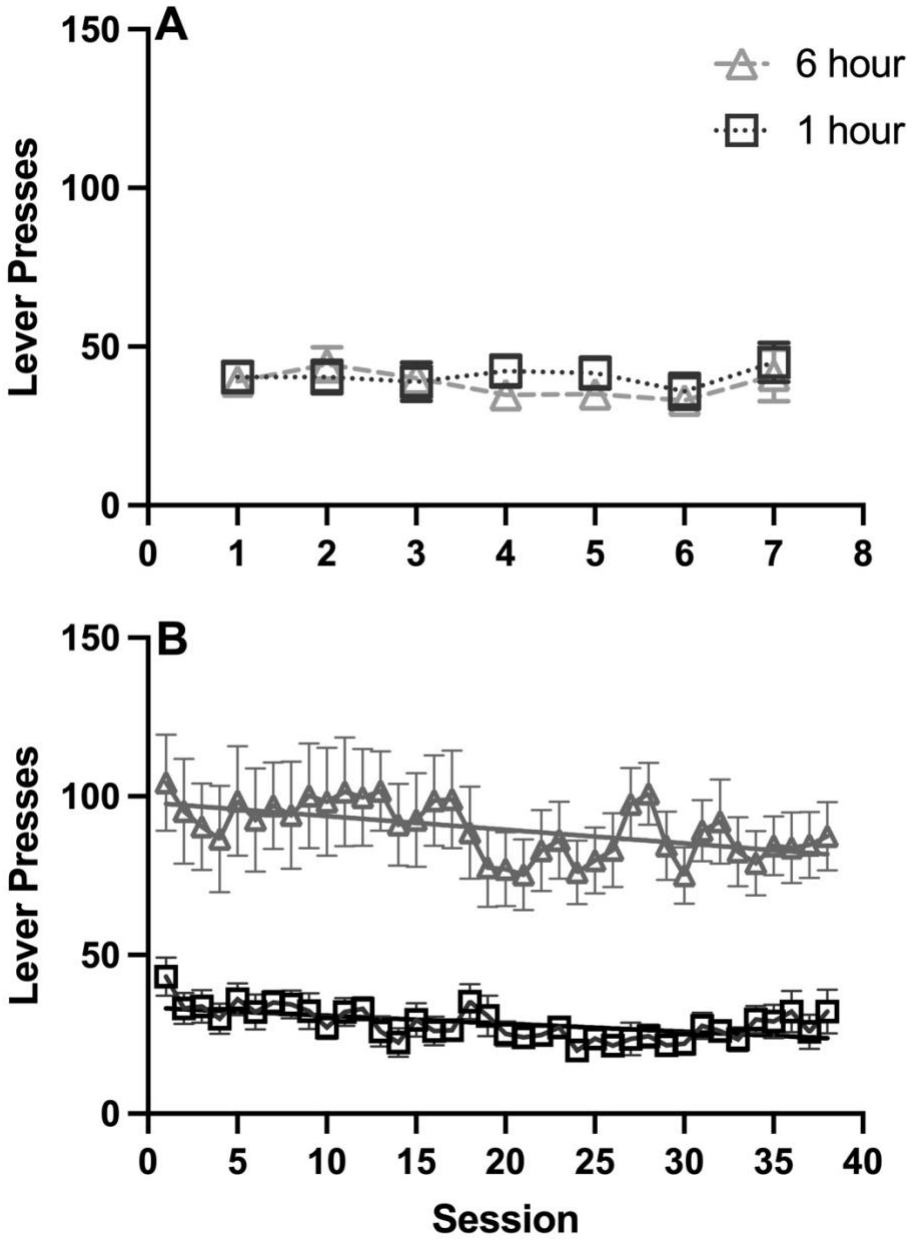

Figure 3.1: Self-administration intake
Mean (±SEM) fructose intake as a function of session during (a) acquisition and (b) extended self-administration.

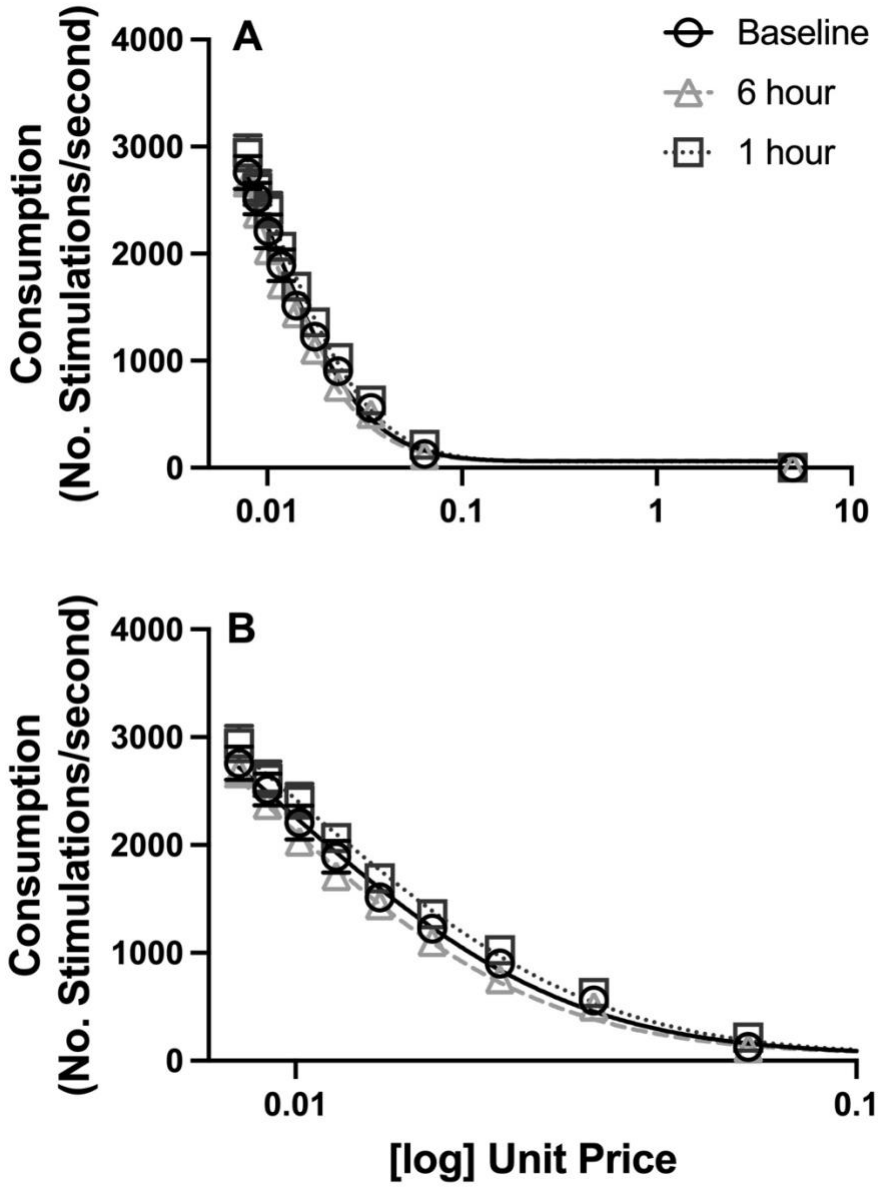

Figure 3.2: ICSS consumption
ICSS Consumption as a function of [log] Unit Price. (a) Mean (±SEM) ICSS consumption over last three sessions. (b) A version of panel (a) with a reduced x-axis scale. These fits were modeled using Prism parameters as opposed to parameters reported in R.

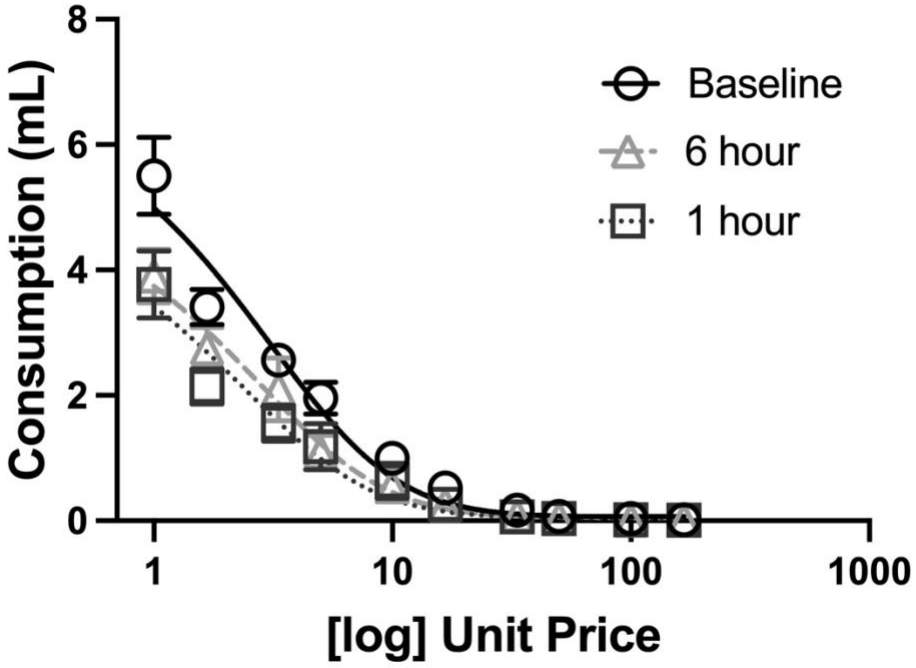

Figure 3.3: Fructose consumption
Mean (±SEM) fructose consumption as a function of [log] unit price analyzed using the exponentiated demand equation. This fit was modeled using Prism parameters as opposed to parameters reported in R.

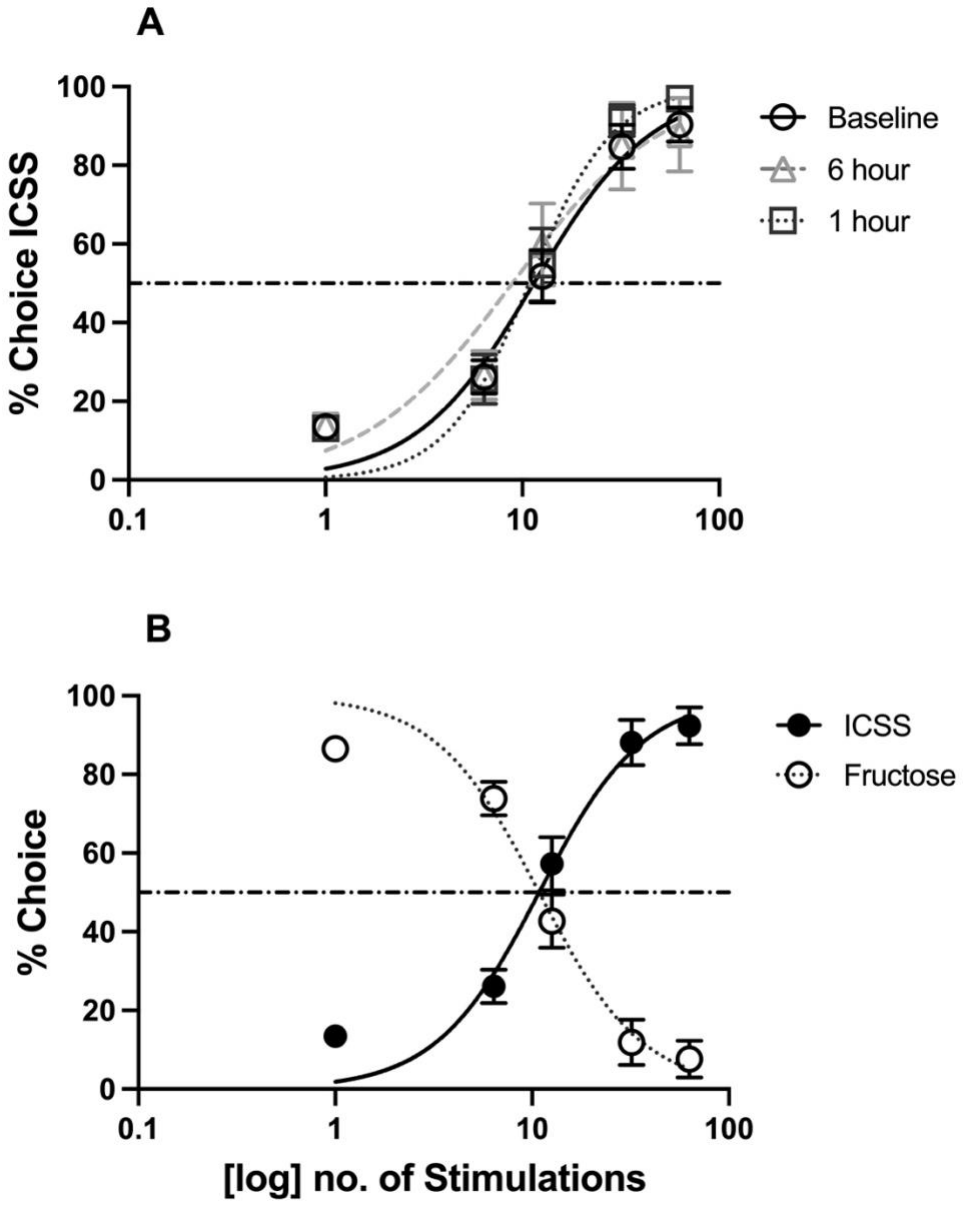

Figure 3.4: Percent choice for ICSS and fructose
Mean (±SEM) percent choice for ICSS and fructose as a function of [log] number of stimulations in fructose CRR. (a) Percent choice ICSS comparing pre-SA fructose CRR with post-SA fructose CRR broken down by access group. (b) Percent choice of post-SA ICSS and fructose collapsed across access group where the intersection in preference indicates the exchange rate.

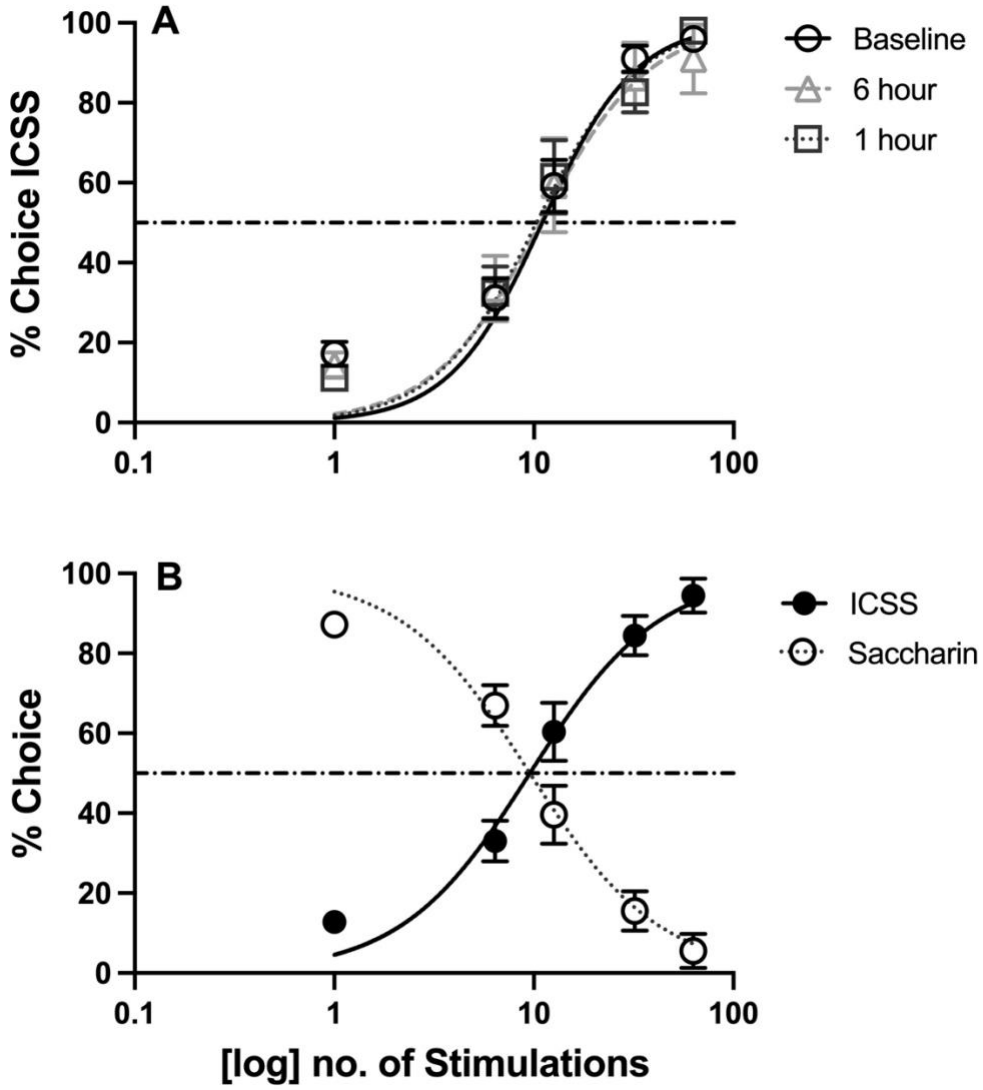

Figure 3.5: Percent choice for ICSS and saccharin
Mean (±SEM) percent choice for ICSS and saccharin as a function of [log] number of stimulations in fructose CRR. (a) Percent choice ICSS comparing pre-SA saccharin CRR with post-SA saccharin CRR broken down by access group. (b) Percent choice of post-SA ICSS and saccharin collapsed across access group where the intersection in preference indicates the exchange rate.

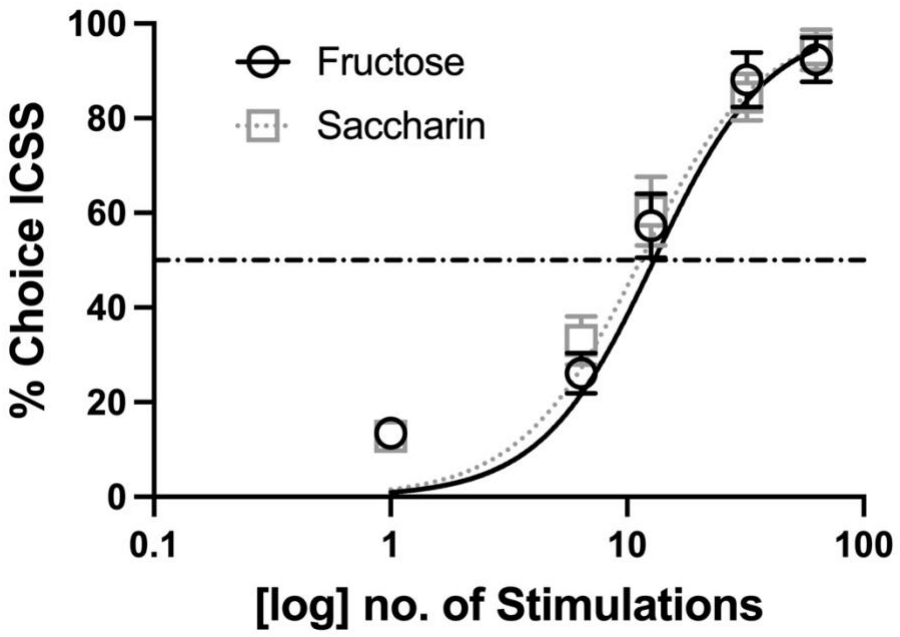

Figure 3.6: Percent choice for ICSS as a function of reinforcer type
Mean (±SEM) percent choice for ICSS as a function of [log] number of stimulations in fructose CRR based on reinforcer type.

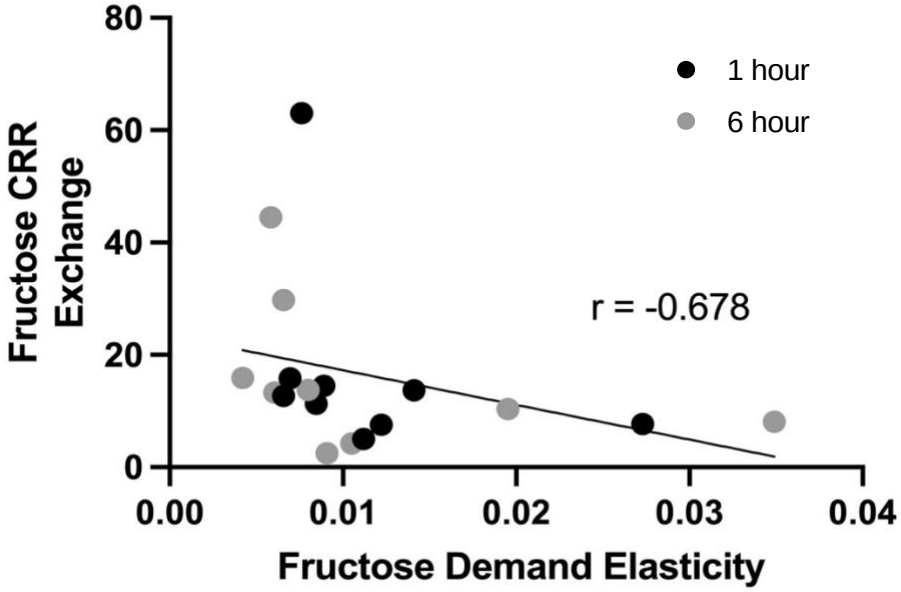

Figure 3.7: Correlation between pre-SA fructose demand elasticity and pre-SA exchange rate

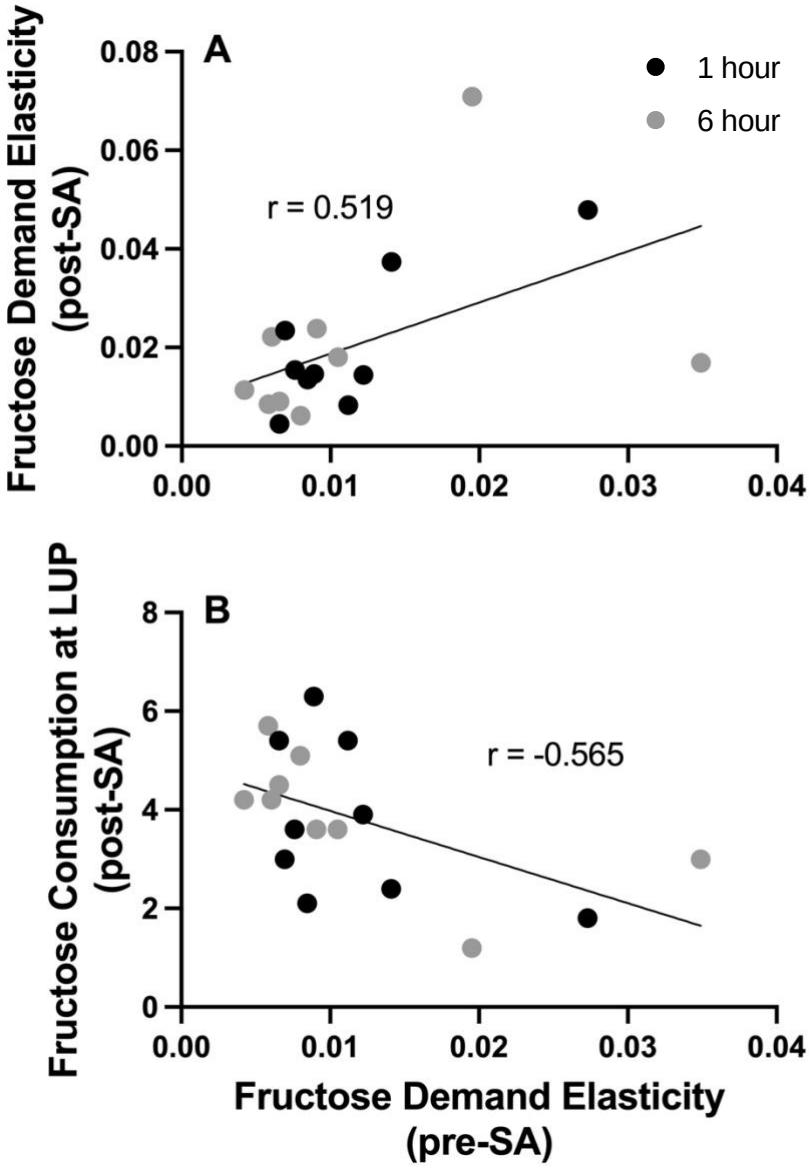

Figure 3.8: Correlations between pre-SA fructose demand elasticity and post-SA parameters

(a) Positive correlation between pre-SA and post-SA fructose demand elasticity. (b) Negative correlation between pre-SA fructose demand elasticity and post-SA fructose consumption at lowest unit price.

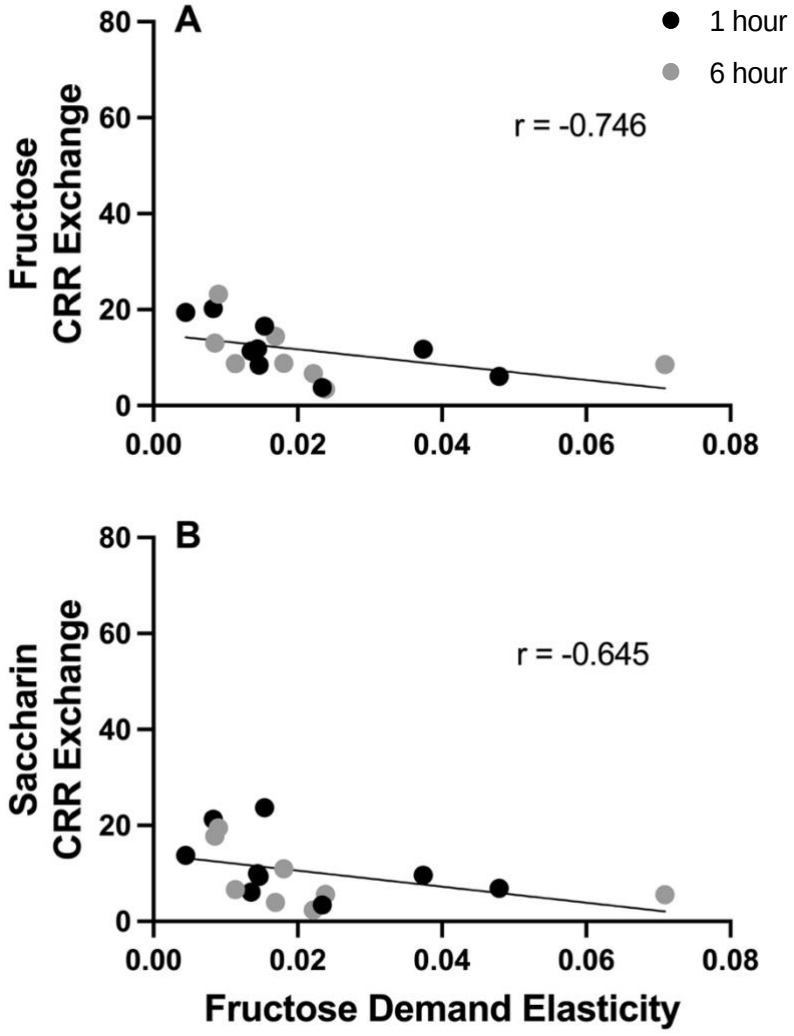

Figure 3.9: Correlations between post-SA fructose demand elasticity and post-SA parameters

(a) Negative correlation between pre-SA fructose demand elasticity and post-SA fructose exchange rate in CRR. (b) Negative correlation between post-SA fructose demand elasticity and post-SA saccharin exchange rate.

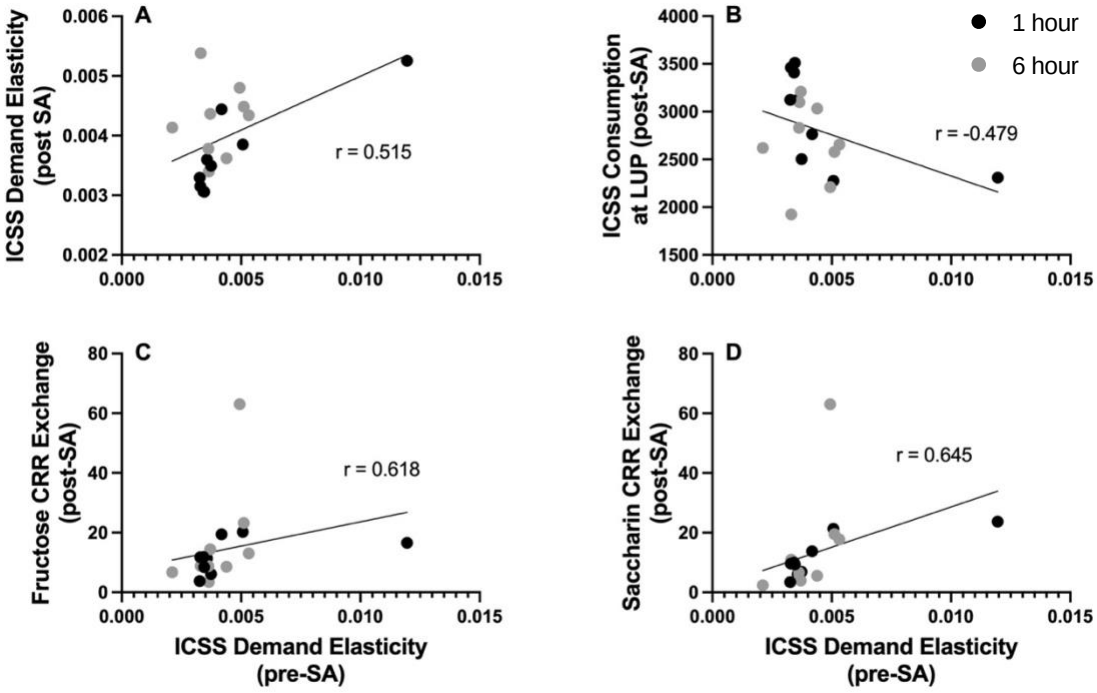

Figure 3.10: Correlations between pre-SA ICSS demand elasticity and post-SA parameters

(a) Positive correlation between pre-SA and post-SA ICSS demand elasticity. (b) Negative correlation between pre-SA ICSS demand elasticity and post-SA ICSS consumption at LUP. (c) Positive correlation between pre-SA ICSS demand elasticity and post-SA fructose exchange rate in CRR. (d) Positive correlation between pre-SA ICSS demand elasticity and post-SA saccharin exchange rate in CRR.

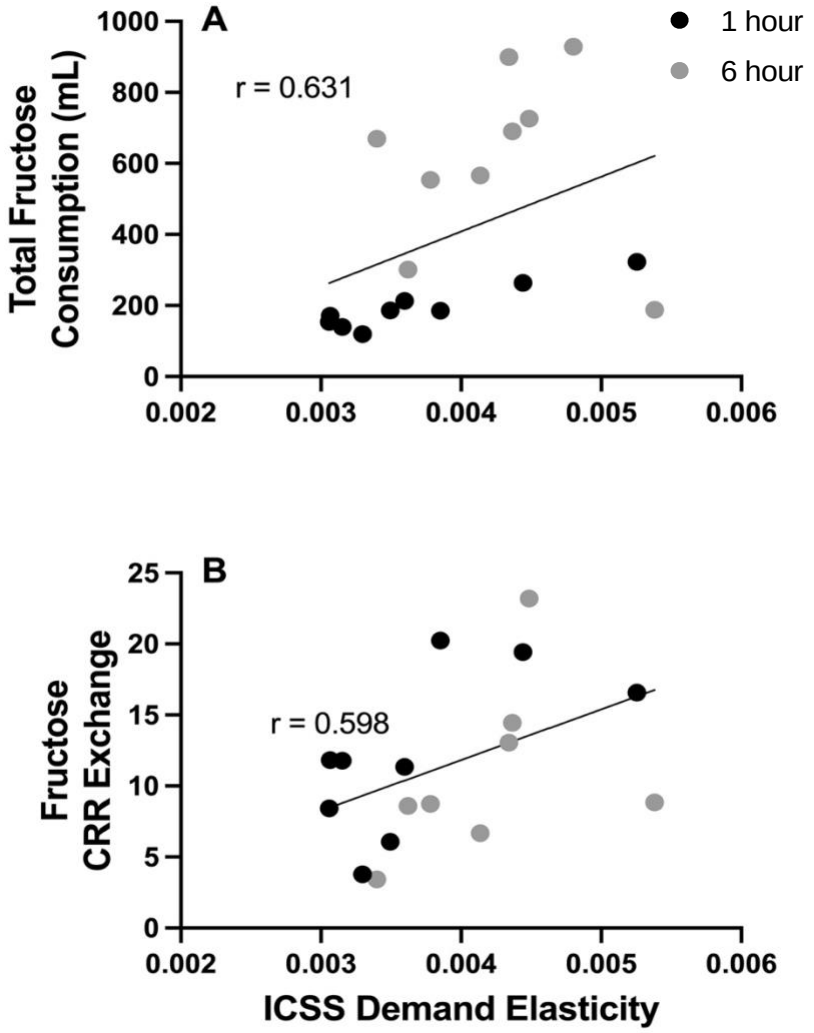

Figure 3.11: Correlations between post-SA ICSS demand elasticity and post-SA parameters

(a) Positive correlation between post-SA ICSS demand elasticity and total fructose consumption during self-administration. (b) Positive correlation between post-SA demand elasticity and post-SA fructose exchange rate in CRR.

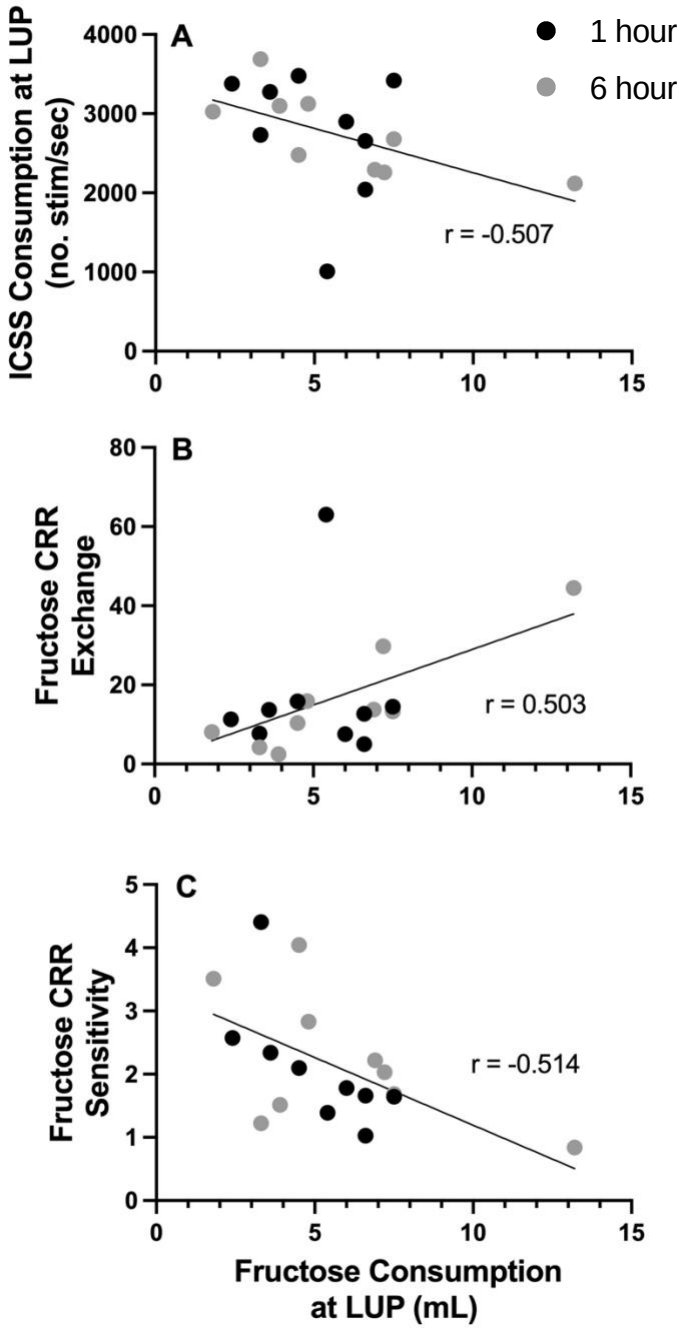

Figure 3.12: Correlations between pre-SA fructose consumption at LUP and pre-SA parameters

. (a) Negative correlation between pre-SA fructose consumption at LUP and pre-SA ICSS consumption at LUP. (b) Positive correlation between pre-SA fructose consumption at LUP and pre-SA fructose exchange rate in CRR. (c) Negative correlation between pre-SA fructose consumption at LUP and pre-SA sensitive during fructose CRR.

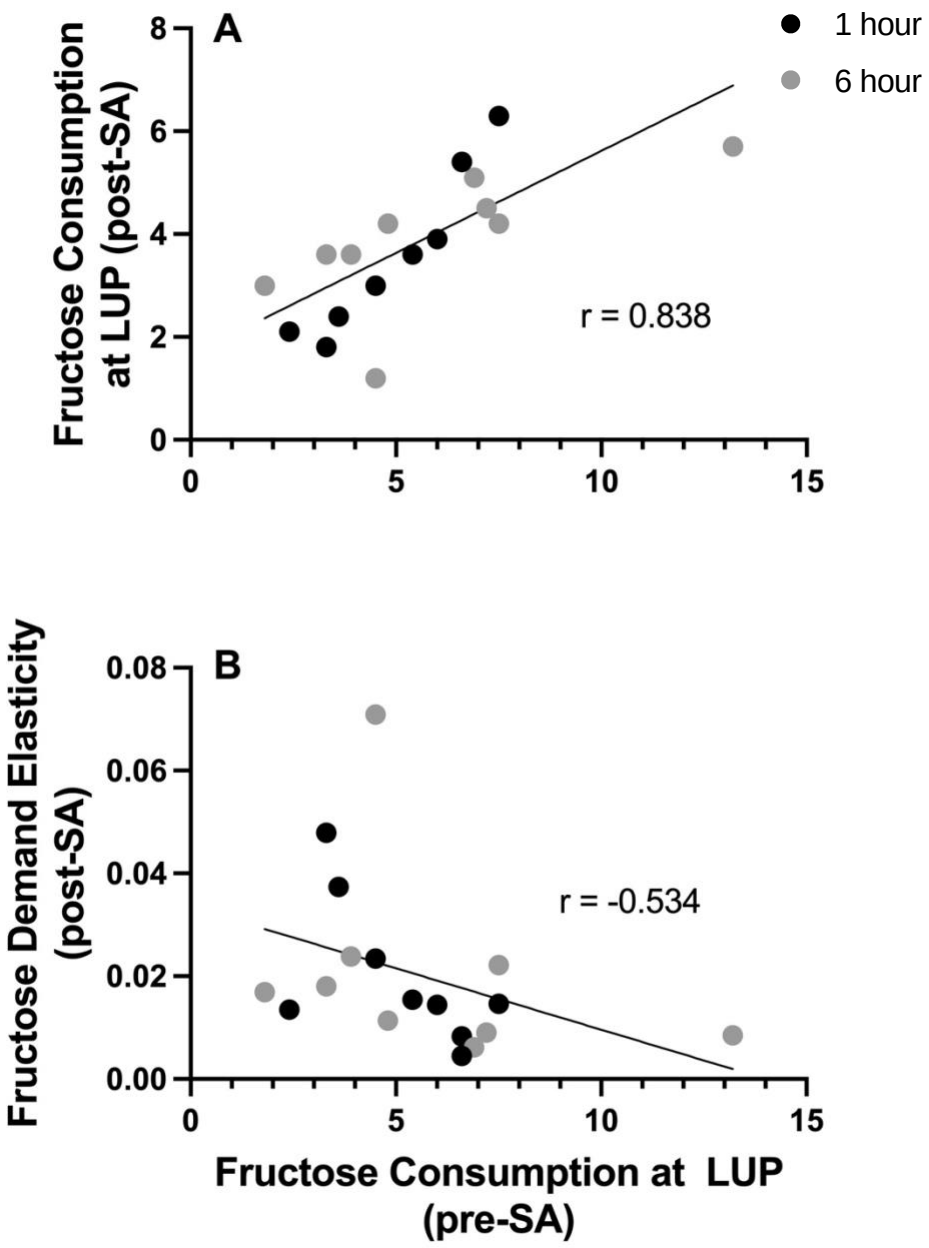

Figure 3.13: Correlations between pre-SA fructose consumption at LUP and post-SA parameters
(a) Positive correlation between pre-SA and post-SA fructose consumption at LUP. (b) Negative correlation between pre-SA fructose consumption at LUP and post-SA fructose demand elasticity.

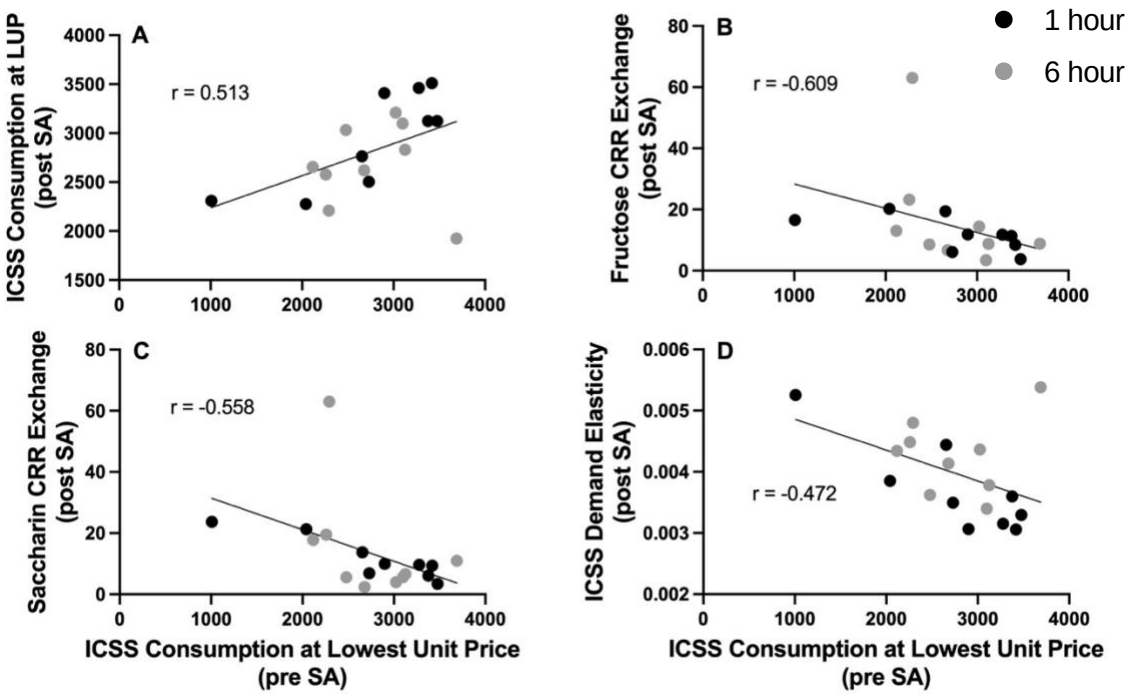

Figure 3.14: Correlations between pre-SA ICSS consumption at LUP and post-SA parameters

(a). Positive correlation between pre-SA and post-SA ICSS consumption at LUP. (b) Negative correlation between pre-SA ICSS consumption at LUP and post-SA fructose exchange rate in CRR. (c) Negative correlation between pre-SA ICSS consumption at LUP and post-SA saccharin exchange rate in CRR. (d) Negative correlation between pre-SA ICSS consumption at LUP and post-SA ICSS demand elasticity.

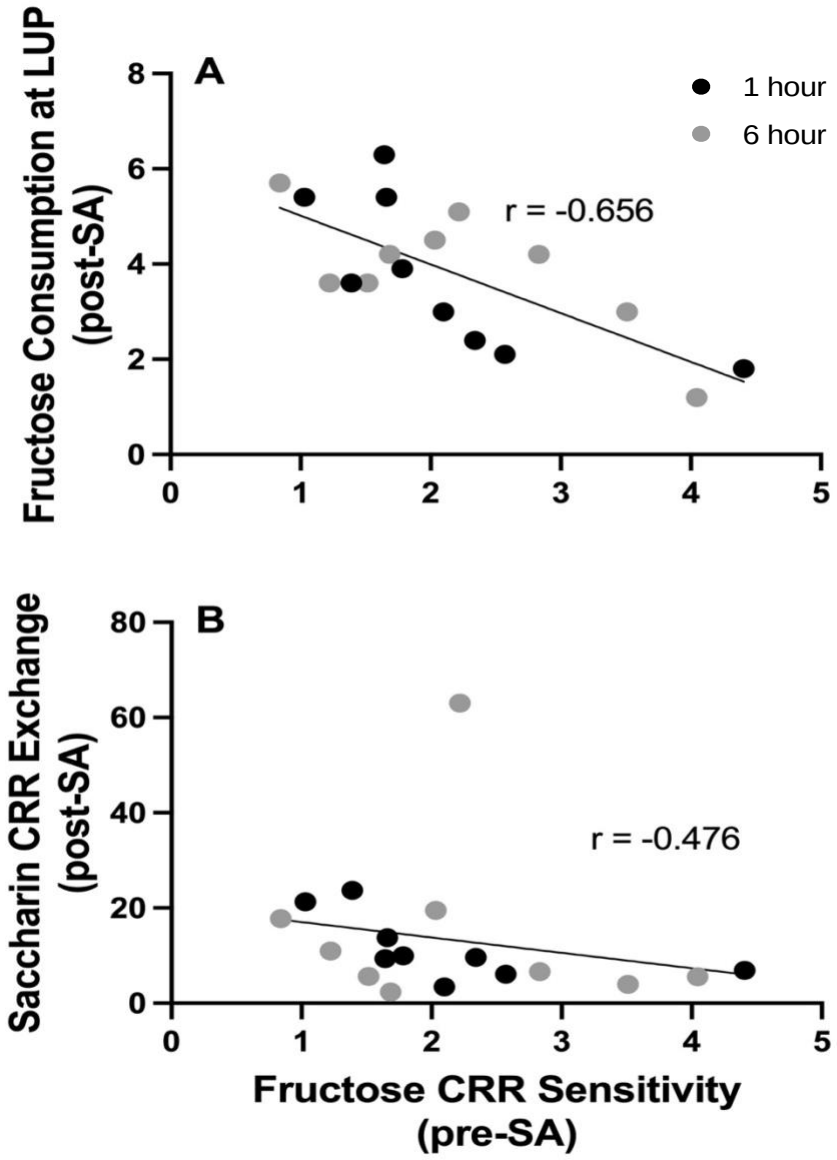

Figure 3.15: Correlations between pre-SA sensitivity in fructose CRR and post-SA parameters

(a) Negative correlation between pre-SA sensitivity in fructose CRR and post-SA fructose consumption at LUP. (b) Negative correlation between pre-SA sensitivity in fructose CRR and post-SA saccharin exchange rate in CRR.

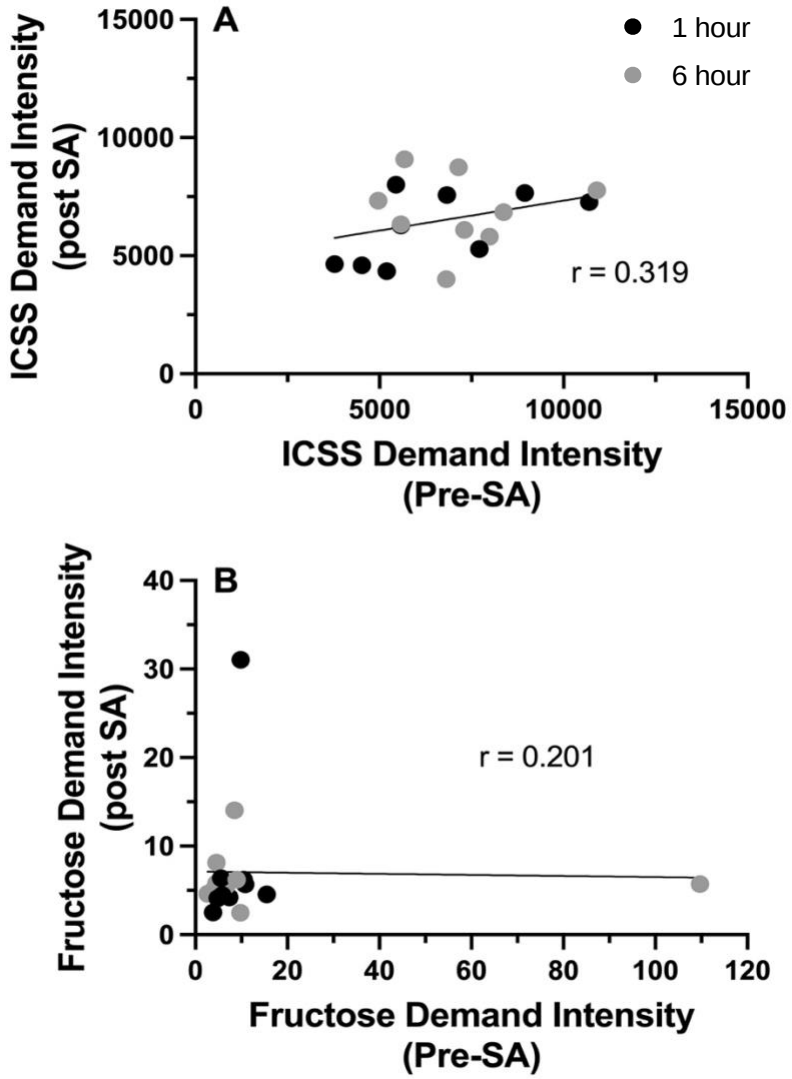

Figure 3.16: Correlation between pre-SA fructose demand intensity and post-SA demand intensity
(a) ICSS demand intensity and (b) fructose demand intensity.

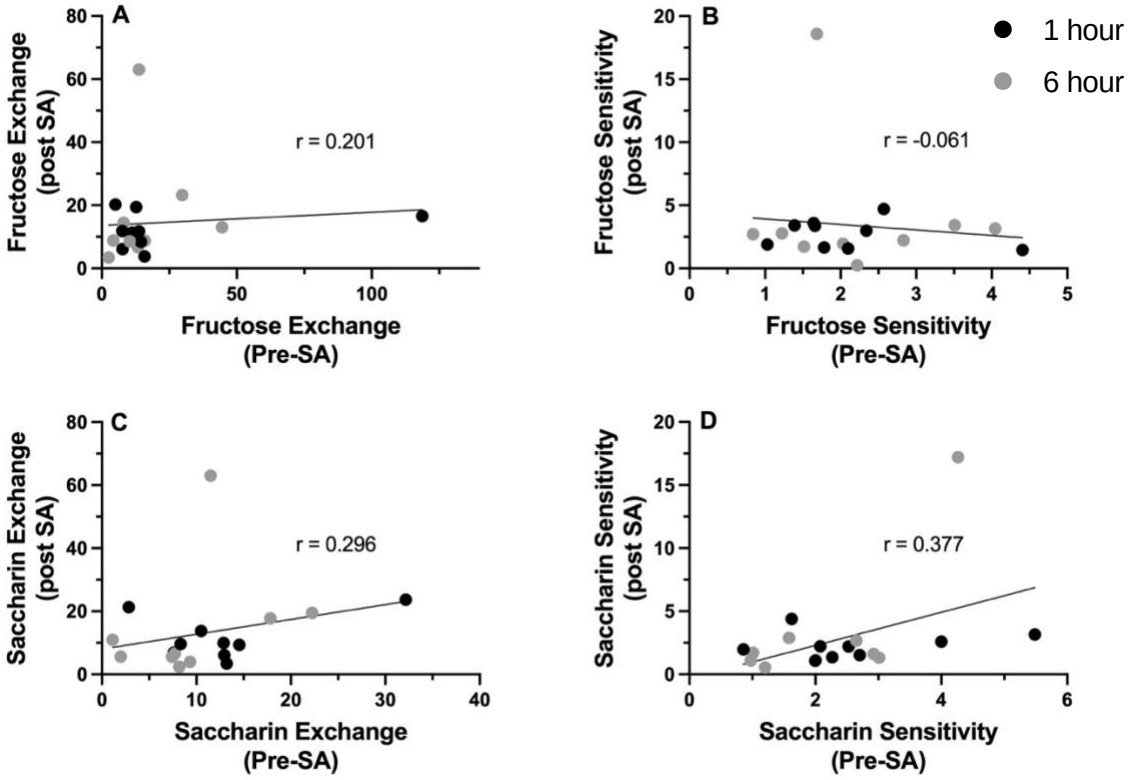

Figure 3.17: Correlations between pre-SA and post-SA choice parameters
(a) Non-correlation between pre-SA and post-SA fructose exchange rate in CRR. (b) Non-correlation between pre-SA and post-SA sensitivity in fructose CRR. (c) Non-correlation between pre-SA and post-SA saccharin exchange rate in CRR. (d) Non-correlation between pre-SA and post-SA sensitivity in saccharin CRR.

CHAPTER 4.DISCUSSION

General Discussion

Due to the parallels drawn between SUD and FA the overall purpose of the present study was to assess the validity of FA as a construct using SUD experimental methodologies. While many similarities have been noted between SUD and FA including the binge-withdrawal cycle (Hone-Blanchet & Fecteau, 2014; Rogers, 2017), increasing intake in extended access preclinical paradigms (Ahmed & Koob, 1998; Ahmed at al., 2000; Corwin et al, 2011), and effects on the dopaminergic mesolimbic pathway (Unterwald et al., 1996; Colantuoni et al., 2001), the literature lacks an analysis of FA as it relates to choice behavior. Therefore, this study aimed to evaluate FA using a controlled reinforcement rate choice procedure to better understand the existing parallels between SUD and FA. This experiment also aimed to assess inconsistencies when using single-schedule models vs choice models. Both ICSS and fructose were evaluated using single-schedule measures (i.e., threshold models) and compared to choice behavior in CRR.

As mentioned previously, current FA research has shown an escalation in sugar intake during extended access (typically 12-hr) as compared to limited access (typically 1-hr) conditions (Corwin et al, 2011). As such, this mirrors data in SUD research showing increased intake during long-access (6-hr) to drugs of abuse as compared to short-access (1-hr; Kitamura et al., 2006). This is in contrast with the present study as no escalation of intake was observed. In fact, a significant decrease from the first day of self-administration to the last day was noted for both the 1-hr and 6-hr access groups. This result is potentially due to the differences in methodology between the standard FA study and the current study. Namely, in the present study, animals were given *ad libitum* access to regular rat chow throughout the entirety of the experiment whereas most FA studies have a food deprivation period of 12-hr (Avena, 2006) or 3-hr (Goeders et al, 2009). Further, these studies typically begin the “binge” period during the dark cycle, which is the time period

that rats are most active and consume the majority of their calories (Avena et al, 2008). While a lack of escalating intake makes interpreting the present results challenging, a food deprivation preclinical model does not provide good translational evidence for FA as a clinical condition. If escalation for food only occurs under very specific conditions, particularly if those conditions are dissimilar to the human experience, making claims about the validity of FA and its relation to SUD is untenable. Despite the lack of escalation in the current study, there was a significant difference in total fructose consumption between the 1-hr and 6-hr groups, therefore results will be interpreted as a difference in total intake as opposed to escalating intake.

Threshold

As expected, in both ICSS and fructose threshold there was a decrease in consumption as unit price increased during both pre-SA and post-SA measurements. For ICSS threshold, an increase in demand intensity (Q_0) was observed during the post-SA condition as compared to the pre-SA condition regardless of access group. In contrast, a decrease in fructose demand intensity was observed for both access groups post-SA as compared to pre-SA. These opposing effects on demand intensity may be explained with an economic theory.

Changes in demand intensity for each reinforcer may be due to an economy-type effect. It is well established that the availability of a reinforcer outside of the experimental paradigm (i.e., fructose availability outside of threshold) can affect the value for that reinforcer in a demand paradigm (Kearns, 2019). In this study, for both access groups, fructose was freely available (during self-administration) outside of the threshold or CRR procedure thereby creating more of an open economy for fructose. In contrast, ICSS was only available during the experimental procedure (i.e., closed economy). Studies have shown that in open economies there is a decrease in value for food (Hursh et. al., 1989) as well as drugs of abuse (Mitchell et al., 1998) whereas a closed economy results in an increase in value. Essentially, because ICSS is only available during a distinct time period and fructose is available at multiple time periods, ICSS becomes potentially

more valuable due to its scarcity. This could explain the opposite effects noted with ICSS and fructose demand intensity post-SA. It is important to note that while demand intensity is a critical component of demand analysis, most researchers emphasize demand elasticity as a “true” measure of reinforcer value and acknowledge that demand intensity typically does not predict responding at higher prices. Therefore, demand intensity and elasticity are typically treated as independent measures (Bickel et. al., 2014).

In addition to a main effect of phase on demand intensity, there was also an interaction between access and phase on ICSS demand elasticity. Specifically, there were no differences in demand elasticity at baseline between the 1-hr and 6-hr groups, but the 6-hr access group showed an increase in demand elasticity after self-administration, while the 1-hr group exhibited no change in demand elasticity. This is consistent with sugar-binge models that suggest a blunted reward response in animals with extended access to sugar (Avena et al., 2008). Overall, animals in the 6-hr access group consumed significantly more fructose during self-administration as compared to the 1-hr group which may have resulted in the increased demand elasticity in ICSS. While this effect seemingly mirrors the effect on demand intensity, recall that an increase in demand elasticity is thought to reflect a decrease in reinforcer value. Therefore, this result is contrary to the effect observed with demand intensity in the 6-hr group. Perhaps, due to ICSS having more of a closed economy, the demand intensity initially increased, but due to a blunted reward response, the 6-hr group experienced a greater sensitivity to changes in price and therefore did not defend their consumption as strongly as the 1-hr group following self-administration.

It is important to note that demand intensity is often interpreted as the hedonic set-point and can therefore be related to a reinforcer’s overall value, but demand elasticity is a measure of sensitivity to changes in price, reflecting value across many price points. While both may reflect some aspects of reinforcer value, this highlights how no single demand measure can accurately and definitively reflect value of a particular reinforcer (Bickel et al., 2000). This is particularly

evident when comparing the results of the demand analysis to the choice parameters in CRR.

Controlled Reinforcement Ratio

In the CRR paradigm animals exhibited a preference for food (both fructose and saccharin) in early blocks, when stimulation was low, and a preference for ICSS in later blocks, when stimulation was high. For both fructose and saccharin, exchange rate and sensitivity to relative changes in magnitude were unaffected by access group or self-administration phase. The lack of change from pre- to post-SA in choice parameters highlights the disconnect between single-schedule measurements and behavior in choice paradigms. Since both demand intensity and elasticity have been emphasized as measures of value, changes in either measure in demand analyses should be reflected in choice paradigms. For example, if demand intensity is considered a “true” measure of value, as demand intensity increases, there should be a reflective change in exchange rate during choice (i.e., an increase in fructose demand intensity reflects an increase in exchange rate). Additionally, if elasticity is considered a “true” measure of value, then a decrease in demand elasticity should reflect an inverse change in exchange rate (i.e., a decrease in fructose elasticity reflects an increase in exchange rate).

As noted, no changes in choice behavior were observed following self-administration. This is particularly interesting in comparing the 6-hr demand metrics to choice. This group exhibited an increase in both intensity and elasticity in ICSS and a decrease in intensity for fructose. Taken together, the changes in intensity suggest an overall increase in ICSS value and a decrease in fructose value, while the increase in elasticity for ICSS should reflect a decrease in ICSS value. Within the SUD literature, elasticity is generally considered the *essential value* of a given reinforcer; thus, if this definition of elasticity is accepted, a decrease in ICSS value is expected. If elasticity was a measure of “true”, invariant value, an increase in exchange rate during the choice paradigm for both fructose and saccharin should be reported, indicating a decrease in ICSS value. Conversely, if the single-schedule metric of demand intensity were a measure of

“true”, invariant value, then the increase in ICSS demand intensity, coupled with the decrease in fructose demand intensity for the 6-hr group should culminate in a decrease in fructose exchange rate. Importantly, neither of these results were observed in choice.

As mentioned previously, there are a number of issues associated with the interpretation of single-schedule measures, particularly as they relate to reward value. Critically, response rate is not indicative of reward value as this measure assumes a proportional relationship between value and rate of responding (Banks & Negus, 2012), with many choice models illustrating that single-schedule measures do not predict preference in choice models (Johanson & Schuster, 1975; Negus, 2006; Beckmann et al., 2019). Additionally, there are inherent issues surrounding the use of essential value when comparing commodities in similar demand paradigms including differential scaling of reward dimensions (Stevens, 1957) and differences when challenged with a concurrent choice model (Carroll & Rodefer, 1993; Smethells et al., 2018). This further emphasizes the importance of studying reinforcers in contextual decision-making tasks, as opposed to primarily in isolation, to determine relative value in specific experimental contexts. This is particularly important for FA research due to the lack of concurrent choice paradigms in the literature and an integral component of drawing comparisons between preclinical and human populations where many alternatives are available at any given time.

Additionally, there were differences in exchange rate when comparing global parameters for fructose and saccharin, with a lower exchange rate observed for saccharin CRR as compared to fructose CRR. This suggests that, perhaps, generalization between caloric and noncaloric reinforcers is not perfect. This is consistent with the literature as studies suggest that caloric sweeteners are preferred over noncaloric sweeteners (Collier & Novell, 1967; Smith & Sclafani, 2002) which can be interpreted as greater relative value and therefore may result in a difference in exchange rates. This may additionally point to the ability to use ICSS as quantitative measure of value that can be compared across commodities. In this way, it may be possible to predict preference between two options by

comparing exchange rate as a function of ICSS. Further, homeostatic components of reward may be responsible for the greater exchange rate observed in fructose CRR as compared to saccharin CRR.

Correlations

Several correlations were observed in analyzing both demand and choice parameters with notable trends occurring amongst similar parameters. When assessing demand elasticity, there was a negative correlation between fructose demand elasticity with fructose (pre/pre, pre/post) and saccharin exchange rate (pre/post) indicating that a decrease in fructose demand elasticity was associated with an increase in exchange rate. As stated previously, lower values for demand elasticity are interpreted as an increase in value, which may be reflected by the correlation with higher exchange rates. Relatedly, there was a positive correlation between ICSS demand elasticity and fructose (pre/post, post/post) and saccharin (pre/post) exchange, suggesting some relationship between exchange rate in choice models and elasticity in demand models.

These correlations are supported by studies in which drug and non-drug demand elasticity are compared to preference in choice procedures. Kearns and colleagues (2016) found a positive correlation between essential value for cocaine and preference for cocaine coupled with a negative correlation between essential value for food and preference for cocaine. Importantly, the choice procedure presented only one magnitude of each reinforcer and was conducted as a free-choice model (i.e., rate of reinforcement was uncontrolled). However, as stated previously, preference for one option over another can be affected by magnitude changes as well as rate of reinforcement (Chow & Beckmann, 2021). So, in this instance, essential value predicted preference in one specific context, but does not provide support for preference when reinforcer dimensions are altered. Therefore, while demand elasticity may correlate to exchange rate (with lower fructose elasticity associated with higher exchange rates), this correlation does not predict changes in relative exchange rate as was observed in the present study. This is further supported by research showing that saccharin is preferred and has lower

demand elasticity as compared to heroin, but even after extended heroin access and decreased heroin demand elasticity, there is no change in saccharin preference (Schwartz et. al., 2017). This further supports the dissociable nature of essential value and preference in choice.

Additionally, both pre-SA fructose demand elasticity and ICSS demand elasticity were negatively correlated with post- consumption at the lowest unit price (LUP) for their respective reinforcer (i.e., fructose elasticity with fructose consumption). This may appear to suggest that demand intensity is correlated with elasticity, but it is important to note that the LUP measure is experimentally determined based on the lowest cost available in the experimental paradigm and is distinct from demand intensity, which is a theoretical value (Y-intercept for the function) when cost is zero and is derived from the demand equation (Equation 2). Therefore, these correlations are supported by demand analysis as demand elasticity is, by nature dependent on changes in price and actual consumption at the lowest price is also price-dependent, whereas demand intensity is price independent. Importantly, no correlations were noted between demand elasticity and demand intensity values for fructose or ICSS, which again supports that intensity and elasticity are independent measures of demand (Bickel et al., 2014). Finally, ICSS demand elasticity was positively correlated with total fructose intake during self-administration, indicating that increases in demand elasticity (i.e., decrease in value) were associated with greater fructose intake. This further supports the idea that extended access to sugar may result in a blunted reward response (Avena et al., 2008) when self-stimulation is offered in isolation, paralleling the interaction results in ICSS in which only the 6-hr group exhibited increases in demand elasticity for ICSS.

When looking at additional fructose consumption at LUP relationships, a negative correlation with ICSS consumption at LUP (pre/pre) was noted. Following this trend, there was a negative association between fructose consumption at LUP and fructose demand elasticity (pre/post) as well as ICSS consumption at LUP and ICSS demand elasticity (pre/post). Taken together, these correlations suggest a relationship between the actual consumption, as opposed to theoretical

consumption, at the lowest unit price and demand elasticity in which baseline measures of elasticity are associated with post-SA measures of LUP consumption and baseline measures of LUP consumption are associated post-SA measures of elasticity within the same reinforcer type. This suggests that consumption at LUP may be related to later measures in demand elasticity (and vice versa) and therefore in value when commodities are assessed in isolation which is supported by the previous correlational data.

Additionally, pre-SA fructose LUP was positively correlated with fructose exchange rate in CRR (pre), but negatively correlated with sensitivity in fructose CRR (pre). These results insinuate a relationship between LUP and exchange rate in which greater consumption is associated with greater value for fructose as measured by exchange rate. This follows the correlations between elasticity and LUP and further supports the price-dependent nature of consumption at LUP. Further, the negative association with sensitivity may relate to the correlation with exchange rate. It stands to reason that as exchange rate (or value for fructose) increases, an animal would be less sensitive to change in ICSS reward magnitude. While this was not evident in the relationship between fructose sensitivity and fructose exchange, there was a negative correlation between sensitivity in fructose CRR and saccharin exchange rate which could point to a generalization between the two reinforcers and a potential relationship between exchange rate and sensitivity. In continuing the trend, ICSS consumption at LUP generally exhibited opposite correlations in comparison to fructose consumption at LUP. Specifically, ICSS LUP was negatively correlated with both fructose and saccharin exchange rate in CRR (pre/post). Taken together, these associations suggest an overarching theme in which an inverse relationship exists when comparing ICSS and fructose against similar parameters suggesting a relationship between demand analysis. With correlational data, an exact cause for this relationship is unclear. Previous studies have shown that while demand elasticity measures cannot always predict preference in choice procedures (Carroll & Rodefer, 1993; Smethells et al., 2018) there is a relationship between demand elasticity and value and in some instances demand parameters align with choice preference (Kearns et. al., 2016). This

indicates that demand can be used as a tool to inform preclinical models but should be utilized in tandem with choice models to understand the context-dependent nature of value. In this particular study, parameters may be more closely related because ICSS may serve as a common currency by which value can be elucidated (Levy & Glimcher, 2012).

Finally, many parameters positively correlated to themselves (i.e., pre-SA fructose demand elasticity to post-SA fructose demand elasticity) when analyzing pre-SA and post-SA relationships including demand elasticity for both fructose and ICSS as well as consumption at LUP for both reinforcers. Surprisingly, there were a number of parameters that did not correlate including demand intensity for both fructose and ICSS as well as exchange rate and sensitivity in CRR for both fructose and saccharin. This is an unexpected result and is not due to any outliers included in the data (results were non-significant with or without outliers). This suggests that for a number of parameters, there is no relationship between measurements pre-SA and post-SA. This may be explained by a group effect whereby animals differentially and independently had increases or decreases in these parameters that overall resulted in a non-significant correlation. Said another way, individual changes in parameter value did not occur in the same direction for each animal resulting in a noncorrelation.

Limitations & Future Directions

The present study's major limitation was the lack of escalating intake in the 6-hr self-administration condition. As stated earlier, this may have resulted due to the unrestricted access to chow in their home cages as well as the completion of self-administration during the light cycle. Additionally, rats may have been affected by a ceiling effect in that maximal intake was reached during the first session, due to satiety, and therefore escalating intake was unattainable. Despite this the present experiment provided more evidence to support the use of choice models to assess reinforcer value in context-dependent models.

While this experiment did not support the validity of FA, there is merit in studying other models that may contribute to the understanding of this potential

process. Given that escalation of intake has predominantly been observed in food-deprived subjects, assessing relative value shifts may only be possible using a deprivation model. While this is not directly translatable clinically, it may provide insight into the mechanisms by which escalating intake affects choice behavior. Further, SUD studies have shown greater support for an intermittent long-access model in which animals are given distinct windows in which to self-administer (i.e., 5-min) followed by a time-out period (i.e., 25-min) over a 6-hr period. This more similarly parallels drug-taking in human populations as there is continually spiking drug levels as opposed to steady-state levels (Zimmer et. al., 2012). This model may be beneficial in studying FA as it could reduce the potential for satiety and may better represent binge-like eating behavior.

Finally, it may be that FA as a construct is purely a human condition. In evaluating an eating related disorder, it is difficult to compare behavior from non-human animals. For example, it would be impossible to assess anorexia or bulimia in preclinical models as they are disorders unique to our species. Given the number of strictly human factors that are associated with the development of FA, — social, emotional, availability of hyperpalatable foods, socioeconomic status etc. — creating an animal model that mimics this may be challenging. Therefore, it is important when developing animal models to use caution when extending interpretations to clinical conditions until similar patterns of evidence are observed in clinical models.

Conclusions

The purpose of the present experiment was to assess the validity of FA under SUD-like conditions, specifically that extended access to fructose would result in an increase in value for fructose in a choice task. While the self-administration data lacked escalating intake, there were changes in demand analyses parameters based on access group, but no parallel changes in exchange rate during choice. These findings contribute to the current literature in a number of ways. First, it confirms the necessity of including choice models in tandem with single-schedule models to fully assess all facets of value (i.e., demand elasticity and intensity;

preference when many alternatives are available). Additionally, it helps to disassociate the current use of ICSS (single-schedule threshold models) and their potential use as a quantitative measure of value in choice procedures. Finally, it provides support for FA potentially being described using relative value theory in which individuals who “compulsively” consume food may overvalue hyperpalatable food as compared to other non-food, or less palatable food, alternatives though further research, in which escalating intake is observed, is necessary to draw sound conclusions on the relationship between FA and relative value theory.

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Publications

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