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# Decision-Making In Rats: Effects Of Drug Abuse

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## Dedication

This work is dedicated to my family.

It is their endless love for me that made me reach my goal.

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by

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THESIS

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**“Surely, with each difficulty, there is ease (94:6)”**

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# Abstract

Decision-making is a critical cognitive function, often impaired by substance abuse. Understanding the underlying mechanisms in both human and animal models is essential for developing effective treatments. This thesis aims to study approach-avoid decision-making in rats and focuses on the impacts of oxycodone self-administration and alcohol abuse on approach-avoid decision-making.

We hypothesize that oxycodone self-administration will alter decision-making in female rats, revealing sex differences and distinct psychometric functions, alcohol habituation will similarly affect decision-making in male rats.

The study involved 23 Long Evans rats (11 males and 12 females) for decision-making behavioral study connecting multiple levels of rewards and costs combinations. For the oxycodone self-administration experiment, 33 rats (5 experimental males, 5 experimental females, 11 control males and 12 control females) were trained in a decision-making task involving cost-benefit analysis, with rewards and costs signaled by sucrose concentration and LED light intensity, respectively. Oxycodone self-administration was conducted over 14 days, followed by a period of abstinence to assess changes in decision-making behavior. Another group of 45 rats (10 experimental males, 12 experimental females, 11 control males and 12 control females) was used to investigate the effects of alcohol habituation on decision-making. Behavioral features such as distance traveled, approach time, and stopping points were extracted and analyzed using custom scripts and a PostgreSQL database.

This study provides comprehensive insights into the effects of drug abuse on decision-making, emphasizing the importance of sex differences and task variability. The findings underscore the

relevance of animal models in studying human cognitive functions and pave the way for targeted therapeutic interventions.

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# A. Chapter 1: Introduction

Every day, individuals face decisions that involve different levels of risk. In cognitive neuroscience, decision-making refers to the mental process of choosing a specific action from a set of options. These options vary in terms of the uncertainty surrounding potential rewards and losses(Zhang and Guo 2018). In our daily life decision-making is a common behavior(Glimcher and Fehr 2013); for an example, everyday around 200 decisions about food alone are made by us (Wansink and Sobal 2007). The process that enables any decisions requires various neural circuits that also compute individualized evaluations of rewards and costs(Glimcher and Fehr 2013). These evaluations are then used to determine whether a reward/cost combination is worth pursuing, usually shaped by the subject's age(Orsini et al. 2023), sex(Van Den Bos, Homberg, and De Visser 2013), and life experience. Problems with these neurobiological circuitries can result in improper assessments of rewards or costs, causing abnormal decision-making. Abnormal decision-making is also considered an indicator of transdiagnostic symptom(Endrass and Ullsperger 2021) of several disorders like anxiety, depression, post-traumatic stress disorder, and substance use disorders(Aupperle and Paulus 2010; Brady, Back, and Coffey 2004). Therefore, measuring, following, and evaluating decision-making is vital for recognizing psychiatric disorders.

**Decision-making.** Decision-making is a complex cognitive process that relies on various cognitive functions such as perception, attention, and memory. In everyday life, individuals must make a series of decisions, with each decision influenced by feedback from the environment, which can change over time(Prezenski et al. 2017). Studies have identified several brain regions involved in decision-making, including the orbital and frontal cortex, prefrontal lobe, anterior cingulate cortex, amygdala, hippocampus, limbic system, parietal lobe, cerebellum, and midbrain(Paulus et al.

2003; Sanfey et al. 2006). These regions can be categorized into two functions in terms of decision-making: "loss utility calculation" and "reward utility calculation". In different decision-making scenarios, individuals evaluate and differentiate between the benefits and drawbacks of a choice, with brain areas related to "loss" and "reward" being activated. This leads to a decision indicating a tendency towards or away from a certain choice. Initial studies suggest that the ventrolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, ventral striatum, and mesolimbic dopaminergic system play roles in reward-based decision-making. Activation of these reward-related brain areas occurs when an expected gain is received or a practical outcome results in a gain, influencing behavioral tendencies(Erk et al. 2002; Forbes et al. 2006; Knutson et al. 2001; Shin and Ikemoto 2010).

The Prefrontal Cortex (PFC) and hippocampus are crucial brain regions involved in decision-making(Saberi Moghadam, Samsami Khodadad, and Khazaeinezhad 2019). The prefrontal cortex (PFC) is responsible for executive functions like reasoning. The decision-making process involves four main steps. Initially, sensory inputs generate some initial stimuli that excite a set of hippocampal neurons. Subsequently, a set of secondary stimuli reaches the hippocampus, eliciting a stimulus-driven neural response that provides initial information for two entry stimulus sets in the hippocampus. In the third step, this initial information is transmitted to the PFC. The PFC then determines the additional information required and retrieves complementary information from the hippocampus(Wang 2008). In the final step, based on this processed information, the PFC makes the decision. Importantly, there is bidirectional communication between the PFC and hippocampus through neural connectivity. This neural wiring forms closed-loop neural circuits that generate a preferred decision(Saberi Moghadam et al. 2019).

**Decision-making in everyday life.** Decision making is relevant in everyday life. In a single day, an individual can make hundreds of decisions, each reliant on the balance between rewards and costs. In turn, balancing valuation is essential to determining whether to approach or avoid an offer. To appropriately evaluate an offer, one draws on their previous experiences where, for example, a person makes over 200 food-based decisions daily(Wansink and Sobal 2007). In turn, the inability to make properly informed decisions can lend itself to monumental effects when trying to navigate varying areas of life.

**Baseline decision-making and individual differences.** Baseline decision-making varies across individuals, yet similarities across groups of people can be observed. To navigate these areas of life, individuals are reliant on the utilization of previous experiences(Kahneman and Tversky 1979). A culmination of an individual's experiences is essential to distinguish which decision-making strategy a person may choose given a context. For example, a decision that contains a social context will be reliant on an individual's valuation of social contact as a high weighing reward, low weighing reward, or even a cost. For some, the ability to interact with their family socially may be a heavy reward because of their positive childhood lending them to accept this offer(Baumeister and Leary 1995)**.** Or they may view this as a cost due to their negative childhood, lending them to avoid this offer. While these differences can vary across individuals, similarities in decision-making can be observed across groups of people. For example, individuals of the same gender, location, ethnicity, and so on, will have similar experiences. These similarities lend themselves to the development of distinct decision-making strategies, as seen in our study below. Considering this, while baseline decision-making can differ across individuals due to variance in

experiences and subjective values placed on rewards or cost, constrained heterogenic decision-making strategies can still be observed across groups of people.

**Decision-making in neurological disorders.** Abnormal decision-making is a symptom for neuropsychiatric disorders (Endrass and Ullsperger 2021; Goschke 2014; Moutard et al. 2012). Coupled with diagnosis of a neuropsychiatric disorder, another reasoning for variance in decision-making is the induction of a state. Heavily affected by neuropsychiatric disorders, alterations in decision-making can be noted in PSTD, OCD, anxiety, depression, and stress(Aupperle and Paulus 2010; Friedman et al. 2015, 2017, 2020; Gleichgerrcht et al. 2010; Goldstein Ferber et al. 2021; Lee 2013; Russo and Nestler 2013; Szanto et al. 2015). Not uncommonly, the impacts of these disorders on decision-making cause individuals to develop difficulties navigating social interaction, financial situations, moral obligations, or health decisions(Gleichgerrcht et al. 2010).

**Decision-making is context dependent.** A variety of contexts exist when making a decision, for example there are moral contexts, social contexts, or business/neuroeconomic contexts. To navigate these differing decision types, decision-making schemas are utilized to approach decision-making using a context specific strategy. For example, an individual may use one decision-making strategy when in a social context and use an alternative strategy when making decisions in a moral context. These decision-making schemas demonstrate constrained heterogeneity across groups of people(Otto et al. 2022). Furthermore, shifting decision-making from a baseline state to a disordered state can cause shifts in the subjective value of rewards and cost in a context specific manner. For example, in the context of social interaction, an altered state may cause an individual to weigh costs more heavily than their baseline state, setting them up to

cautiously participate in social offers. One major example of this is PTSD, where individuals often avoid social activities due to the possibility of encountering crowded spaces, loud noises, and being touched, each representing a now heavier weighed cost than their baseline valuation(Kessler 1995). While this state heavily impacts decisions within a social context, it may not impact decisions containing a moral obligation. In turn, treating neuropsychiatric disorders is clinically relevant since as many as 1 in 4 adults suffer from a diagnosable mental disorder(World Health Organization 2001).

**Decision-Making studies.** Studies of decision-making can quantify and parametrize concepts, such as cognition(Shadlen and Kiani 2013), subjective value(Glimcher and Fehr 2013), and help identify the biological correlates of decision-making related processes(Amemori, Graybiel, and Amemori 2021; Friedman et al. 2015; Johnson and Redish 2007; Kira et al. 2023; Xiang et al. 2019), thus many methods have been developed and employed to study decision-making in rodents. One example is the T-maze. T-mazes examine decision-making by offering a subject two options in branching arms at the end of the maze(Friedman et al. 2015; d'Isa, Comi, and Leocani 2021; Johnson and Redish 2007; Xiang et al. 2019). T-mazes are also used with virtual reality systems, allowing for two-photon calcium imaging during task performance. Another common method used for studying decision-making in rodents is operant conditioning tasks(De La Crompe et al. 2023; Kapanaiah et al. 2021; Lottem et al. 2018; O'Leary et al. 2018). Operant conditioning tasks have subjects perform actions (e.g., nose-pokes(Vassilev et al. 2022; Vollmer et al. 2021) or lever presses(De Visser 2011) in response to cues. Rodent versions of the Iowa Gambling task are also used to explore DM, since it mimics making decisions in uncertain conditions (typically by providing multiple options that have different probabilities of reward/cost being dispensed,

depending on the magnitude of predictive stimuli), a common occurrence in day-to-day life(Miller, George A., Eugene, G., and Pribram, K. H. 2017).

**Drug-seeking behavior.** Effects of drugs of abuse on behavior and drug seeking neurocircuitry are interrelated to striosomes. In the United States widespread opioid usage alone has caused the highest rate of drug overdose(CDC/NCHS n.d.), and it is extremely important to identify the root cause -the behavioral and neurological inputs behind this drug seeking epidemic situation. It has been found that the main alarming reason behind overdosing is relapsing after a period of short/long term break or abstinence(Webster 2017)**.** Usually, the longer the period of staying away, the longer the drug seeking behavior has been observed in case of opioids(Altshuler et al. 2021; Bossert et al. 2020; Fredriksson et al. 2020, 2021)**.** This increased drug seeking behavior increases the possibility of relapse leading to drug overdose(Venniro et al. 2021)**.** Henceforth, it is crucial to understand the motivating dynamics in drug-seeking behavior for opioid addictions.

**Substance use disorders can be an effect of abnormal decision-making.** The most common denominator of substance use disorder is continued use of the substance despite acknowledging the consequences(American Psychiatric Association 2013)**.** That is why substance use disorders are known by abnormal decision-making that comes with high costs. To support this statement various studies have displayed various drugs of abuse like opioids causes to make suboptimal choices during decision-making(Glimcher and Fehr 2013; Zhao et al. 2017)**.** The abnormal decision-making usually has two major impacts – first**,** it messes up an individual's daily routine (e.g. difficulties in social interactions, maintaining a job, maintaining finances)(Bechara 2005)**,** second, it messes up an individual's capability to stay away from drug of abuse. Ultimately the

poor decision-making forecasts high relapse(Turner et al. 2021) or drug-seeking(Perry, Nelson, and Carroll 2008).

**Drug-self administration model in addiction behavior.** Drug self-administration models for studying addiction are predicated on the idea that drugs reinforce the behaviors leading to their acquisition. Various methods of drug self-administration have been crafted to mimic different facets of addiction, and these methods can easily be integrated with numerous neuroscience techniques(O'Leary et al. 2018). Drug self-administration methods are utilized in laboratory settings to explore addiction in a controlled manner. In these experiments, an animal or human participant engages in an action, like lever pressing, to administer a drug dose, commonly through intravenous catheters, though other delivery methods such as oral or inhalation are also used, especially with human subjects. These procedures closely mirror real-world addictive behaviors, lending them a high degree of face validity. The precise simulation these methods offer enables researchers to tailor the conditions to study specific elements of addictive behavior. The behaviors exhibited in these models are notably responsive to changes in environmental and pharmacological conditions. Therefore, these approaches not only deepen our understanding of the dynamics influencing addiction but also facilitate the evaluation of potential treatment strategies(Kapanaiah et al. 2021).

**Opioid in reckless behavior.** Reckless and risky behavior is connected to opioid addiction/dependence. Besides, it has been found in pre-clinical studies that opioids can raise reckless choice in non-humans(Hunt, Hughes, and Pitts 2020). Exploitation of opioids, including prescription opioid medications, has become a major health concern and the U.S. Department of Health and Human Services declared opioid exploitation a public health emergency in 2017.

Abusing drugs including opioid-related disorder(American Psychiatric Association 2013), is connected to reckless and risky behavior(Carroll et al. 2010, 2010, 2010; Madden et al. 1997; Perry and Carroll 2008; Weafer, Mitchell, and De Wit 2014). These behaviors are responsible for individuals to be at risk of repeated drug abuse and can raise the probability of drug dependence and overdose. Even though there are demonstration from studies that reckless and risky traits are pre-existing causes related to drug abuse(Perry and Carroll 2008; Weafer et al. 2014), also direct drug use can also cause an increase in reckless and risky behaviors(Madden et al. 1997; Simon, Mendez, and Setlow 2007; Weafer et al. 2014). Hence, it is important to distinguish how opioids affect the underlying activities contained in making reckless and risky decisions.

**Pharmacological profile and impact of oxycodone.** Oxycodone is considered a semi-synthetic opioid and usually recommended for the treatment of moderate-to-severe pain(Riley et al. 2008). It is derived from thebaine, a minor constituent of opium(Kimishima et al. 2014). Even though some argument regarding its pharmacological profile exists (e.g., (Kalso 2007; Riley et al. 2008)), like other μ-opioid agonists oxycodone is also a potent μ-opioid agonist with a similar behavioral profile(Beardsley et al. 2004). In some of the countries of this world, it has replaced morphine as the most widely prescribed opioid painkiller(Söderberg Löfdal, Andersson, and Gustafsson 2013). Oxycodone has seven folds higher ability to cross the blood brain than morphine along with a faster onset and longer duration of action than morphine(Olkkola et al. 2013). In combination of fewer side effects(Compton, Jones, and Baldwin 2016) and powerful actions on reward circuitry, oxycodone is considered as one of the most highly exploited drugs available in today's world. Notwithstanding it being the most abused prescription opioids(Johnston et al. 2018) and its vital role in the exposed opioid crisis(Van Zee 2009), there is insignificant research exploring its effects on reckless and risky choice.

**Gender differences in opioid abuse.** In general, men have been seen to be abusing drug more than women. Though, now women started abusing prescription opioids as much as men(Simoni-Wastila, Ritter, and Strickler 2004). Moreover, usually majority of women who reported using opioids is to control stress(McHugh et al. 2013), and it has been observed that women's advancement from primary opioid abuse to opioid use disorder is faster than men(Hernandez-Avila, Rounsaville, and Kranzler 2004). It has been found that widespread prescription opioid disproportionally affects women(Chartoff and McHugh 2016). Sadly, there's lack of enough preclinical studies on prospective sex differences in opioid related addiction. It has been observed in rodent studies that female rats in case of heroin self-administration they acquire it faster than male rats even though the total heroin consumption does not differ(Lynch and Carroll 1999). It has been reported that female rats show an ascending heroin dose-response compared to males, but there is no significant sex differences in food self-administration(Cicero, Aylward, and Meyer 2003), which actually generate the likelihood of females having increased exposure of addiction to opioid.

**Incubation of craving.** Due to re-exposure to drug related cues it has become one of the major hurdles to address relapse to opioid abuse leading to epidemic(Gostin, Hodge, and Noe 2017; Kariisa et al. 2019). Lately, it has been demonstrated that adult rats increasingly seeks oxycodone after abstinence from oxycodone self-administration(Altshuler et al. 2021; Fredriksson et al. 2020, 2023). This incubation of craving incident has also been previously viewed in rats with a past usage of cocaine(Grimm et al. 2001), heroin(Shalev et al. 2001), nicotine(Abdolahi et al. 2010), alcohol(Bienkowski et al. 2004), methamphetamine(Shepard et al. 2004), and sucrose(Grimm, Fyall, and Osincup 2005) self-administration.

**Alcohol use in early adulthood.** A top cause of morbidity and mortality worldwide is alcohol use(Chassin et al. 2013; Thompson et al. 2014). Between the ages of 20 and 24 the global occurrence of heavy occasional drinking peaks in(Thompson et al. 2014) and this emphasizes the significance of initial adulthood as a period when drinking habit forms and related problems advance or accelerate(Goschke 2014; Hinckers et al. 2006; Wichers, Gillespie, and Kendler 2013; Zucker et al. 2006). Various factors, like genetic variations, personality traits, social networks, and environmental stimuli are responsible behind forming these responses(Chassin et al. 2013; Hinckers et al. 2006; Wichers et al. 2013; Zucker et al. 2006).

**Impact of cognitive control on decision-making and alcohol consumption risks.** Decision-making ultimately gets affected by internal and external factors related to drinking alcohol as well as subjective values to states, goals, and actions(Chassin et al. 2013; Goschke 2014; Guttman, Moeller, and London 2018). Usually the behavior that is goal directed typically adjusts to new experiences, contexts, and demands(Goschke 2014). This kind of behavior involves withholding disturbing stimuli, unnecessary thoughts, and prepotent responses while focusing on cognitive control to capture, maintain, and exploit relatable information(Goschke 2014). Naturally people with low cognitive control have a tendency to make inconsistent and impulsive choices by limiting attention, patience, foresight, planning, and reflection(Goschke 2014). These autonomous reckless choices essentially advance drinking, which is supported by instant rewards (e.g., stimulation, relaxation) despite prolonged costs (e.g., intoxication, withdrawal) and various risks (e.g., accidents, addiction;(Camchong, Endres, and Fein 2014; Herman and Duka 2019).

**Decision biases in alcohol use disorder: delay discounting, risk-seeking, and loss aversion as predictors of drinking behavior.** It has been observed that people prefer smaller instant rewards over bigger rewards at a later period when they are suffering from moderate or severe Alcohol Use

Disorder and this choice is usually linked to earlier disorder onset, heavier drinking, and more disorder severity(Camchong et al. 2014; Herman and Duka 2019). It has also been noticed that chronic alcohol use a also causes low response to considering costs(Bernhardt et al. 2017), probably independent of strong delay discounting(Thrailkill, DeSarno, and Higgins 2022). There has been some opposing reports on delay discounting and loss aversion as well especially focusing non-dependent drinking(Campbell et al. 2021; Herman and Duka 2019; Mayhew et al. 2020; Poulton et al. 2022; Stancato et al. 2020; Tucker et al. 2021; Zorick et al. 2022). Some studies displayed that delay discounting typically cannot consistently differentiate between different levels, patterns, or problems of non-dependent drinking(Campbell et al. 2021; Herman and Duka 2019; Mayhew et al. 2020; Poulton et al. 2022; Stancato et al. 2020; Tucker et al. 2021). Correspondingly, there is e scarcity of probability discounting researches to observe the risky instant reward seeking and disregarding high costs behavior in less problematic drinking but is already established in moderate to severe Alcohol Use Disorder(Bernhardt et al. 2017). Additionally, alcohol has no typical acute effects on delay or probability discounting or loss aversion(Bernhardt et al. 2017; Herman and Duka 2019). These studies suggest that after shifting to Alcohol Use Disorder there is a gradual increase in delay discounting, risk-seeking for gains, and risk aversion for losses and a decreasing trend in loss aversion. Remarkably, it has been noted that only risk aversion for losses predicted relapse to heavy drinking within a year in freshly abstinent patients with Alcohol Use Disorder(Bernhardt et al. 2017).

**Variability in decision-making among non-severe alcohol users: gender, age, and drinking patterns.** Inconsistencies in value-based decision-making in people who use alcohol without being in the range of moderate or severe Alcohol Use Disorder expose the divergency in classifications (e.g., threshold for low-risk consumption), measures (e.g., frequency, quantity), and periods (e.g.,

past month or year) of drinking(Kalinowski and Humphreys 2016; Thompson et al. 2014), including dichotomizations (e.g., non-binging vs. binging). These studies are also staggered gender differences in decision-making(Green and Myerson 2019) and alcohol involvement(Vereinte Nationen and Büro für Drogenkontrolle und Verbrechensbekämpfung 2018). Additionally, drinking patterns form distinctively across the lifespan(Chassin et al. 2013; Thompson et al. 2014; Wichers et al. 2013; Zucker et al. 2006) and may connect in a different way to dimensions of decision-making. There is not enough systematic research done in non-clinical populations on the effects of trivial alcohol intake on decision making. The reason may be due to the difficulties in designing these types of studies(Karlsson et al. 2022)

**Impact of alcohol intake on reward processing, mood, and cognitive function: insights from recent studies.** Although effects vary depending on gender and genetics alcohol intake can impact reward stimulus through activation of canonical dopaminergic brain reward system in healthy volunteers(Boileau et al. 2003; Gilman et al. 2008; Ramchandani et al. 2011; Urban et al. 2010). In non-hostile conditions increased emotional activity and positive mood is found to be linked to alcohol intake (Fairbairn and Sayette 2013; Sayette et al. 2012). There is a popular opinion about non-selective impairments of cognitive function caused by, but this perception has recently been doubted. Recent studies suggests that alcohol consumption results in selective deficiencies of attention, automatic auditory processing, and performance monitoring (Sayette et al. 2012). Likewise, it is believed that alcohol enhances impulsivity, but there is not enough studies to determine to what extent impulsivity is a cause vs. a consequence of alcohol use, and at what point it influences emotional states (Herman and Duka 2019).

**The impact of alcohol consumption on decision-making: insights from behavioral and neuropsychological studies.** Continued alcohol consumption causes problems in individuals like

poor decision(American Psychiatric Association 2013). This profile of abnormal decision-making due to alcohol consumption has been proved in various researches like in the Iowa Gambling Task (IGT; (Bechara et al. 1994)). The main point of IGT is to skip short-term rewards for long-term rewards, a process that is assumed to be severely disturbed in substance (e.g. drugs, alcohol, tobacco) and non-substance addictions (e.g. gambling)(Noël et al. 2007). As an example it has been found that usually a high percentage of alcohol-dependent patients even though they undergo detox and extinction from alcohol for a short time like a few weeks e.g. (Kornreich et al. 2013; Noël et al. 2007) or long term like several years(Fein, Klein, and Finn 2004) normally make choices that is related to short term rewards that may lead to severe delayed punishment instead of later long term reward. From all this research it is prevalent that abnormal decision making does not recover over time like even after a long-term abstinence of alcohol there is always a chance of relapse after months or even years. Significantly, it has been highlighted by neuropsychological studies that alcohol addiction is connected to abnormal functioning, including working memory, planning, and flexibility e.g.(Blume, Schmaling, and Marlatt 2005; Dao-Castellana et al. 1998; Noël et al. 2001).

**Alcohol's impact on cognitive functioning in aging humans and rodents.** In adult humans and rodents the effects of alcohol on the nervous system have been well observed. Alcohol depresses central nervous system by showing anxiolytic, sedative, and memory-disrupting properties(Eckardt et al. 1998). Furthermore, alcohol causes alterations in learning and memory developments(White 2003). Though there is limited research on alcohol in aging subjects, studies in humans has showed that compared to younger adults older adults perform worse in tests assessing working memory, attention(Garcia et al. 2020; Han and Jia 2021; Lewis et al. 2016;

Price et al. 2018). Even in animal studies the effects of alcohol that have been assessed are cognition, ataxia, hypothermia, and sedation.

**Gender similarities in cue-triggered alcohol seeking behavior.** Alcohol seeking behaviors can be triggered by environmental stimuli and cause problematic alcohol use. There have been no gender differences found in the implicit associative learning process allowing environmental stimuli together with alcohol to trigger alcohol seeking behaviors. It is believed that Pavlovian or classical cue conditioning in a fundamentally similar way in males and females. Nonetheless, gender differences may exist on problematic alcohol use based on the how cues can effect(Barker and Taylor 2019).

**Developmental changes and gender differences.** To understand how biological factors initiate developmental changes due to ethanol consumption, animal models are necessary and rodents have proved to be the best model which is well-characterized model with adolescence appearing over a brief period of time(Spear 2000). Adolescence in rodents is denoted as postnatal day [P] 28 – P42, with the beginning of adulthood delaying to roughly P55(Vetter-O'Hagen and Spear 2012).The behavior relevant to alcohol consumption in adolescent include increased impulsivity, novelty-seeking, and final maturation of executive function, following a similar pattern appearing during human adolescence(Spear 2000, 2011; Varlinskaya, Vetter-O'Hagen, and Spear 2013). Additionally, rodent puberty time overlapping with adolescence, primary sex differences, especially the earlier pubertal development of females than males are also similar to human development(Varlinskaya et al. 2013).

**Sex differences in long-term effects of adolescent ethanol exposure on adult ethanol intake.** To see if adolescent ethanol experience affects ethanol intake in adulthood animal models for voluntary consumption (two-bottle choice, drinking in the dark, scheduled high-alcohol

consumption) or forced administration (intragastric gavage, intraperitoneal injections, ethanol vapor inhalation, forced drinking) have been used. Even though some studies have displayed the relation of adolescence ethanol exposure and excessive adult alcohol intake (*c.f.*,(Towner and Varlinskaya 2020)), there is not enough study focusing on sex differences in long-lasting effects of adolescent ethanol exposure. Additionally, some papers describing no significant effects of Adolescent Intermittent Ethanol (AIE) on drinking ethanol(García-Burgos et al. 2009; Varlinskaya, Kim, and Spear 2017), some others studies reported similar effects in both males and females(Amodeo et al. 2018; Broadwater, Varlinskaya, and Spear 2013; Moore et al. 2010; Younis et al. 2019), and some of the studies claiming changes in ethanol consumption based on sex(Gamble and Diaz 2020; Maldonado-Devincci et al. 2010, 2022; Siciliano and Smith 2001; Strong et al. 2010).Some factors like exposure regimens, duration, route of ethanol administration, blood ethanol concentrations attained, mode of testing, and animal strain may be responsible behind inconsistency in findings(Robinson et al. 2021).

In animal models like Sprague Dawley rats, both sexes showed increased ethanol consumption later in life(Maldonado-Devincci et al. 2010), or had no effect on social drinking irrespective of sexes(Varlinskaya et al. 2017). In case of Long-Evans rats more noticeable sex differences was observed when they were forced fed ethanol in adolescence, where males had a gradual increasing and females gradual decreasing ethanol intake trend later in life(Siciliano and Smith 2001). In general, the degree of sex effects is mostly dependent on specific experimental parameters but undoubtedly sex is a substantial factor in the effect of exposure to adolescent ethanol drinking behavior later in life.

Depending on the route of administration, AIE can increase adult life ethanol consumption and affect response of ethanol(Robinson et al. 2021). Eight out of ten review studies reviewed increase

of ethanol intake in male adults than female adults. Hence, male rodents are prone to excessive adult drinking after getting exposed to adolescent ethanol intake which may be main factor behind ethanol sensitivity in sex differences. These findings are a bit consistent with the literatures focusing on human epidemiology(Flores-Bonilla 2020; White 2020), and highlights on the facts that animal models can provide useful information to the probable risks for humans of substantial ethanol exposure during adolescence.

**Relationship between adolescent alcohol use, anxiety, and mood disorders.** During adolescence, anxiety and mood disorders are most frequently observed which can lead to and also be an aftermath of abusing alcohol. Social anxiety is found to be responsible for problematic drinking during the developmental period(Terlecki, Ecker, and Buckner 2014), with decrease in interpersonal relations which is also an indication of AUDs in older adolescents(Chou et al. 2011). Inevitably, anxiety and depression are consequences of alcohol use in adolescence in human(Marmorstein 2009). The NIAAA-funded National Consortium on Alcohol and Neurodevelopment in Adolescence and others have focused on finding the underlying causes responsible for adolescent alcohol consumption in human, as well as sex differences both in sociability and brain activity. For instance, while engaging in social drinking was linked to more frequent alcohol use for both genders, females showed signs of peer influence at an earlier age than males. Additionally, social situations influenced drinking behavior in males later in adolescence, whereas this effect was not observed in females(Boyd et al. 2018).

**Developmental aspects and impacts of adolescent alcohol exposure.** Behavioral flexibility, also known as cognitive flexibility, involves the ability to adapt one's behavior in response to shifting environmental conditions and personal factors(Diamond 2013; Luna 2009). This capability is built upon other cognitive functions such as inhibitory control and working memory(Diamond 2013)

which rely on the activity of the prefrontal cortex(Nowrangi et al. 2014). The process of adjusting behavior or shifting viewpoints typically requires stopping a current action, initiating and maintaining a new approach, and continuing this adjusted behavior in response to feedback. Therefore, behavioral flexibility plays a crucial role in how both animals and humans make decisions and the outcomes of those decisions.

Behavioral flexibility begins to develop in early childhood and becomes more complex through adolescence, corresponding with the development of the prefrontal cortex (PFC)(Best and Miller 2010; Broadwater et al. 2013; Diamond 2013; Luna 2009; Nowrangi et al. 2014), This indicates a link between the maturation of the PFC and executive functions(Nowrangi et al. 2014). Consequently, it can be anticipated that factors which affect the development of the PFC, such as exposure to alcohol during adolescence, could influence executive functions overall, including behavioral flexibility.

While the majority of the referenced studies involved male subjects, fewer than half included female subjects, and none were exclusively focused on females. Notably, the effects of adolescent intermittent ethanol (AIE) on behavioral flexibility seem to be present in both genders, though there are certain distinct differences between males and females(Robinson et al. 2021).

The role of biological sex is becoming increasingly recognized as a critical factor in understanding the effects of alcohol on neurodevelopment. Recognizing the subtleties of how alcohol impacts males and females differently can enhance our knowledge of the mechanisms behind sex-specific behavioral deficits caused by alcohol and could influence the effectiveness of future treatments for each sex(Robinson et al. 2021).

**Expected outcome.** We expect to observe approach-avoid decision-making of rats in multiple levels of rewards and costs combinations and before and after oxycodone self-administration we expect to observe individual and group decision-making changes in rodents, sex differences and distinction in psychometric functions. We also expect that before and after alcohol habituation we will be able to observe individual and group decision-making changes in rodents, sex differences and distinction in psychometric functions.

## A. 2 Significance

**Critical knowledge gap that my dissertation studies will address:** The experiments will directly address individual variability in decision-making, offer and connect multiple levels of rewards and costs combinations alone and along with drug-seeking behavior. Additionally, the experiments will focus on understanding decision-making in a context dependent manner which is critical to developing treatment options for individuals experiencing neuropsychiatric disorders.

Finally, we will also focus on the distinction in psychometric functions, heterogeneity of decision-making clusters, and similarities across human rodent decision-making patterns and these findings can be applied to addresses several gaps in the field such as modeling state dependent decision-making, evaluation of decision-making within a singular context, access to a foundational model by which decision-making can become predictive, translational gaps between rodent-human work, and lastly inclusion of complex physiological measurements with decision-making.

## A.3 Specific Aims

**Aim 1:** Understanding cost-benefit decision-making in an open filed environment and the effect of sex difference.

**Aim 2:** Understanding the effect of drugs of abuse-oxycodone in altered decision-making behavior.

**Aim 3:** Understanding the effect of drugs of abuse-alcohol in altered decision-making behavior.

## A.4 Hypothesis

In Aim 1 we hypothesize that sex difference exists in approach-avoid decision making.

In Aim 2 we hypothesize that females self-administer more oxycodone and show a shift in the approach-avoid decision-making behavior.

In Aim 3 we hypothesize that females consume more alcohol and show a shift in the approach-avoid decision-making behavior.

## B. Materials and Methods

**Experimental Design for rodent subject:**

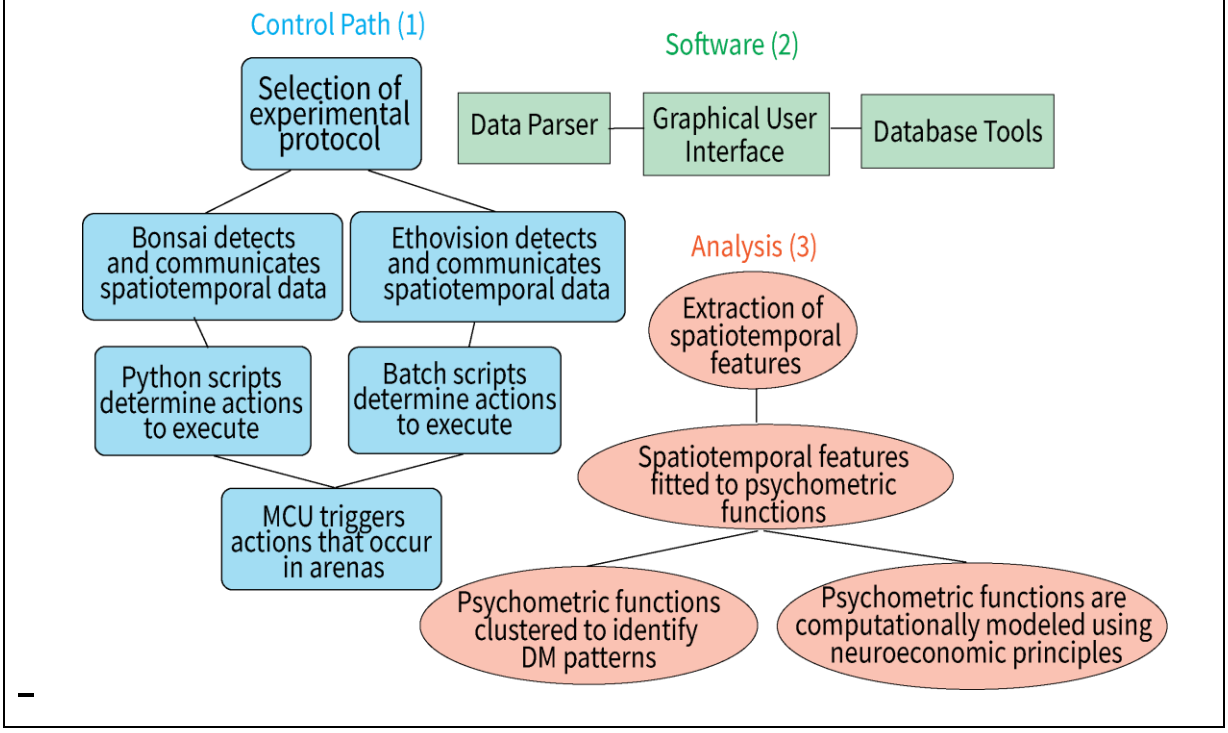



**Figure 1: Rodent decision-making system.**

Firstly, depending on the selected experiment, either Bonsai or NOLDUS was utilized to detect information. Custom Python or batch scripts were then employed to determine the actions to be executed, transmitting this information to the MCU. Subsequently, the MCU executed preprogrammed actions in the arenas, such as illuminating LEDs or dispensing rewards.

Secondly, data from a session was sent to one of two custom parsers, depending on the experiment conducted. These parsers combined the trials, checked for mismatches and consistency, and made the data accessible through a custom Graphical User Interface (GUI). Database tools were developed to facilitate data retrieval and analysis.

Lastly, codes were utilized to extract behavior features based on animal location, time, and choice. These features were then used to create modeling and analysis tools. Additionally, synchronization scripts were developed to enable our system to function with calcium imaging.

**The system for task-development.** We used our precise and sensitive system Reward-Cost in Rodent Decision-making (RECORD) to detect and analyze decision-making behaviors in both individual level and group level for all the rodent experiments. There are 7 major components that built the system as a whole:

1) 3D-printed arenas/mazes,
2) microcontroller and related connecting devices
3) infrared cameras for tracking rodent movements,
4) software for data acquisition,
5) software for data parsing,
6) software for databasing, and
7) software for data analysis.

**Maze layout.** One of the major physical components for the system to run is the mazes where the rodents go through their decision-making tasks. The mazes/arenas had 4 distinct floor patterns (Diagonal, Grid, Horizontal, Radial) where each one connected to specific costs and reward. This multiple reward-cost combination option provides the rodent to make informed choices. The arenas measured 64 cm along each side **(Fig. 2)**. Rewards are usually sucrose solution of different concentrations for each feeder (Diagonal 9%, Grid 5%, Horizontal 2% and Radial 0.5%). Costs are blue LED lights with intensity adjusted in between 15Lux-320Lux based on the type of experiment run. These LEDs also indicated which feeder would dispense a reward for each trial. Usually in tasks involving cost/benefit conflicts, variable light intensities were used as aversive stimuli, while sucrose solutions served as rewarding stimuli(Friedman et al. 2015, 2017, 2020).

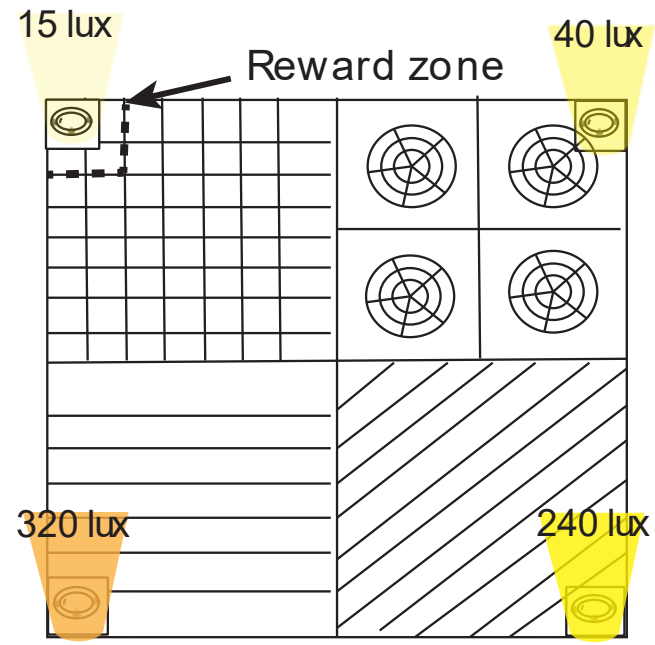



**Figure 2: Maze for conducting decision-making tasks.**

3D-printed maze floor with four different patterns to indicate the locations of four feeders. Each feeder delivers a specific concentration of liquid reward (9%, 5%, 2% and 0.5% sucrose solution). LED light intensities are shown, from lowest to highest (upper left, moving clockwise) (15LUX-320LUX).

**Tracking and recording.** The system executes reward disposition based on the animal location and the whole approach-avoid behavior towards the reward-cost (LEDs) is tracked and recorded through IR-sensitive cameras by the system. Experiments were run in a dim room since light was used as an aversive stimulus and rodents are more active in low-light conditions(Evans 1971). Data from camera was saved as raw data in table file format. Spatial data was sampled for every frame captured by the camera.

Ethovision XT was used to track animal location and response inside the arena. Bonsai computer vision library was used as well to continuously record the animal's position. Since Ethovision requires a paid license, we also tested the system with a free alternative, Bonsai. Also, the behavior tracking software was easy to link to our microcontroller-driven electronics.

**Subjects.** For all experiments, adult Long Evans male and female rats (~8 weeks old) were housed either individually or two per cage (sexes housed separately) and maintained on a 12-hr. light: 12

hr. dark photoperiod (lights on at 06:00 hr.) with unlimited water and rat chow and allowed at least seven days acclimation before the beginning of any experiment. Rats were then housed singly following acclimation, and body weight was measured monthly and determined to the nearest gram, while food and fluid intakes were determined by weight to the nearest 0.1 g and 0.1 ml respectively. All experimental procedures described are approved by the UTEP Institutional Animal Care and Use Committee.

**Decision-making task batteries.** The behavioral tasks consisted of numerous trials, each lasting from 30 to 50 seconds. They are designed to be highly flexible, allowing researchers to modify variables like cost, reward, and timing.

We used three types of tasks having different decision-making approaches:

- Reward/cost association task: animals were trained to relate light cues with rewards and rewards with specific spatial locations separated by different floor patterns. This task did not involve a choice action as it was used more like an arena habituation and task learning phase, which limits the activation of multiple brain circuits. The reward is given regardless of whether the animal approaches the light.

The task comprises three stages **(Fig. 3)**:

1. Tone Presentation: A 4-second trial start tone is played as a condition for the rodent indicating the start of a trial.

2. Cue Presentation: Low-intensity light is presented at a predetermined location, which varies pseudo-randomly across trials. The light must be bright enough for the rodent to see but not so bright as to stress the animal; a range of 15 to 20 lux is used in this particular study.

3. Reward Delivery: A sucrose reward at a specific concentration (9%, 5%, 2%, 0.5%), determined by the location of the feeder, is given to the rodent.

Experimental trials were usually run 5 days a week for 2-4 weeks until the rodents learned the task. This task also enabled the identification of each rat's individual reward preferences based on their approach rate versus avoidance rate.

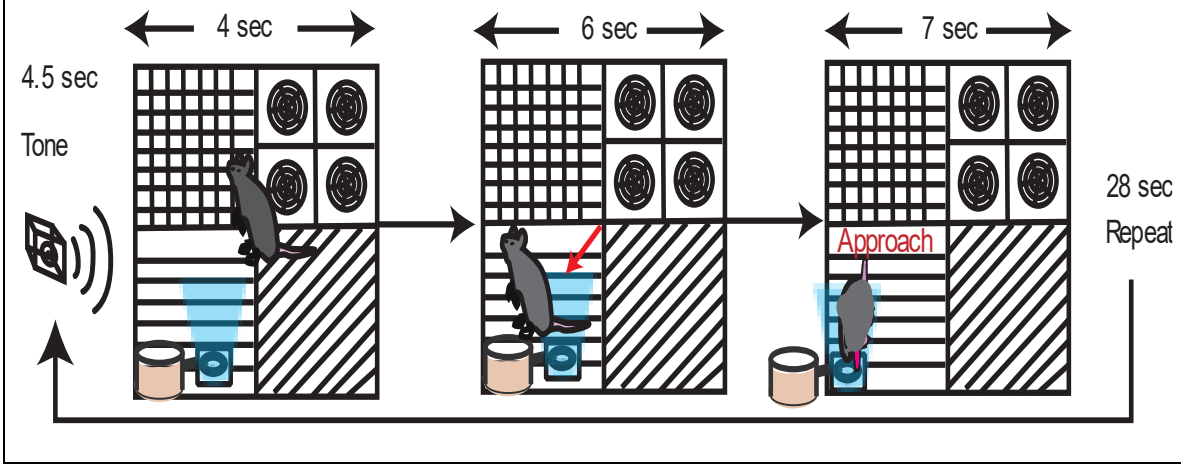



**Figure 3: Decision-making task trial.**
In a typical decision-making (DM) task trial, four key phases are involved. First is the tone presentation, marking the trial's start. Next, the offer presentation occurs, where light indicates a cost-reward scenario. Following this is the approach/avoid phase, where the animal decides to accept or ignore the offer. Lastly, the delivery phase involves dispensing the reward if the offer was accepted. Each trial is separated by a 28-second inter-trial interval, during which the system resets, and hardware is re-synchronized.

- Low-cost cost-benefit tasks: these tasks were developed, offering different reward/ low cost (only 15 Lux) pairings on each trial. In this task the light turned on indicating the location of the offer and the offer/reward was dispensed only if the rodent approached that feeder and entered the specific feeder quadrant. If the rodent didn't approach the offer, the

light turned off and no offer was delivered, and it was considered avoid or rejection. After a variable delay (e.g., 6 seconds), the system uses camera-based tracking to determine if the animal remains in the active quadrant or moves to another region **(Fig. 4)**.

- High-cost cost-benefit tasks: these tasks were developed, offering different reward/ higher cost (15 Lux-320 Lux) pairings on each trial. The tasks were run following the same settings as the Low-cost cost-benefit tasks, but the only difference was the low and high light intensities were randomly set to turn on different feeders **(Fig. 4)**.

Adjustments were made to the intensity of the light associated with the cost, as there was notable variability in how individual rats recognized the light. Some rats seemed to recognize the light as either stronger or weaker than others, despite the brightness being the same across all cost levels.

The tasks we run are self-sufficient and not inherently dependent on each other; each task can function independently as a significant experiment. Although the association task can lay the groundwork for the high- and low-cost cost-benefit tasks, it is not mandatory. Typically, rats needed around 9 weeks to complete training for these tasks.

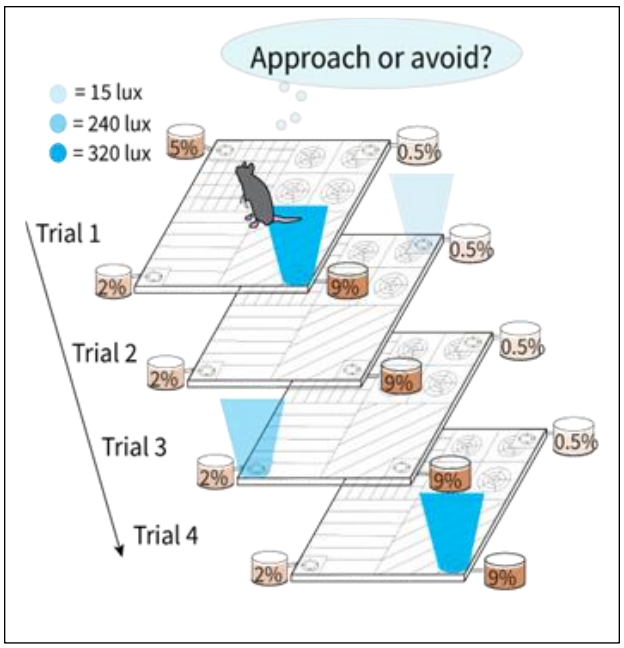



**Figure 4: Cost-benefit decision making task.**

In each trial, an LED is lit around one of the bowls, indicating that the reward will be placed in that bowl. The reward is consistent across all locations (0.5% to 9% sucrose). The rodent then chooses whether to approach the feeder and consume the reward under the LED light or to avoid the feeder. The specific feeder lightened is randomly selected for each trial. The intensity of the LED ranges from 15 lux to 320 lux and is determined by the behavioral protocol.

**Decision-making task: calibration phase.** The calibration phase, performed before any implant procedure, allowed us to determine the range of cost-benefit combinations for each rat that yielded a similar sigmoidal psychometric function across all rats. For each rat, we determined the percentage of sucrose that corresponded to the following levels of choice behavior: Level 1--rat chose the sucrose reward 20% of the time, Level 2-- rat chose the sucrose reward 40% of the time, Level 3—rat chose the sucrose reward 60% of the time and Level 4-- rat chose the sucrose reward 80% of the time. All of these were assessed when the cost was minimal (light intensity = 40 lux).

The levels of cost were also calibrated. For each rat, we determined the LED intensity that altered approach behavior in the following specific ways: Level 1-- the rat chose the reward paired with this level of cost 20% less vs the same reward with no cost; Level 2-- the rat chose the reward paired with this level of cost 40% less vs the same reward with no cost.

**Decision-making task learning phase.** Each day, we loaded all corner ports with 4 concentrations of sucrose which were different for each rat (but consistent across days within a rat) by providing different concentrations of sucrose that were determined at the start of the experiment (as described in Calibration above) for each rat.

Each corner port delivered a specific sucrose concentration for each rat across all trials, The rat identified the cost level based on intensity of LED presented (lights appear in one of two intensities) and reward level based on reward location. Each day we loaded each corner port with a specific concentration of sucrose and only one port delivered sucrose on any given trial.

Each day a rat on average performed at least 40 trials and up to a maximum of 150 trials. Each trial was organized in the following way: at the beginning of the trial, a tone was played to indicate the start of the trial. Afterwards, an offer was presented, indicated by an LED light around the feeder. A rat could approach an offer by moving towards a port, or rat could avoid an offer by moving out of the port to another zone, triggering the LED lights to turn off. The reward port that was lit, as well as the level of cost (light intensity), was presented randomly.

**Analyzing decision-making strategies: feature extraction.** We pinpointed some features to extract and study individual decision-making from the data obtained during behavioral trials. These features include metrics such as speed, orientation, and position. The extracted features were then analyzed and stored in a dedicated table within a PostgreSQL database. Below is a compilation of the features extracted, along with their respective definitions.

1. Distance traveled: Overall Euclidean distance traveled by the animal in the normalized trajectory.

2. Travel pixel: The number of pixels that were traveled by the animal between trial start and trial end in the normalized trajectory.

3. Proportion of high-speed runs: The total number of outliers present in a set of acceleration measurements. We calculated this based on the median and the standard deviation of the acceleration data divided by distance traveled.

4. Stopping points: Defined as the number of times the rat comes to a complete stop (moves < 0.1 units in both X and Y direction within a three second window) during the trial.

5. Rotation points: Defined as the number of rotations performed by the animal during each trial. A vector was defined from the center point of the rat to the head of the rat. Angular changes greater than 180 degrees in the vector within a 1.5 second window were defined as one rotation.

6. Approach time: Refers to the time it takes the animal to reach an offer location after the "trial start" tone is presented.

7. Proportion of trial outside all reward zones: Time the animal spent in the center of the arena divided by the number of trials in a session.

**Surgical procedure.** We used Oxycodone in combination with High Cost (High light intensity). Cather surgery was done to make easy administration of oxycodone instead of intravenous penetration every time. After the surgery the rats had a week's rest and during that time, they got familiar with the maze. After that week they got introduced to the addiction process. They used to get oxycodone everyday through self -administration process (0.1 mg/kg/infusion for day 1-7, 0.05

mg/kg/infusion for day 8-14) for 14 days. After self-administration for the next 15-30 days, they ran trials with normal food and water and this phase was also known as Incubation of craving.

**Oxycodone self-administration and abstinence.** The self-administration task was based on one used in multiple published experiments(Altshuler et al. 2021; Bossert et al. 2020; Moschak, Terry, et al. 2018; Moschak and Carelli 2017, 2021b, 2021a; Moschak, Wang, and Carelli 2018). Mildly water-deprived rats self-administered either oxycodone or water reward (with yoked saline)6 hr. / day for 14 days. During each trial in the task, a nose poke aperture illuminated. Nose pokes into the illuminated aperture resulted in a bolus of oxycodone (0.05956 mg/kg/infusion) or water/yoked saline (volume matched) coupled with a 20 second tone/house light stimulus. During the 20 second tone/house light stimulus, the nose poke aperture was darkened, and further nose pokes were recorded but did not result in drug delivery. Animals were also tested on extinction of self-administration both day 1 and day 30 following cessation of self-administration; this paradigm was sufficient to induce an 'incubation of craving' for oxycodone, that is, an increase in drug-seeking behavior at 30 days(Friedman et al. 2020). During extinction, nose pokes resulted in tone/house light stimulus, but no oxycodone or water/yoked saline.

**Oxycodone behavioral task.** During the behavioral sessions, rats performed a slightly modified version of the cost/benefit association task with the same rewards being dispensed, however only 280 lux was used as a cost as opposed to varying light intensities. This modification to the protocol was made due to a perceived hypersensitivity to the cost light, which we believed was due to the introduction of oxycodone. Additionally, we found that during self-administration and abstinence, some rats became increasingly aggressive toward experimenters and spent a large amount of time biting at the arena components instead of participating in the trial. These rats (n = 2) were removed from the study entirely.

**Alcohol Experiment.** For this experiment we used 11 experimental rats (6 females and 5 males) and 11 control rats (6 females and 5 males). Alcohol administration was designed to be in the following 3 different sections:

a. **Alcohol habituation.** For the first section the experimental rats ran trails in the decision-making mazes, and they were introduced to 4 different concentrations of alcohol along with different sucrose concentrations (0.5 % Sucrose+ 20% Alcohol, 2% Sucrose + 10 Alcohol, 5% Sucrose + 4% Alcohol, 9% Sucrose + 1% Alcohol). The control rats ran the same decision-making trials for the same amount of time as well, but they received regular sucrose solutions only.
b. **Alcohol liquid diet introduction.** The second section was where rats stayed in their home cage and got addicted to alcohol starting from 10% alcohol to finally 20% alcohol along with liquid diet for 4 weeks. The regular chow diet was replaced with a liquid diet(Serrano et al. 2018) consisting of chocolate-flavored Boost nutritional supplement fortified with vitamins and minerals (Nestle HealthCare Nutrition, Florham Park, NJ, USA). The rats were divided into two groups: the alcohol group, which received a diet containing 10% (w/v) alcohol, and the control group, which received an alcohol-free diet supplemented with sucrose to match the caloric intake of the alcohol group. The diet was available 24 hours a day, 5 days a week. On weekends, the animals had ad libitum access to chow and water.
c. **Alcohol induced decision-making trials.** The last section was where we repeated the first section but the only difference with the first section was the third section recorded the behavior and decision-making patterns after the rats developed alcohol addiction

# D. Results

**Aim 1: Understanding cost-benefit decision-making in an open filed environment and the effect of sex difference.**

To look at the decision-making behavior of the rodents we used our printed mazes designed to have distinctive patterns on arena/maze floors (diagonal, grid, horizontal, radial) **(Fig. 2)** to associate to different concentrations of sucrose solutions which were dispensed as rewards through the feeders **(Fig. 2)**. Each feeder had a ring of LEDs with different intensities as cost surrounding each feeder **(Fig. 2)**. Reward concentrations for the distinctive patterns radial, horizontal, grid and diagonal were respectively 0.5%, 2%, 5%, and 9%. And intensities of the LEDs as cost ranged 15-320 Lux). The distinctive maze patterns as visual cues along with different intensities of lights as costs and different concentrations of sucrose solutions as rewards helped the rodents to make decisions combining reward and cost.

We used three independent tasks- reward/cost association, low-cost cost-benefit, and high-cost cost-benefit **(Materials and Methods)** to evaluate rat (Male = 11, Female = 12) decision-making behavior. For all the tasks each trial began with a tone, followed by lighting of a feeder, giving rats 6 seconds to reach the reward zone. Successful trials kept the feeder illuminated for reward consumption, while unsuccessful ones resulted in the feeder deactivating **(Fig. 3)**. The reward/cost association task taught rats to link each reward level with a specific floor pattern. This task did not involve a choice action as it was used more like an arena habituation and task learning phase, which limits the activation of multiple brain circuits. The reward is given regardless of whether the animal approaches the light **(Fig. 5)**. From the task learning phase we have noticed that females were significantly faster to learn the task compared to the males. Average time to learn task (FvM)

statistical significance was determined by paired t-test using SPSS 2324 software package (F = 12, M = 11). p-vale for sex difference: 0.01.

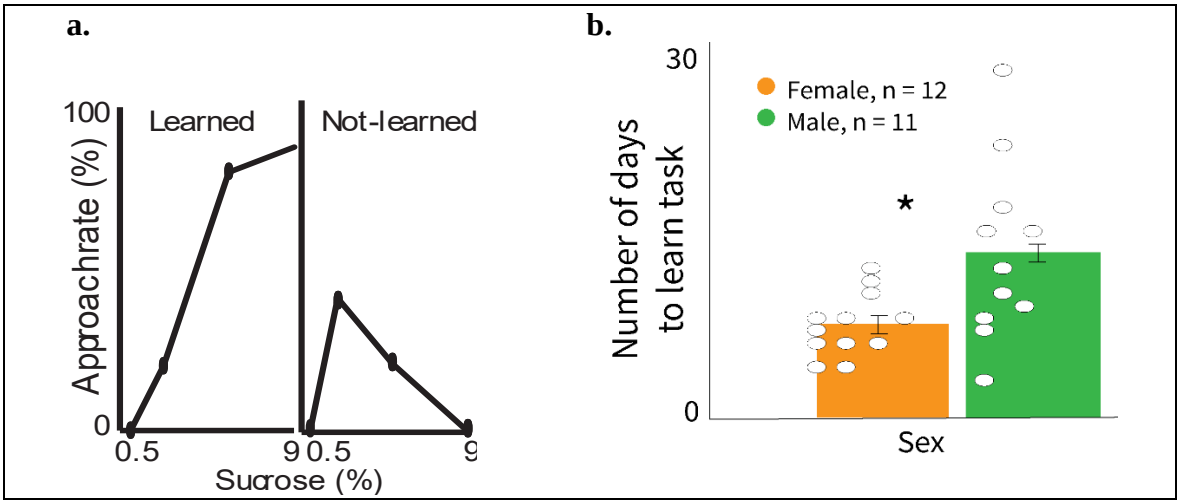



**Figure 5: Decision-making Task Learning.**
**a.** Example of individual rats performance in the reward/association task in a session. In the left the rat learned to approach the reward compared to in the right graph where the rat has not yet learned the task is shown.
**b.** Graph demonstrating the average time to learn the task in males and females (paired t-test *p = 0.01, mean ± SEM).

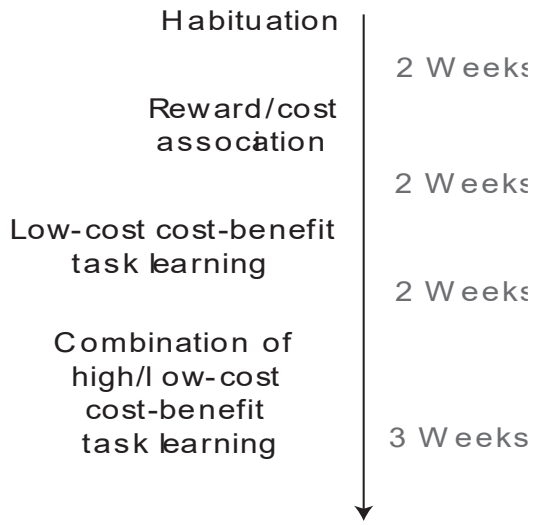



**Figure 6: Task learning timeline.**

After becoming adapted to the arena and understanding the correlation of light with sucrose as indicating cost and reward, the rats were gradually introduced to the low-cost cost-benefit task. Following a two-week training period, they were then exposed to the high-cost cost-benefit task. This was achieved by including both low and high-cost trials randomly throughout the same session.

Next, once the rat learned about the maze and task we slowly introduced them to low-cost tasks. In the low-cost task we offered different reward/ low cost (only 15 Lux) pairings on each trial. In

this task the light turned on indicating the location of the offer and the offer/reward was dispensed only if the rodent approached that feeder and entered the specific feeder quadrant. If the rodent didn't approach the offer, the light turned off and no offer was delivered, and it was considered avoid or rejection. After a variable delay (e.g., 6 seconds), the system uses camera-based tracking to determine if the animal remains in the active quadrant or moves to another region **(Fig. 3, 4)**.

When the rodents were comfortable with low cost and understood the concept of cost-reward association we introduced them to the high-cost tasks. For high-cost tasks we gradually increased the light intensities from 15 lux to 40, 140,160,240,260,320 lux. In these tasks we offered different reward/ higher cost (15 Lux-320 Lux) pairings on each trial. The tasks were run following the same settings as the Low-cost cost-benefit tasks, but the only difference was the low and high light intensities were randomly set to turn on different feeders **(Fig. 4)**.

As soon as the rodents were completely aware of the tasks, they approached reward/cost combinations more as sucrose concentration increased and this was supported by a significant main effect of sucrose concentration in the repeated measures ANOVA **(Fig. 8a,** RM ANOVA, $p < 0.0001$**)** and less as light intensity increased **(Fig 8b,** RM ANOVA, $p < 0.0001$**)**. Analyzing approach rate across a spectrum of cost (light intensity) revealed context-dependent decision-making. The acceptance rate of rewards paired with 15 lux was approximately 80% when only 15 lux was presented, but significantly lower in sessions with trials of higher light intensities **(Fig. 7,** $p < 0.0001$ from Bayesian analysis**)**. Also, Post-hoc analysis indicated significant sex differences at 15 lux ($p = 0.0006$), 240 lux ($p = 0.0002$), and 260 lux ($p = 0.0002$). However, there was no overall main effect of sex on approach rate (RM ANOVA, $p = 0.8$).

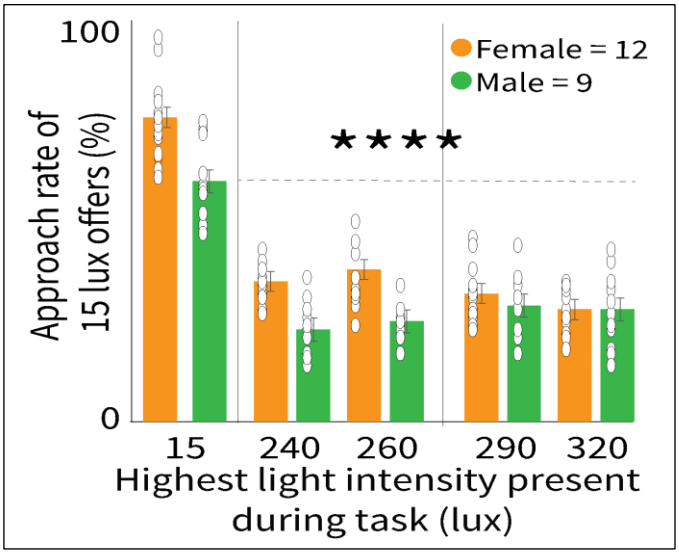



**Figure 7: Approach rate for all the rewards and costs together.**

A Bayesian analysis was conducted to assess the approach rate of 15 lux offers across sessions with varying maximum light intensities. The analysis revealed a significant effect of light intensity on approach rate ($p < 0.0001$). There were significant sex differences at 15 lux ($p = 0.0006$), 240 lux ($p = 0.0002$), and 260 lux ($p = 0.0002$).

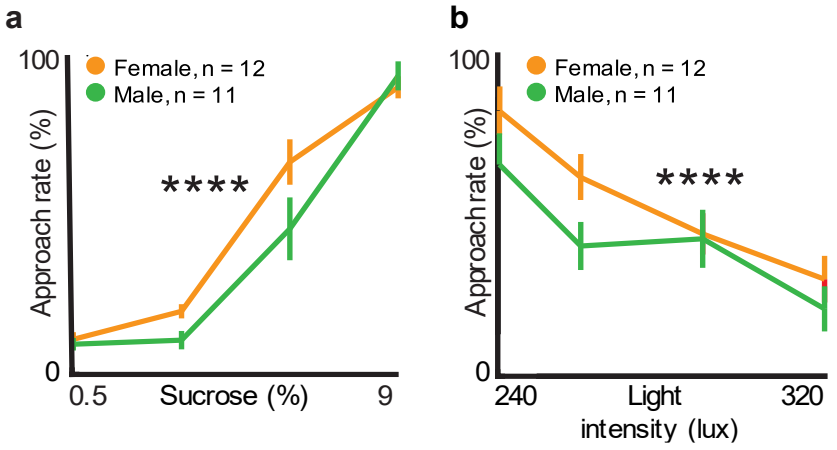



**Fig. 8: Reward-cost combination task.**
**a.** As the sucrose concentration increased, both sexes showed an increase in approach rates towards the reward. There was no significant main effect of sex ($p = 0.06$) but effect of sucrose concentration was significant(RM ANOVA, ***$p < 0.0001$).
**b.** As light intensity increased, the approach rate decreased (****$p < 0.0001$). There was no significant effect of sex on approach rate as light intensity increased ($p = 0.153$).

From all the 3 tasks we have observed that on an average the females took less time to learn any of the tasks compared to the males and started showing their decision-making behavior more prominently by being more responsive to the decision-making tasks. One thing was obvious from

the tasks that even during learning a new task and making decision under normal circumstances or under conditions or context depended decision-making, sex difference persists.

We pinpointed some features to extract and study individual as well as group (male vs female) decision-making from the data obtained during behavioral trials. These features include metrics such as speed, orientation, and position. Behavioral features can be analyzed in various ways. When examined by cost and reward level, some sex differences were observed. Females traveled further than males **(**RM ANOVA ##p = 0.003**, Fig. 9a)**, while males had more high-speed runs (RM ANOVA ##p = 0.002, **Fig. 9b**). Other features showed no significant sex differences (**Fig. 9c-e**). Across both sexes, the number of high-speed runs increased with sucrose concentration (RM ANOVA $p < 0.0001$, **Fig. 9b**), while approach time (RM ANOVA $p = 0.0008$, **Fig. 9c**) and proportion of trial outside all reward zones (RM ANOVA $p < 0.0001$, **Fig. 9d**) decreased as sucrose concentration increased.

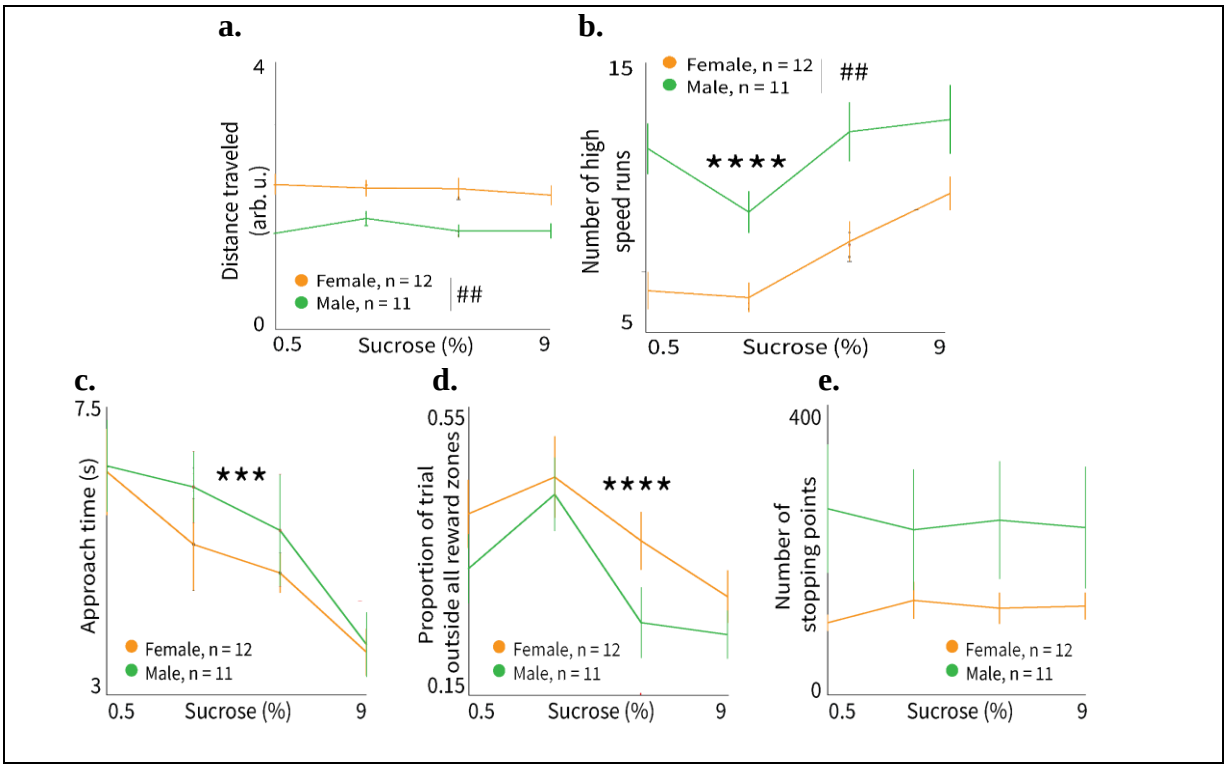



**Figure 9: Behavioral features examined for decision-making study.**
Males and females exhibit distinct patterns in time and movement dynamics from the start of a trial to decision-making.
**a.** Males traveled shorter distances than females showing significant sex differences , ##p = 0.003) with no significant effect of sucrose concentration (p = 0.089).
**b.** The number of high-speed runs increased as sucrose concentration increased (****p < 0.0001). Males had significantly more high-speed runs than females (##p = 0.002).
**c.** Both male and female rats entered the reward zone faster with higher sucrose concentration(***p = 0.0008), but there was no sex difference.
**d.** Rats spent less time in the center of the maze and more time in a reward zone with higher sucrose concentration (****p < 0.0001), with no significant effect of sex
**e.** Stopping points were unaffected by sucrose concentration (p = 0.98) or sex (p = 0.16).
# Indicates a significant effect of sex (# ≤ 0.05, ## ≤ 0.01, ### ≤ 0.001, #### ≤ 0.0001).

We allowed the rats to freely interact with various reward/cost combinations to show decision-making behavior. This enabled us to have a detailed examination of the interactions between reward, cost, and behavior during decision-making. When we plotted behavioral features against sucrose concentration it presented two major psychometric shapes. After creating curves from 23 rats' behavioral sessions, 75.47% were sigmoidal, 9.93% were parabolic (inverted-U), and 14.62% were undefined **(Fig. 10a)**.

Each sigmoid function was described by three parameters: 'Shift' (horizontal distance from the y-axis), 'slope' (linear aspect of the sigmoid), and 'max' (upper limit of the sigmoid) **(Fig. 10b-c)**. We further examined variability in decision-making behavior across animals by comparing how reward and cost impacted different behavioral features (distance traveled, number of stops, etc.). This analysis allowed for the identification of decision-making sub-populations with similar behavioral preferences. This detailed analysis highlighted the 'constrained heterogeneity' of decision-making behaviors across individuals, which may parallel the dimensionality reduction observed in neuronal activity patterns(Bar-Gad, Morris, and Bergman 2003; CDC/NCHS n.d.).

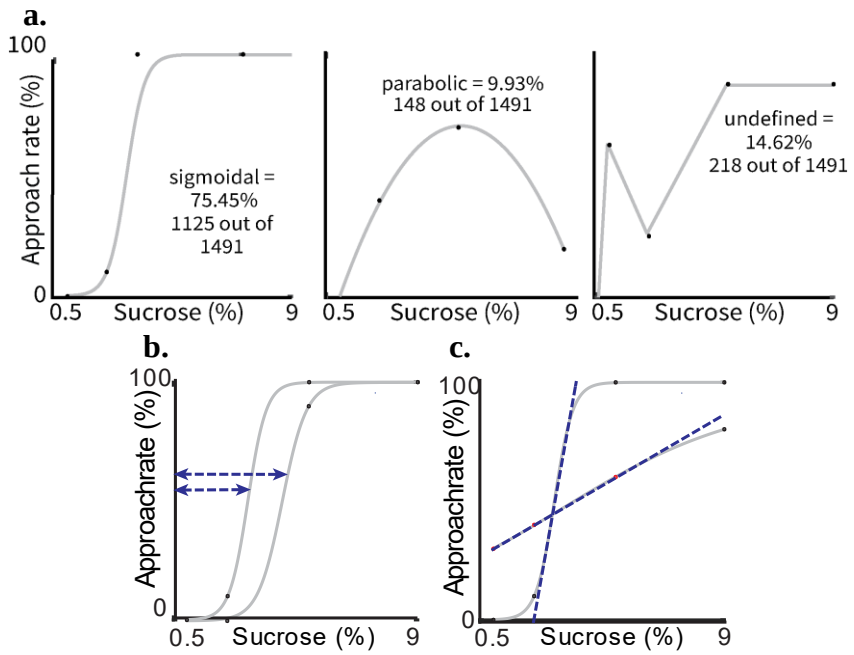



**Figure 10: Functions that can be clustered to identify individual decision-making strategies.**

**a.** For each individual session, we plotted sucrose concentration (SC) against one of the behavioral features (such as distance traveled, number of stops, number of rotations, reaction time, or choice). We observed that all plots could be best fit with one of two distinct shapes: sigmoid (left) or parabolic (middle). Some plots (error greater than 0.4 r2) did not fit either function and were classified as 'undefined' (right). Out of 1491 sessions (from 23 rats), 75.45% showed sigmoidal patterns, 9.93% showed parabolic patterns, and 14.62% were undefined. These were defined as three distinct decision-making patterns. Sigmoidal curves **(b-c)** were characterized by sigmoidal shift, slope, and maximum value.

**Aim 2: Understanding the effect of drugs of abuse-oxycodone in altered decision-making behavior.**

Substance use impacts decision-making in humans(Bechara 2005) and is important to understand given that unusual cost-benefit decision-making may contribute to the choice to pursue drug rewards. Given that opioid overdose deaths increased 14% from 2020 to 2021(CDC/NCHS n.d.), it is increasingly important to develop decision-making tasks that can quantify and explore the neural substrates of altered decision-making that accompany substance use.

We wanted to observe decision-making before, during, and after opioid (Oxycodone) and compare how substance abuse decision-making is different from normal decision-making. For this experiment rats (experimental males = 6, females = 6, control males = 11, females = 12) were habituated and introduced to the reward/cost association tasks and trained on the low-cost cost-benefit decision-making tasks and went under surgery **(Materials and Methods)**. After that they were exposed to oxycodone self-administration for 14 days in an operant chamber. On average, rats self-administered 3.99mg/session (females: 5.6mg/session; males: 2.7mg/session). After three to four hours of self-administration, rats were run on our cost-benefit decision making. After the 14-day self-administration period, rats entered a period of forced abstinence in which they continued to be tested on our cost-benefit decision-making task. Throughout, their performance was compared to the control group of rats who were trained and performed the same tasks without any manipulations (**more details in Materials and Methods**).

Gender difference for choice and cost-benefit is critically important. Addiction has severe impact on both men and women. Despite the existing gender difference, there is surprisingly no study

focusing on sex differences associated with cost-benefit decision-making in disorders like addiction. While looking at the decision-making under the influence of oxycodone, we observed sex differences as well.

The opioid we used for this experiment is Oxycodone which is the most preferable opioid in the US making it one of the most abused drugs. Looking at the psychometric function shapes in **Fig. 11** we see that the first graph is of a "normal" nondrug addicted animal. The animal choices are linear, increasing with the concentration of the sucrose solution. After 3 days of drug administration, we began to see the abnormal psychometric functions- a) Step function: Animal ignores concentration of reward, b) Devaluation: Animal chooses reward equally and c) Cognitive impairment: Not based on concentration.

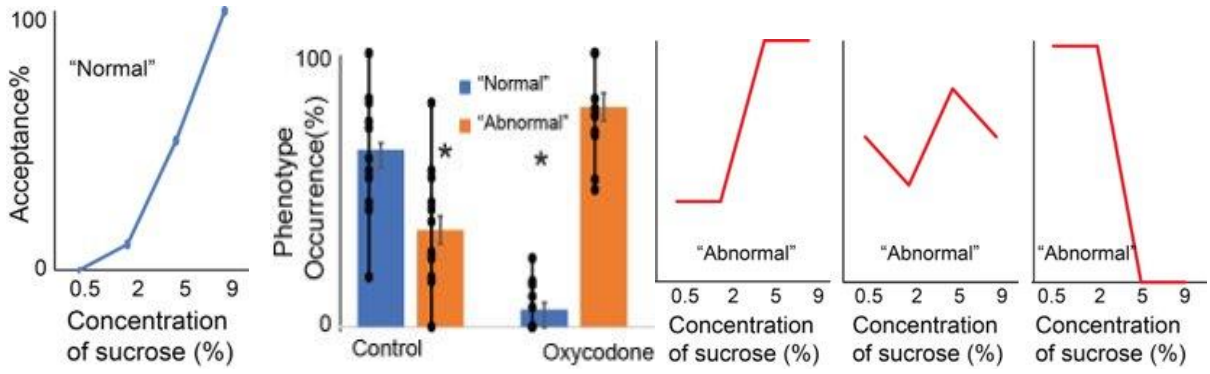



**Figure 11: Shapes of psychometric functions.**

In the oxycodone experiment we observed shift from normal psychometric function to abnormal psychometric function (Step function, Devaluation and Cognitive impairment) with the administration of oxycodone.

While the animal was non addicted it was possible to see some days of abnormal psychometric function, but once opioid administration was introduced the animal had more days of abnormal functions rather than normal.

We pinpointed some features to extract and study individual as well as group (male vs female) decision-making from the data obtained during behavioral trials. These features include metrics such as speed, orientation, and position. Behavioral features can be analyzed in various ways. We further examined variability in decision-making behavior across animals by comparing how reward and cost impacted different behavioral features (distance traveled, number of stops, etc.). This analysis allowed for the identification of decision-making sub-populations with similar behavioral preferences.

During the 14 days of oxycodone self-administration, we tried to focus on decision-making behavioral features **(Materials and Methods)** within sex (control vs experimental) as well as any possibilities of sex differences. And we found that when considering the feature "approach rate" there was a decline in sex differences [**Fig. 12a** $p = 0.17$, Sex X Condition interaction, $*p = 0.04$, Sex X Concentration interaction (Oxy or Con) interaction; $p > 0.05$ for all post-hoc comparisons between Female-oxy and Male-oxy for each sucrose concentration].

For "approach time" there was no significant sex difference (**Fig. 12d**, main effect of sex, $p = 0.0315$; Sex X Condition interaction, $p = 0.3$).

The feature "distance traveled" showed an increase in the distance traveled by males but a decrease in case of females (**Fig. 12b,** Sex X Condition interaction, $p < 0.0001$, n-way RM ANOVA).

Next, in the feature "high speed runs" oxycodone increased the high-speed runs for females but decreased for males (**Fig. 12c,** Sex X Condition interaction, $p < 0.000$, n-way RM ANOVA ).

Subsequently, for the feature "time spent in reward zones" we saw significant interaction only between sex and condition (**Fig. 12e,** Sex X Condition interaction, $p = 0.0005$ n-way RM ANOVA).

Lastly, for "the number of stopping points" feature as well had significant interaction only between sex and condition (**Fig. 12f,** Sex X Condition interaction, $p < 0.0001$, n-way RM ANOVA).

So, all together we can conclude that, oxycodone self-administration had an impact on decision-making behavior within each sex, and significantly altered sex differences in cost-benefit decision-making.

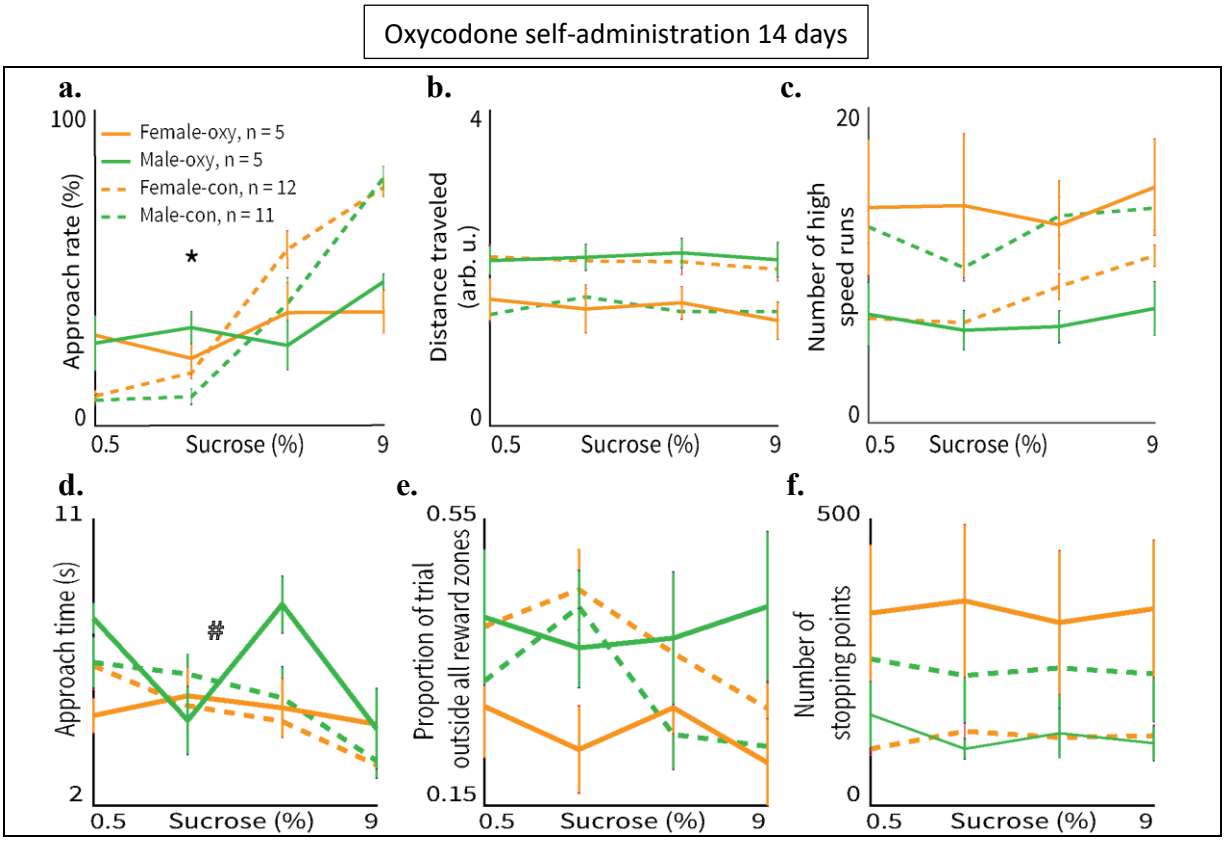



**Figure 12: Behavior features during oxycodone self-administration.**

**a.** Oxycodone self-administration produced a unique set of sex differences in decision-making that differed from those observed in the control group ($p = 0.17$, Sex X Condition interaction, *$p = 0.04$, Sex X Concentration interaction).
**b.** Whereas oxycodone increased the distance traveled for males, it decreased the distance traveled for females ($p < 0.0001$, Sex X Condition interaction).
**c.** Similarly, oxycodone increased the high-speed runs for females, while decreasing them for males ($p < 0.0001$, Sex X Condition interaction).

**d.** Approach time during the self-administration task changed significantly between sexes (#p = 0.0315), mainly due to spikes seen in males at certain sucrose concentrations (0.5%, 5%). Concentration did not have a significant effect, and there were no significant interactions between sex, concentration, and condition.
**e.** The proportion of trials outside the feeder zone did not show significant interactions between concentration or sex. The only significant interaction detected was between sex and condition (p = 0.0005).
**f.** The number of stopping points did not show significant effects of concentration or sex. There were no significant main effects when compared to the control group, but there was a significant interaction between sex and condition (p < 0.0001).

After 30 days of abstinence, we tried to look at the behavioral features again to find similarities and differences with pre-oxycodone levels.

The behavioral feature "approach rate" went back to pre-oxycodone level with no significant sex differences (**Fig. 13a** condition, ++p = 0.0016; Condition X Sucrose Concentration interaction, ****p < 0.0001). No sex differences were observed in the Oxy group for any reward level (post-hoc, p < 0.08 for all points).

"Distance traveled" showed sex differences after 30 days of abstinence. Males travelled significant distance, but females returned to pre-oxycodone level. (**Fig. 13b,** p = 0.0093 and p = 0.4449 respectively, Sex X Condition interaction, p = 0.0165 n-way RM ANOVA). And there was significance in concentration (****p < 0.0001) and condition (++++p < 0.0001) effects.

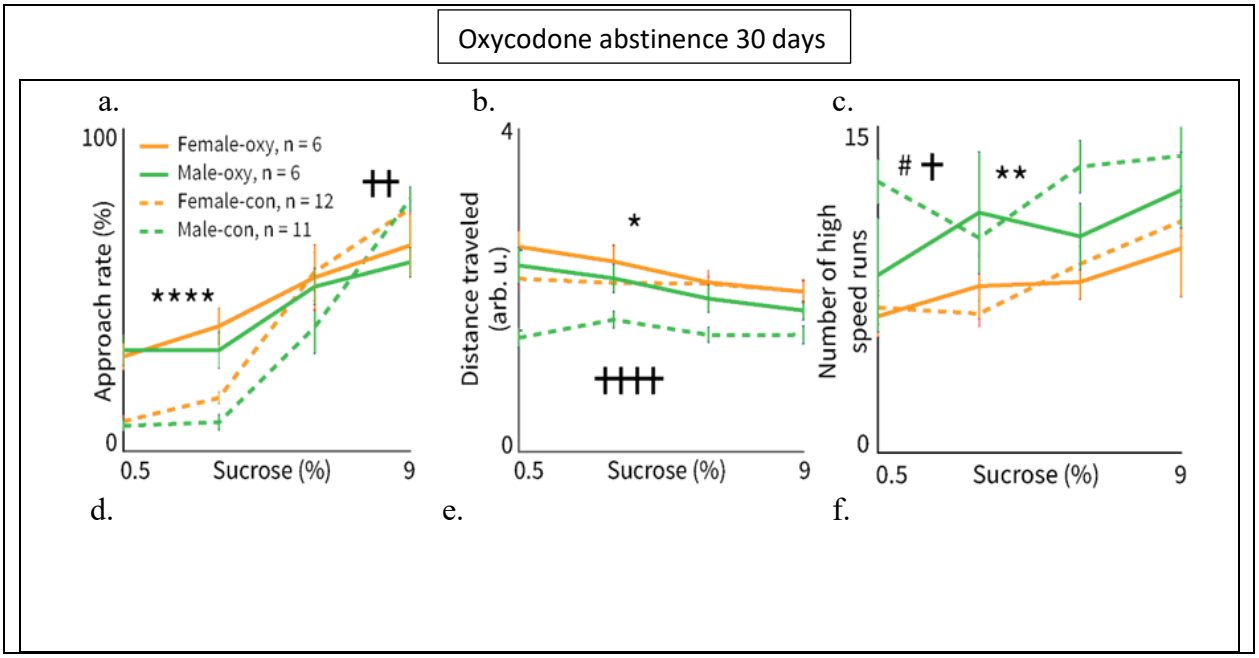
"High-speed runs" showed return to pre-oxycodone level for both sexes (**Fig. 13c**, **p = 0.0057 effect of concentration, p = 0.0853 effect of oxycodone, p = 0.0506 effect of sex, and p = 0.2045 Sex X condition interaction, n-way RM ANOVA).

"Approach time" showed significant effect of sucrose concentration after abstinence (**Fig. 13d**, ***p = 0.0003, n-way RM ANOVA). There were no significant interactions between the control group and the abstinence conditions.

"Proportion of trial spent outside feeder zones" showed a decreasing trend with the increase in sucrose concentration but there were no significant interactions detected between conditions (**Fig. 13e**, Sex, p = 0.0063 and concentration ***p = 0.0006, n-way RM ANOVA).

"Number of stopping points" remained insignificant across concentration and sex for the experimental group (**Fig. 13f**, Sex X Condition interaction, p = 0.7). However, when compared to the control group, there were significant main effects of sex (###p = 0.0005) and condition (++p = 0.006, n-way RM ANOVA), with no significant interactions between sex, condition, or concentration

So, altogether 14 days of oxycodone abstinence had an impact on decision-making behavior within each sex in terms of approach rate, approach time, high speed runs, and significantly altered sex differences in distance travelled and proportion of trial spent outside feeder zones.



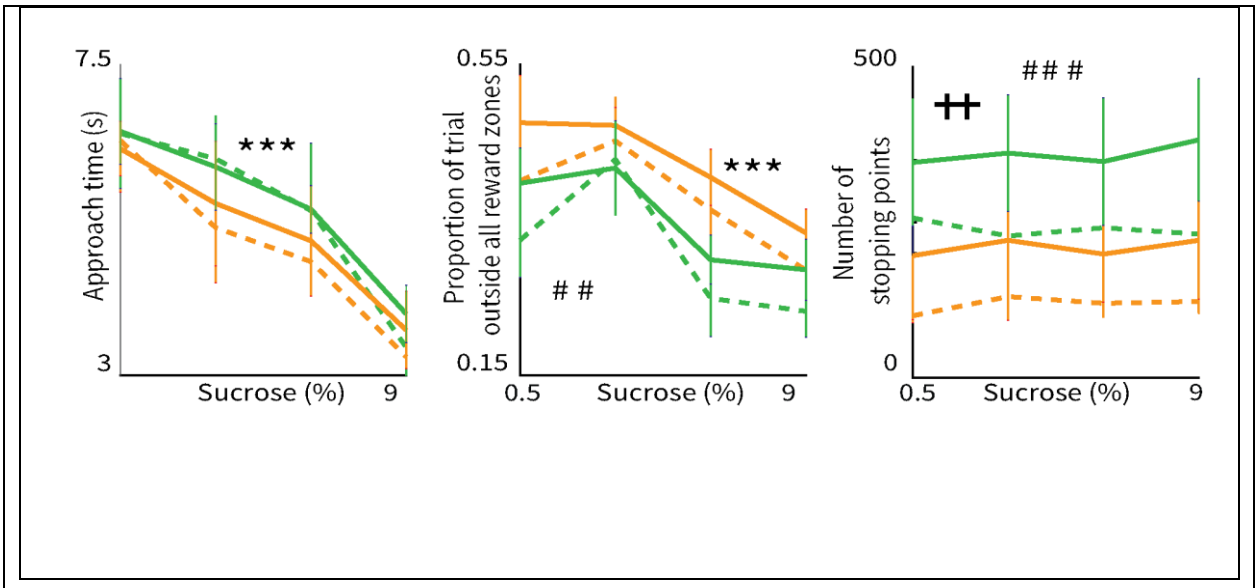



**Figure 13: Behavior features during oxycodone abstinence.**

After 30 days of abstinence, behavioral features altered by oxycodone shift towards pre-oxycodone values for both males and females but remain impacted by prior self-administration.
**a.** The approach rate remained significantly different between the OXY and CON conditions (condition, ++p = 0.0016; Condition X Sucrose Concentration interaction, ****p < 0.0001).
**b.** For females, the distance traveled returned to pre-oxycodone levels, but males still showed significantly greater distance traveled during abstinence (p = 0.4449 and p = 0.0093 respectively, Sex X Condition interaction, p = 0.0165). Concentration (****p < 0.0001) and condition (++++p < 0.0001) effects were significant.
**c.** In contrast, the number of high-speed runs returned to pre-oxycodone levels for both sexes (**p = 0.0057 effect of concentration, p = 0.0853 effect of oxycodone, p = 0.0506 effect of sex, and p = 0.2045 Sex X condition interaction).
**d.** The effect of sucrose concentration, which was not significant during oxycodone self-administration, became significant again after abstinence (***p = 0.0003).
**e.** The proportion of the trial spent outside all feeder zones decreased as sucrose concentration increased, with no significant interactions detected between conditions. The main effects of sex (p = 0.0063) and concentration (***p = 0.0006) became significant between baseline and abstinence groups.
**f.** When comparing abstinence groups, the number of stopping points remained insignificant across concentration and sex. However, when compared to the control group, there were significant main effects of sex (###p = 0.0005) and condition (++p = 0.006).

Besides looking at the decision-making behavioral features within and across the sex we tried to characterize the decision-making profile of subjects in the population and individually. In **Fig. 14** we can see that when we analyzed the frequency of sigmoidal data for approach rate for control group, experimental oxycodone self-administration group and abstinence group we found that oxycodone significantly reduced the percent of session with sigmoidal psychometric functions compared to control and abstinence groups (CON ~90%, Self-admin~40%, abstinence ~55%) (one-way ANOVAs: female CON vs female Self-admin and male CON vs male Self-admin, ****p

< 0.0001, female CON vs female Abstinence, p = 0.01; male CON vs male Abstinence, ***p = 0.0003).

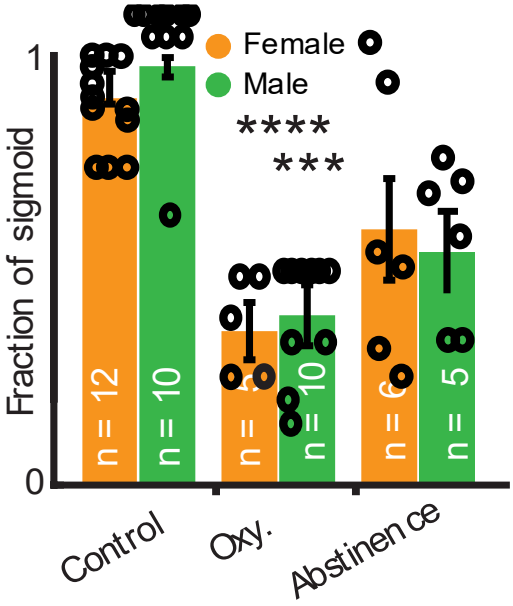



**Figure 14: Comparison of control, oxycodone, and abstinence group's sigmoidal psychometric function.**

After analyzing the frequency of sigmoidal data for the approach rate measure, we found that oxycodone significantly reduced the percent of session with sigmoidal psychometric functions (CON ~90% vs Self-admin~40%). After 30 days of abstinence from oxycodone, sigmoid frequency recovered to ~55% but was still significantly lower than the levels observed in controls (female CON vs female Abstinence, p = 0.01; male CON vs male Abstinence, ***p = 0.0003).

Next we tried to compare sigmoid session frequency across individual rats level. We observed the effect of oxycodone self-administration in all the rats but there was significant inter-individual variation (ranging from 25-65%, **Fig. 15a**).

Examination of the correlation between the amount of oxycodone self-administered and the percentage of sessions that generate sigmoid shaped functions indicated that greater oxycodone consumption led to lower numbers of sessions with sigmoid shaped functions (**Fig. 15b,** r = -0.8, n= 11).

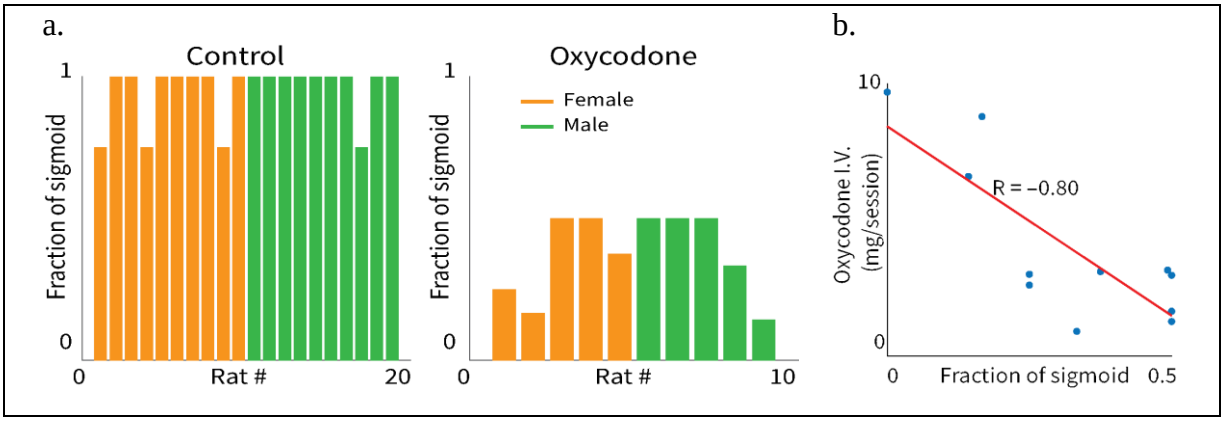



**Figure 15: Sigmoid session frequency in individual level and correlation.**

**a.** Frequency of individual sigmoid shapes observed in both control and oxycodone conditions.
**b.** Correlation between the amount of oxycodone self-administered and the frequency of sigmoid shapes. One rat's opioid self-administration data was not recorded due to technical issues.

Next we focused on looking at if there were any behavioral shifts after oxycodone self-administration and for that we used radar plots. Rader plots are easy to identify any behavioral shifts between prior oxy and during oxycodone administration across all the behavioral features together.

We created individual radar plots comparing baseline cluster probabilities to the last week of oxycodone self-administration (**Fig. 16**) illustrating the behavioral clusters of two individual rats, showing varying degrees of changes in Euclidean distances before and after oxycodone self-administration performance as a representation of all the rats. Rats showed moderate to significant changes in cluster probabilities where arrows indicated large shifts.

Briefly, the oxycodone self-administration experiment revealed that both self-administration and abstinence from oxycodone impacted decision-making behavior within each sex and significantly altered sex differences in cost-benefit decision-making. Oxycodone notably reduced the percentage of sessions with sigmoidal psychometric functions compared to the control and abstinence groups. Additionally, the radar plots indicated moderate to significant changes in cluster probabilities, demonstrating shifts in behavioral features and decision-making under the influence of oxycodone.

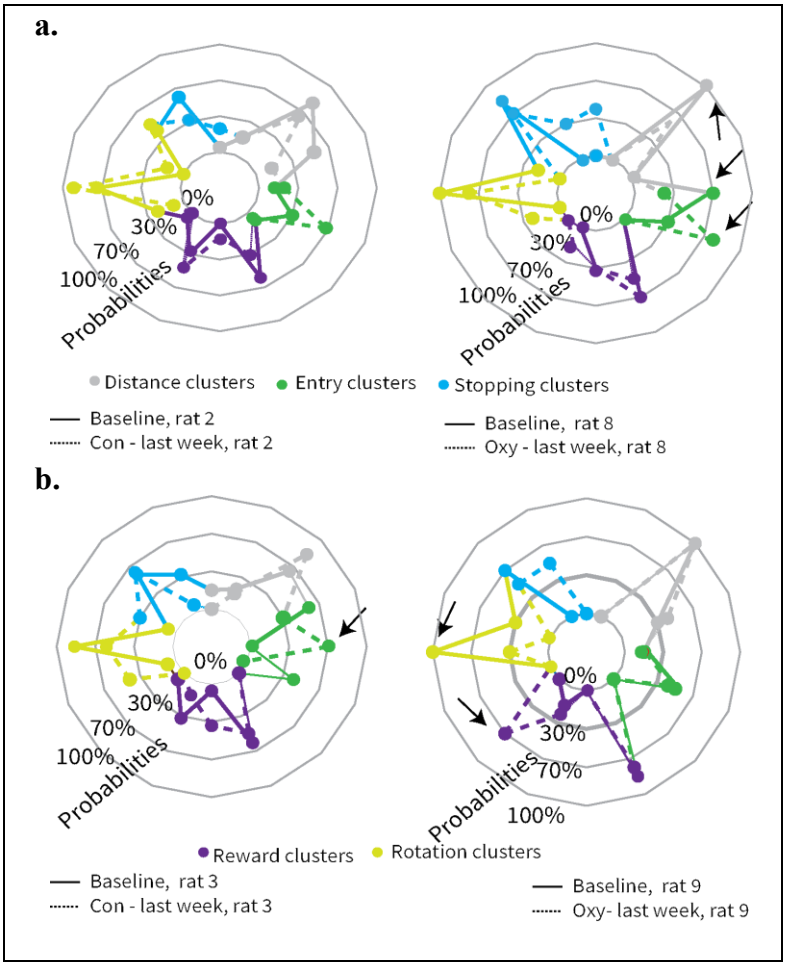



**Figure 16: Radar plots showing shifts in behavioral features pre and during oxycodone self-administration.**

A radar plot illustrates the distribution of clusters, comparing baseline and oxycodone conditions.

**a.** Some rats show minor changes in Euclidean distance. **b**. other rats exhibit more pronounced changes. An arrow indicates a feature that has shifted.

**Aim 3: Understanding the effect of drugs of abuse-alcohol in altered decision-making behavior.**

Continued alcohol consumption causes problems in individuals like poor decision(American Psychiatric Association 2013). While the majority of the referenced studies involved male subjects, fewer than half included female subjects, and none were exclusively focused on females. So, we wanted to see the effect of alcohol using our behavioral features in cost-benefit decision-making in individual level as well as across sex.

At first we introduced a substance of abuse-alcohol into an approach-avoid decision-making scenario where the rats ( Control M = 11, F = 12, Experimental M = 10, F = 12) were free to self-administer as much, or as little alcohol as wanted during a session. We followed the same cost-benefit decision-making task pattern **(Materials and Methods)** for this experiment as well, but the difference was alcohol was mixed with sucrose solutions to make solutions with inverse concentrations of the two substances: 0.5% sucrose and 20% alcohol, 2% sucrose and 10% alcohol, 5% sucrose and 2% alcohol, and 9% sucrose and 0.5%.

We analyzed our behavioral features like approach rate, approach time, distance travelled, number of high-speed runs and stopping points. For a better view of any changes in the decision-making behavior due to alcohol exposure we separated the total 9 weeks of decision-making trials into first half and last half as week 1-3 performance and week 6-9 performance respectively and compared them for different behavioral features.

The feature “approach rate” (**Fig. 17a**) showed that during the 1-3 weeks of task performance the rats approached higher sucrose concentrations more than the lower sucrose concentrations, as higher sucrose concentration contained lowest alcohol amount and the lowest sucrose concentration had the highest alcohol content (sucrose concentration, ****$p < 0.0001$), with no differences observed between sexes (sex, $p = 0.4$). Nevertheless, despite ethanol's unpleasant properties(Anderson, Varlinskaya, and Spear 2010; Pautassi et al. 2011), the approach rate was significantly higher for the alcohol task compared to the control group (Condition X Concentration interaction, $p = 0.0025$). After 6-9 weeks of task performance (**Fig. 17b**), females showed more approach rate compared to males (0.044, sex X concentration, n-way RM ANOVA). All other behavioral features, like “approach time”, “number of high-speed runs”, “distance travelled” had no significant interactions across initial and late task performance (**Fig. 17c-h**)

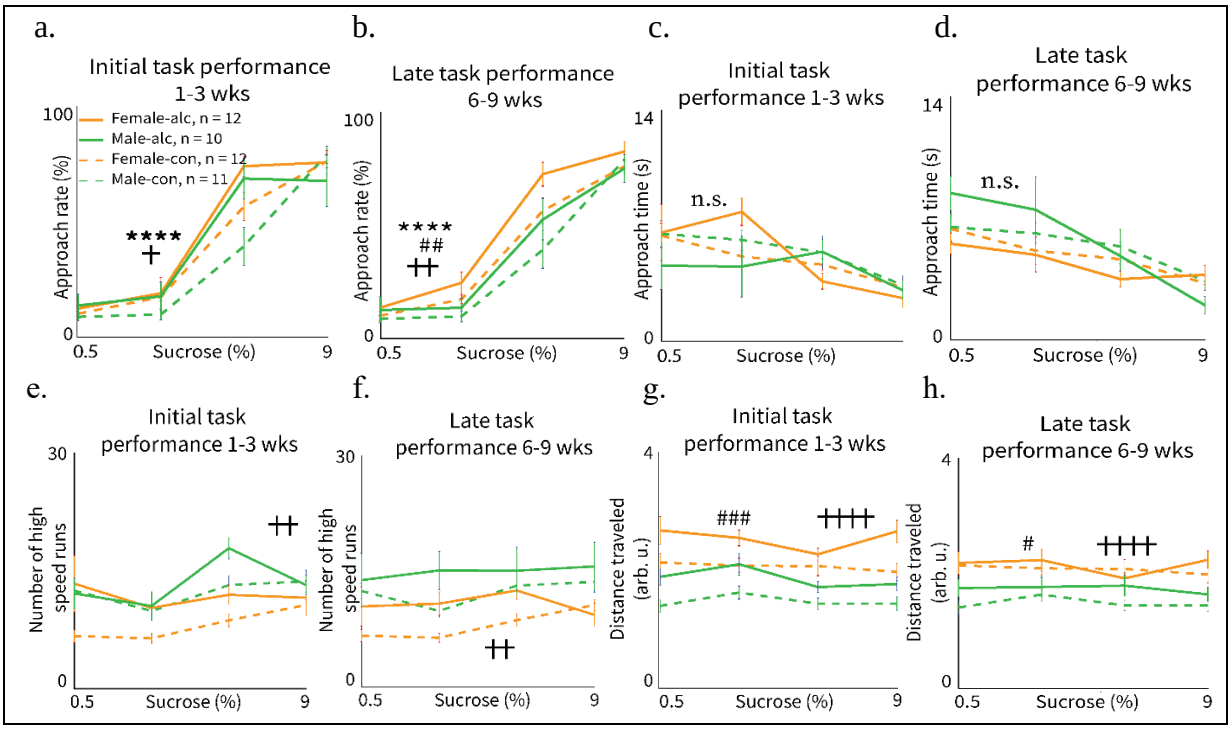



**Figure 17: Effect of alcohol in behavioral features.**
**a.** During the initial performance of the alcohol trade-off task, male and female rats consistently accepted offers with 5% and 9% sucrose while rejecting those with 0.5% and 2% sucrose

(concentration, ****p < 0.0001), with no differences observed between sexes (sex, p = 0.4). However, rats exposed to alcohol exhibited significantly higher approach rates (task type, +p = 0.0178; group X sucrose concentration interaction, p = 0.0025).
**b.** After nine weeks of task performance, all three main effects were significant (sex ##p = 0.0015, condition ++p = 0.01, concentration ****p < 0.0001). The interaction between sex and sucrose concentration was also significant, with females accepting more than males and the control group overall (p = 0.044). Females approached significantly more than males (p = 0.03) when considering both initial and later alcohol task performance groups.
**c.** Approach time recorded during the initial (first 3 weeks) task performance showed a significant main effect of concentration (p < 0.0001), but no other significant interactions when compared to the control group (sex X condition: p = 0.254, sex X concentration: p = 0.2729, task type X concentration: p = 0.7127) or main effects (sex = 0.9775, task type = 0.4457).
**d.** Approach time after prolonged (6-9 weeks) alcohol trade-off task performance continued to show no significant main effects or interactions when compared to the control group. However, there was still a significant response to concentration among the alcohol group (p < 0.0001).
**e-f.** For both the initial and later stages of task performance, the number of high-speed runs showed no significant interactions for sucrose concentration or sex within the alcohol groups. However, there was a notable effect of condition when comparing alcohol and control groups (**a:** ++p = 0.0028, **b:** ++p = 0.0031), as well as a significant effect of sex (**a:** p = 0.0003, **b:** p < 0.0001).
**g-h.** The distance covered during both initial (###p = 0.0004) and later stages (#p = 0.045, RM ANOVA) of task performance was significantly different between sexes, with females traveling greater distances than males, and an overall effect of condition (++++p < 0.0001). There were no significant interactions when comparing initial or late task performance with the control group.

Next, we looked at proportion of sessions with sigmoidal psychometric functions and there was no significant impact of alcohol exposure as there was no significant changes between control and alcohol groups and no sex differences as well (**Fig. 18** one-way ANOVA: male control n = 10 vs. male alcohol n = 10, p = 0.36; female control n = 12 vs. female alcohol n = 10, p = 0.08).

We created radar plots which brings all the behavioral features together to have a better identification of the features affected/shifted more after alcohol exposure as well the individuals who are resilient or vulnerable to the impact of alcohol exposure (**Fig. 19**).

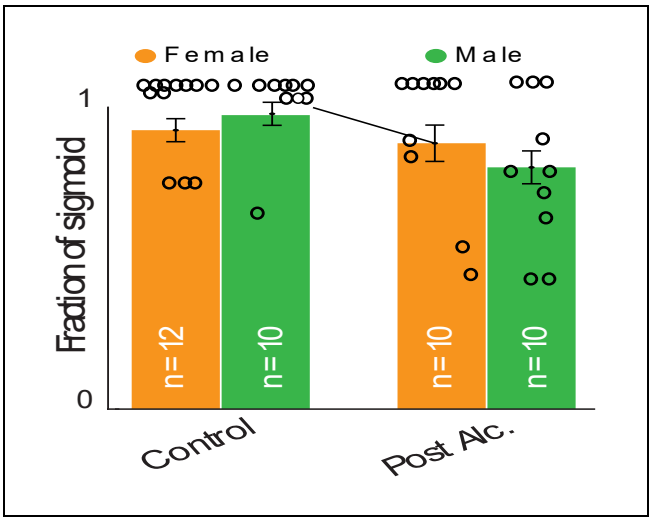



**Figure 18: Sigmoidal psychometric function and clusters.**
The alcohol trade-off task did not significantly affect the sigmoid frequency, which is defined as the proportion of sessions where the approach rate data fit a sigmoid curve rather than a parabolic or undefined curve.

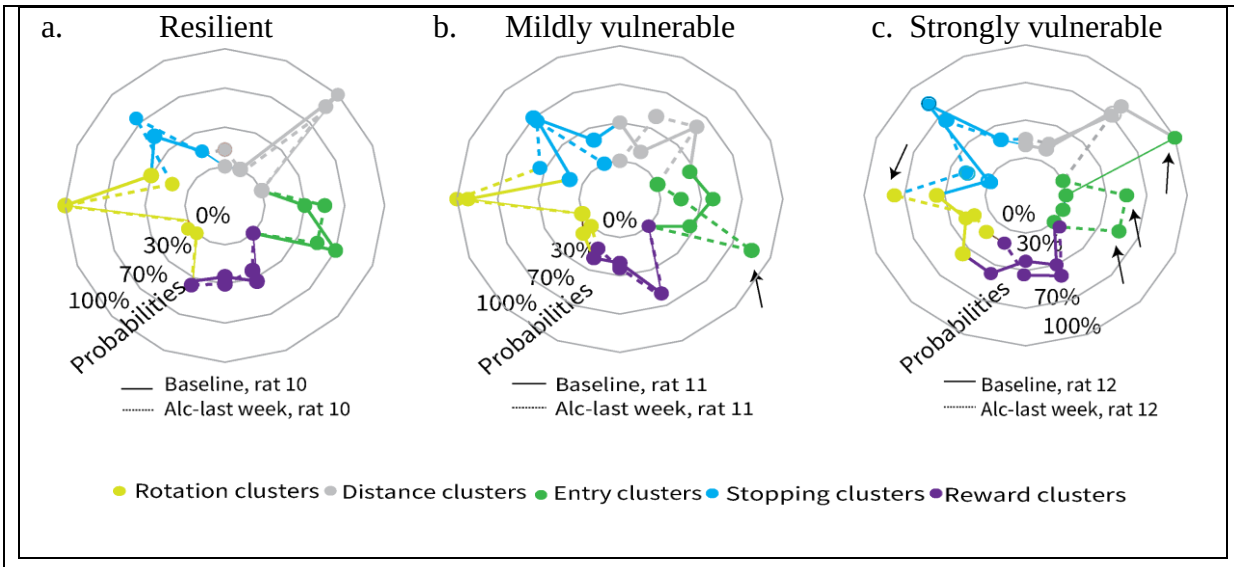



**Figure 19: Radar plots showing resilient and vulnerable population**
**a-c.** Radar plots comparing baseline and alcohol conditions illustrate the behavioral clusters of three individual rats, showing varying degrees of changes in Euclidean distances before and after alcohol trade-off task performance. Some rats maintained consistent cluster probabilities (e.g., left, low), some experienced moderate shifts in cluster probabilities (middle), while others showed significant changes in cluster probabilities, as measured by Euclidean distances. Arrows indicate large shifts.

Briefly, the alcohol experiment revealed that alcohol dependence/addiction impacted decision-making behavior of the female rats and significantly altered sex differences in cost-benefit decision-making. The alcohol trade-off task did not significantly affect the percentage of sessions with sigmoidal psychometric functions compared to the control group. Additionally, the radar plots indicated moderate to significant changes in cluster probabilities, demonstrating shifts in behavioral features and decision-making under the influence of alcohol indicating resilient, mildly vulnerable and heavily affected population.

## E. Discussion

From our experiments we did see the rodents when presented with a combination of reward-cost options, show changes in decision across different levels of rewards and costs and we could also pinpoint when exactly the changes started. We were also able to observe changes in decision-making behavior both in an individual level, across sex and across groups as well.

We observed differences in decision-making behavior using different experimental protocols like oxycodone self-administration and alcohol trade-off. We generated psychometric functions and clusters which helped identify subjects resilient or susceptible to disorders. The clusters and psychometric functions quantified both decision-making and its connected behaviors, changes in these before, during, and after the beginning of a disorder could indicate the disorder's influence on a subject.

Our data revealed significant heterogeneity among individuals in how oxycodone self-administration and abstinence affect decision-making. Though the average psychometric function across abstinent individuals was sigmoidal, this was misleading because about 50% of all sessions during abstinence did not follow a sigmoidal relationship between approach and reward value.

Unlike the oxycodone experiment we provided rats with four different amounts of alcohol solution to choose from during decision-making trials and we identified that unlike oxycodone self-administration, there was no significant impact of alcohol exposure on the proportion of sessions with sigmoidal psychometric functions but, similarly to oxycodone, the percentage of sessions distributed across clusters seemed to vary greatly between the control group and the alcohol group.

We could see significant sex differences with females approaching rate higher than males indicating females getting used to/addicted to alcohol faster and more than males.

We saw from the radar plots that when the clusters were compared between baseline and during alcohol exposure some rats have similar clusters from before and during alcohol exposure which indicated resilient population and some rats showed slightly shifted clusters during alcohol exposure who were considered mildly vulnerable and then greater shift in the clusters indicated highly vulnerable population. Thus, our experiment demonstrated that individual rats are differentially sensitive to the impact of alcohol on decision-making.

# F. Conclusion

This dissertation has provided significant insights into approach-avoid decision-making processes in rodent models, with a focus on how substances like oxycodone and alcohol influence these processes. By employing the Reward-Cost Rodent Decision-making (RECORD) system software, we have been able to understand the complex relationship between costs and rewards that underline decision-making behaviors. The findings reveal significant sex differences in decision-making strategies post-oxycodone administration and during abstinence, highlighting the ways in which addiction and withdrawal impact behavior differently across genders.

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# Curriculum Vitae

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