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Impulsivity or Aversion to Ambiguity? Decision-Making under Uncertainty in Stimulant Use Disorder

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Impulsivity or Aversion to Ambiguity?

Decision-Making under Uncertainty in Stimulant Use Disorder

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy in Neuroscience

by

Zoe Rebecca Guttman

2021

ABSTRACT OF THE DISSERTATION

Impulsivity or Aversion to Ambiguity?

Decision-Making under Uncertainty in Stimulant Use Disorder

by

Zoe Rebecca Guttman

Doctor of Philosophy in Neuroscience

University of California, Los Angeles, 2021

Professor Edythe D. London, Chair

Stimulant misuse and dependence contribute substantially to the global burden of disease. A major component of Stimulant Use Disorder (SUD) is maladaptive decision-making, whereby individuals persist in risky choices that are harmful to themselves and those around them. Decision-making is a complex process that requires an individual to determine which options are worth pursuing. To that aim, the values of possible rewards and costs must be calculated and compared. As most decisions encountered in everyday life present incomplete information about the outcomes of possible choices, individuals have to operate on this uncertainty, which can cause distortions in choice. Individuals with SUD may be especially susceptible to choice biases related

to ambiguity, which arouses negative feelings that can motivate drug use. However, the neural basis of how uncertainty influences decision-making in SUD remains unknown.

The goal of the studies presented in this dissertation was to address this question by combining neuroimaging with computational modeling of decision-making tasks. Studies were performed to compare the behavior and neural function of healthy control participants and those who chronically used stimulants on four decision-making tasks paired with brain imaging. The Balloon Analogue Risk Task (BART), a naturalistic decision-making task, was performed by participants with Methamphetamine Use Disorder (MUD) during functional magnetic resonance imaging (fMRI). A different subset of participants who performed the BART underwent positron emission tomography (PET) for estimation of dopamine D2-type (D2 and D3) receptor binding potential (BP_{ND}). Participants with SUD (cocaine and methamphetamine) performed the Loss Aversion Task (LAT) and also received PET scans. Some participants with SUD also performed the Choice under Risk and Ambiguity (CRA) task to compare aversion to risk (known outcome probabilities) and ambiguity (unknown outcome probabilities), and received fMRI scans for assessment of resting-state functional connectivity (RSFC). Lastly, a delay discounting task (DDT) was performed by participants who performed the CRA task to determine the contribution of risk and ambiguity to intertemporal choice.

The first two chapters present background and methods. Chapter 1 provides a general overview of the neurobiology of addiction and decision-making, with a focus on value computation and how it can be biased. Chapter 2 outlines the tasks, computational models, estimation procedures, and behavioral statistics used in the studies. Brain imaging methods are described in the chapter in which they were used.

Chapter 3 presents the results of using a cognitive model to decompose performance on the BART and associate the resulting parameters with neural function. We found a marked impairment in behavioral updating and adaptive risk-taking in participants with MUD. Risk-taking was negatively correlated with dopamine D2-type BP_{ND} in the striatum and midbrain only in healthy control participants, who also showed nonlinear associations between updating rate and dopamine D2-type BP_{ND} in the insula and medial OFC. No significant relationships between behavioral parameters and dopamine D2-type BP_{ND} were exhibited by MUD participants. However, behavioral updating was correlated with modulation of activation by risk in the dorsolateral prefrontal cortex in both groups, and in the anterior insula only in MUD participants. These findings linked cortical activity and D2-type binding potential to updating behavior during advantageous risk-taking in healthy control participants. In MUD, impairments in adaptive risk-taking and behavioral updating and their lack of association with striatal or cortical dopamine D2-type BP_{ND} suggest D2-type receptor-related deficits in accurately updating behavior under uncertain conditions.

Chapter 4 presents two studies related to loss aversion. The first tested the hypothesis that prefrontal cortical thickness would mediate age-related changes in loss aversion in healthy control participants. The relationship between age and loss aversion followed a quadratic function that was mediated by thickness of the posterior cingulate cortex. The U-shaped function reached a minimum around age 35 before increasing across middle-age, following the developmental trajectory of the cortex and suggesting that thinning of the posterior cingulate cortex may emerge as a contributing factor to loss aversion only once cortical thinning is underway. The second study tested whether loss aversion differed between healthy control and SUD participants and was related to striatal or amygdala D2-type binding potential. In SUD but not in healthy control

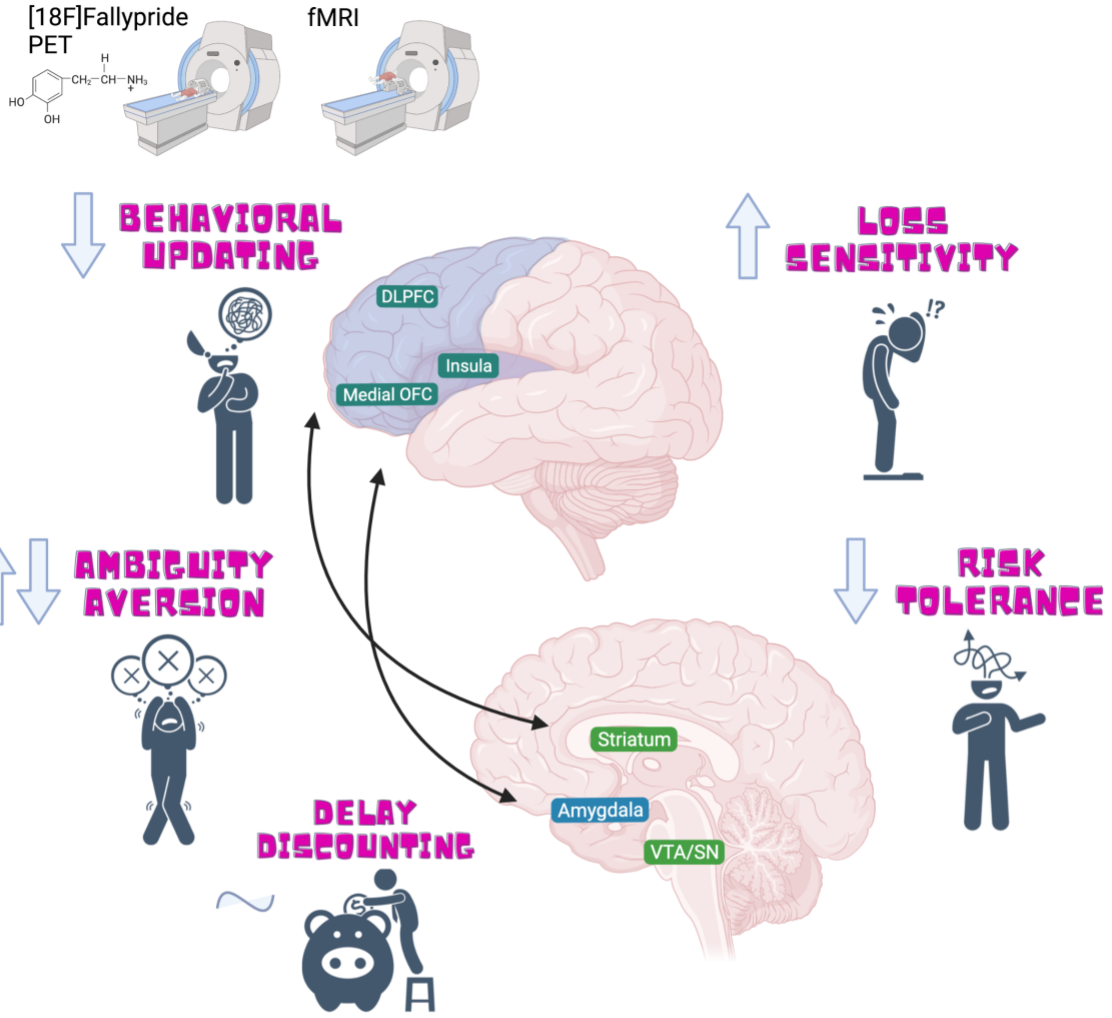
participants, loss aversion and risk tolerance were positively related to striatal D2-type BP_{ND}, establishing a role for D2-type signaling in risky decisions involving loss in SUD, perhaps through neuroadaptations related to drug use.

Chapter 5 introduces ambiguity aversion as an important yet underexplored factor in SUD. Participants with SUD who were in inpatient treatment were more extreme in their aversion to ambiguity but not to risk, and ambiguity aversion was associated with stimulant (methamphetamine or cocaine) use in the 30 days prior to entering treatment. Ambiguity aversion in SUD participants was correlated positively with cortico-amygdalar RSFC and negatively with frontostriatal RSFC. To obtain an accurate assessment of differences in delay discounting between SUD and healthy control participants, a DDT was given in tandem with the CRA task. Group differences in delay discounting were eliminated when accounting for risk aversion. Further, ambiguity aversion and delay discounting showed a correlation that disappeared when risk tolerance was taken into account. These findings suggest that ambiguity aversion—and not the desire for immediate gratification—underlies delay discounting in SUD and that ambiguity aversion is related to frontostriatal function and cortico-amygdalar connectivity.

Taken together, these studies suggest that people with SUD have an impairment in advantageous risk-taking under uncertainty, perhaps due to a difficulty estimating ambiguous risk and an exaggerated response to ambiguity. Our methods demonstrate the advantages of pairing a visceral, naturalistic risk-taking task with computational modeling and economic choice tasks. In combination with brain imaging, these methods can clarify the neural substrates of complex behavior, including those that drive maladaptive choices in addiction. Characterizing the behavior of individuals who use drugs provides a stronger foundation for therapeutic strategies that address decision-making, for instance by introducing ambiguity aversion as a novel target. While

clarifying suboptimal decision-making can refine policy toward addiction, understanding behavioral biases can be applied broadly to improve choices made in everyday life.

Decision-Making Under Uncertainty in Stimulant Use Disorder



(BART)	(BART, LAT, CRA)	(CRA, DDT)
• Marked deficits in **behavioral updating** on the BART • Updating rate related nonlinearly to dopamine D2-type receptor availability in the insula & medial OFC of healthy control participants • Updating rate correlated with modulation of activation by risk in the DLPFC & anterior insula	• Impairments in adaptive **risk-taking** during **loss** & uncertainty • Risk-taking on the BART related to midbrain & striatal dopamine D2-type receptor availability only in healthy control participants • Loss aversion & risk tolerance related to striatal & amygdala dopamine D2-type receptor BPND only in SUD	• More extreme values of **ambiguity aversion** • Ambiguity aversion associated positively with cortico-amygdala RSFC & negatively with frontostriatal RSFC • Ambiguity aversion correlated with **delay discounting** • Group differences in delay discounting disappear when accounting for risk tolerance

Tasks: BART = Balloon Analogue Risk Task, LAT = Loss Aversion Task, CRA = Choice under Risk and Ambiguity Task, DDT = Delay Discounting Task. Brain imaging: RSFC = resting-state functional connectivity. Brain regions: DLPFC = dorsolateral prefrontal cortex, OFC = orbitofrontal cortex, VTA/SN = Ventral Tegmental Area/Substantia Nigra.
Created with BioRender.com

DEDICATION

For my cousin, Bradley Bongar, the coolest guy around.
02/07/1983 – 05/02/2019

And for all those still sick and suffering.

The dissertation of Zoe Guttman is approved.

Catherine Sugar

Paul Glimcher

Craig Fox

Martin Monti

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2021

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I would first like to acknowledge the research participants who participated in these studies. Without their dedication and willingness to help progress our understanding of addiction, our research would never be possible. While we perform studies in the laboratory, it is the hope of most scientists—including this one—that our research reverberates beyond the bench. Addiction is a torrent of pain and suffering, and I hope that this work can in some way contribute to helping people understand and perhaps recover from what is a seemingly hopeless state of mind and body.

I would also like to acknowledge the numerous sources of funding that I was lucky enough to receive, including awards from the UCLA Brain Research Institute, a Translational Neuroscience of Drug Abuse Training Grant, and a National Research Service Award Predoctoral Fellowship. Much of this funding comes from the National Institutes of Health and I recognize how crucial federal research support has been. Without the privilege of federal funding, this and much research would not be completed.

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Aggarwal A, **Guttman Z**, Wagner L, Tam K (*in review*) Plug and Chug: Strategies to Remediate California's Unplugged Oil and Gas Wells.

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CHAPTER ONE

Neural Underpinnings of Maladaptive Decision-Making in Addictions

1.1 Addiction and Decision-Making

Substance use disorders have been linked with the propensity to make maladaptive decisions, and individuals with addictions persist in harmful and even destructive behaviors despite negative consequences, often against their own desires to resist. Suboptimal choices can reflect problems in decision-making, which requires the integration of various neural functions [1]. Of particular interest is reward valuation, a process by which an individual computes and compares the values of alternatives in order to select the most advantageous option [2]. Reward valuation is subject to modulation by various factors, such as the timing of reward receipt [3], the risk and uncertainty involved [4], internal signals, including autonomic [5] and affective responses [6], environmental cues [7], and social influences [8]. These factors produce predictable choice biases in healthy individuals [9], but subjective valuation and how it guides choice is disordered in addiction [10,11]. This chapter focuses on departures from normative choice behavior in individuals with addictions, and how these problems are linked to abnormalities in brain function.

The chapter begins with an overview of the neurobiology of reward-based decision-making, focusing on mesocorticolimbic and corticostriatal circuitry, and then presents a description of three general paradigms that are used in addiction research to assess decision-making. The rest is organized around specific modulators of reward value: uncertainty, temporal delay, and internal and external factors. Each section briefly presents certain relevant tasks, information regarding how individuals with substance abuse disorders perform on these tasks, and the brain structures and neural circuitry involved. Although there is a wealth of preclinical literature on this topic, the present chapter is limited to human neuroimaging research on decision-making. Finally, the implications and potential future directions of these areas of exploration are discussed.

1.2 Neurobiology of Decision-Making

Value-based decision-making involves a distributed network of cortical and subcortical areas. Abnormalities in brain structure and neural circuitry related to performance of addicted individuals on choice tasks have been identified. The focus has been on frontolimbic systems, specifically mesocorticolimbic and corticostriatal circuitry [12,13].

1.2.1 Reward processing

Behaviors that increase evolutionary fitness tend to be repeated, and therefore function as rewards [14]. Because natural rewards and drugs of abuse act on the reward circuitry of the brain in similar ways [15], drugs can exert powerful effects that bias behavior. Central to this action is the mesolimbic dopamine system, which has long been implicated in reward processing [16-19] and plays a crucial role in habitual and goal-directed behaviors [20]. Within this system, midbrain dopamine neurons project to the ventral striatum, other limbic regions, such as the amygdala and hippocampus, and the prefrontal cortex (PFC) [21]. All drugs of abuse, whether directly or indirectly, increase synaptic dopamine in the ventral striatum, and modulation of dopaminergic signaling in the mesocorticolimbic pathway is likely a central mechanism by which decision-making is biased in addiction [22,23].

1.2.2 Reward valuation

Economists have long reasoned that, in order for different options to be compared, their values must be represented on a common scale. These subjective values should be encoded in the brain, and functional magnetic resonance imaging (fMRI) has identified brain regions where activation, indicated by the blood-oxygen level dependent (BOLD) signal, scales with subjective

or objective reward values. The brain regions most consistently activated during the encoding of value are the ventral striatum and medial PFC, including the orbitofrontal cortex (OFC) [24-26]. The ventral striatum projects to the medial PFC, and activity in both regions scales with the magnitude and probability of expected rewards [27,28]. The OFC, densely connected with the basolateral amygdala and nucleus accumbens, is implicated in addiction through its role in evaluation of economic value, associative learning, and habit formation [29-31].

1.2.3 Reward-based choice

A distributed network of cortical and subcortical regions contributes to reward-based decision-making (**Fig. 1.1**). Reward valuation in the ventral striatum and medial PFC is modulated by uncertainty, which involves processing in the anterior cingulate cortex (ACC) and insula [32,33]. The ACC and insula share bidirectional connections [34] and are implicated in a variety of functions related to decision-making, such as risk and error awareness [35,36], performance monitoring and model updating [37,38], and, through connections with the ventromedial PFC, the integration of visceral and affective information into choice [39,40]. Cognitive control tends to rely on the dorsolateral PFC [41,42], which is crucial for the maintenance of goal values [43]. The influence of the dorsolateral PFC on valuation is especially relevant for addictions because of its hypothesized role in self-control [44].

Much of this frontoparietal circuitry operates inefficiently in addiction [12,45], and research participants with drug use disorders exhibit structural differences in this circuitry compared to healthy control participants [46-48]. This chapter focuses on the neural circuitry of reward valuation; brain function related to choice selection and learning is not covered, although both have implications for addiction. Very generally, acting upon the appropriate choice is thought to involve

the lateral PFC and areas of the parietal cortex [1,2], and the updating of values through learning, such as through prediction errors [49], relies on dopaminergic function in the ventral striatum and midbrain [50].

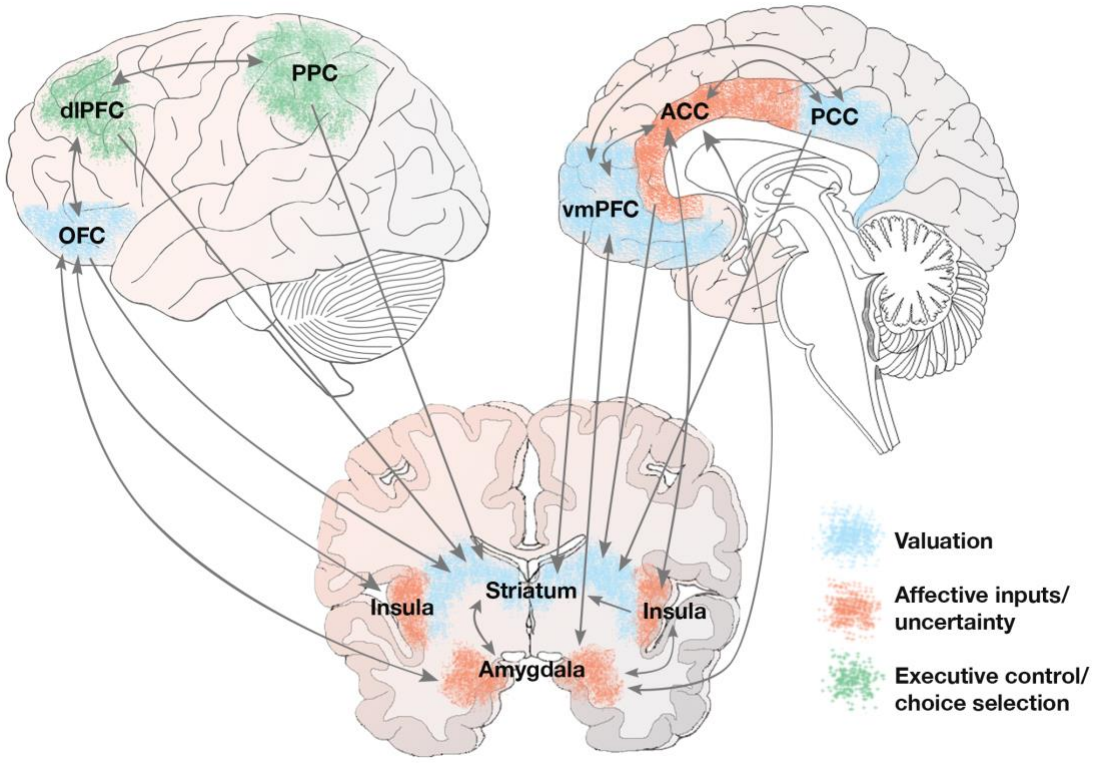

Figure 1.1. Decision-making circuitry. Decision-making relies on a converging network of cortical and subcortical regions. *Blue areas*: reward valuation is primarily associated with the ventral striatum, ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), and posterior cingulate cortex (PCC). *Red areas*: the amygdala, insula, and anterior cingulate cortex (ACC) are involved in processing uncertainty and emotional inputs into choice. *Green areas*: the dorsolateral cortex (dlPFC) and posterior parietal cortex (PPC) are involved in executive control considerations and choice selection.

1.3 Decision-Making Paradigms in Addiction

Choice tasks relevant to addictions can be broadly grouped into three categories: (1) those that present direct choices for real drug, such as self-administration paradigms, (2) those that present choices for hypothetical drug rewards or drug-related cues, and (3) those that test behaviors

considered intricately linked to the risk of developing and/or maintaining addictions, including risk-taking and decision-making in the face of uncertainty. The present review briefly covers these three general paradigms and then continues with a consideration of modulators of value.

1.3.1 Drug Choice

Drug choice procedures use self-administration in the laboratory to present competition between actual drug and alternative reinforcers, such as money or food [51]. Notably, the choice to self-administer a substance is modulated by complex interactions [52], especially motivational contexts such as craving [53], which should be considered. Drug choice procedures have been paired with neuroimaging to investigate the neural factors that influence drug choice, and have been used to evaluate a potential dopaminergic deficit.

While a deficit in striatal D2-type dopamine receptor availability, observed using positron emission tomography (PET), is a general finding across substance use disorders [54], striatal D2-type dopamine receptor availability is not associated with heightened cocaine choice over monetary reward in the laboratory [55]. However, in cocaine-dependent participants, amphetamine-induced dopamine release does show a negative relationship with the preference to self-administer cocaine rather than monetary reward [56]. Thus, the choice to self-administer cocaine is apparently associated with phasic striatal dopamine release. Although no difference in striatal D1 receptor availability has been observed between healthy control participants and those who use cocaine controls, D1 receptor availability in the ventral striatum is negatively associated with the choice to self-administer cocaine [57]. Compared to healthy controls, people who misuse heroin also display lower striatal D2-type receptor availability and less dopamine release, measured after methylphenidate administration, although neither is predictive of choice to self-administer heroin [58]. These results,

which point to a dopaminergic deficit related to drug choice, link low dopamine release with the preference to self-administer cocaine.

1.3.2 Drug-related choice

Similar paradigms that use virtual rewards or drug-related stimuli can be highly informative, especially because drug-related cues can intensify decision-making deficits [59]. These paradigms offer an advantage over actual drug procedures, which are ethically not possible when participants are in treatment or long-term abstinence. For example, in the drug-picture procedure, participants choose between viewing cocaine-related or affectively positive, negative, and neutral pictures [60]. Choice to view drug-related pictures is related to both current and future drug use, especially when outcomes are probabilistic rather than certain [61]. A role of dopamine in this paradigm is inferred from the finding that people who misuse cocaine and are carriers of the 9R-allele of the dopamine transporter gene (DAT1) are more reactive to drug-related reinforcement, measured by event-related potentials, self-reported valence and arousal, simulated cocaine choice, and fMRI during exposure to cocaine-related and unrelated stimuli [62]. Compared with the 10R-allele, the 9R-allele is related to greater expression of the dopamine transporter in the striatum [63], presumably leading to a shorter half-life of extracellular dopamine, and less activity at presynaptic dopamine D2-type receptors (autoreceptors) that inhibit phasic dopamine release [64]. Greater phasic dopamine release in the striatum may explain why 9R-allele carriers show heightened cue-reactivity to drug-related reinforcement.

The authors are aware of few other paradigms that use hypothetical drug rewards as alternatives in choice tasks. Some studies using delay discounting tasks, which are described below, also have used hypothetical drug rewards as options [65-67]. The main results point to steeper

discounting of hypothetical drug rewards than monetary rewards, as would be expected.

1.3.3 Decision tasks

Other tasks that do not directly involve choices for drug or drug-related stimuli investigate components of decision-making that contribute to the development and maintenance of addictive disorders. These include tasks that assess risk-taking and advantageous decision-making. The following sections consider these types of choice tasks, and how varying the costs of rewards affects the computation of value, and therefore choice.

1.4 Choice under Uncertainty

Because choices in daily life rarely contain complete information about potential costs and benefits, most choices involve a balance between risk and reward. This balance is skewed in individuals with substance abuse disorders, who engage in risky behaviors related to drug-taking and make disadvantageous choices under uncertainty in the laboratory [68]. A "risky" decision typically connotes one that involves danger or a high probability of negative outcome, but this definition of risk may differ from those used in the laboratory [69]. Economists define a choice containing risk as one between options with different distributions of known outcomes, and laboratory tasks can distinguish between uncertainty due to risk, with known outcome probabilities, from uncertainty due to ambiguity, with unknown outcome probabilities. Decisions under uncertainty are especially relevant because they go against traditional decision theories that state that knowledge of probabilities should not change stated preferences [32,70]. These decisions are also notoriously aversive: people make choices that go against their own benefit just to reduce uncertainty [71].

This section provides an overview of brain function relevant to decision-making under risk and ambiguity in individuals with drug use disorders. Decision-making under ambiguity is discussed by focusing on two of the most commonly used uncertainty tasks: the Iowa Gambling Task (IGT) [72] and the Balloon Analog Risk Task (BART) [73] and then tasks that present clear outcome contingencies are reviewed. These typically take the form of probabilistic gambling tasks and assess uncertainty due purely to risk, following the relatively recent merging of neuroscience with behavioral economics [74]. Finally, studies that directly compare uncertainty under conditions of risk and ambiguity are discussed.

1.4.1 Decision-making under ambiguity

Both the IGT and the BART incorporate elements of reward, punishment, learning, and adaptive risk-taking. On the IGT, participants progress through trials by picking cards from four different decks. Healthy participants typically learn to identify decks that deliver small immediate gains and small losses as leading to higher average gain, and they alter their behavior to sample more from the advantageous decks. The IGT is thought to measure choice under ambiguity at the start of the task when stimulus-outcome contingencies are still being learned, but to involve risk alone after the contingencies have been learned [75]. The ventromedial PFC is especially implicated in this sort of adaptive decision-making, as people with ventromedial PFC lesions show impairment on the task [72], as do many people who misuse substances [76] and at-risk populations [77].

Findings from studies of region cerebral blood flow, measured using PET and ^{15}O-water, suggest that in individuals with substance abuse disorder performing the IGT, dysregulated striatal and ventromedial PFC/OFC activity is likely related to reward anticipation/valuation, while lower dorsolateral PFC activity contributes to dysregulated executive control inputs into reward

valuation. In healthy control participants, decision-making accompanies activation in the OFC, dorsolateral PFC, ACC, insula, inferior parietal cortex, and thalamus predominantly in the right hemisphere, and the cerebellum predominantly in the left [77]. Individuals who chronically use marijuana perform worse than controls on a variant of the IGT that focuses on punishment, and exhibit stronger activation than controls in the ventromedial PFC during the standard IGT [78]. People who misuse cocaine also exhibit performance below control levels and greater activity than controls in the putamen and OFC, but less activity in the dorsolateral and medial PFC, during choice [79]. A similar pattern has been observed in abstinent marijuana users, who exhibit less activation in the lateral OFC and dorsolateral PFC compared to control participants [80].

Certain fMRI studies have investigated brain activity in response to wins and losses on the IGT and have the potential to elucidate differences in approach and avoidance behavior related to rewards [81]. People who chronically use marijuana may be less sensitive to negative feedback, as they exhibit weaker responses to losses in the ACC and medial frontal cortex compared to controls, and do not show a correlation between task performance and activity in the ACC, ventromedial PFC, and rostral PFC, as is demonstrated in controls [82]. In response to wins, people who chronically use marijuana also respond more strongly in the right OFC, superior temporal gyrus, and insula than controls, and superior temporal gyrus activity is correlated with higher marijuana use in the 6 months following testing [83]. These observations of dysregulated responses to outcomes suggest that individuals with substance abuse disorders may have increased approach and decreased avoidance behaviors that could translate to enhanced reward-seeking and reduced sensitivity to negative outcomes.

Similar deficits are seen in the brain function of individuals with substance abuse performing the BART, in which the participant makes a series of choices either to pump a virtual

balloon to increase monetary reward or to stop pumping and "cash out", retaining the earnings from the trial. If the balloon pops, the rewards accrued on the trial are lost. Risk, defined as probability of explosion, increases with each pump, and participants effectively set the level of risk as they pump. In this way, risk preferences are determined in a naturalistic setting, which is enhanced by the visceral states surrounding the repeated pumping of the balloon and threat of explosion [69]. Risk on the BART differs from that on the IGT, in which risk is defined by stimulus-outcome contingencies. The task has shown evidence of ecological validity in some studies: the average number of pumps correlates with self-reports of substance use, drinking, and smoking [84,85], although in some cases, substance users take less risk on the BART than controls [86-88].

When participants take risk on the BART during fMRI, risk level parametrically modulates activation in a set of mesolimbic-frontal regions, including the midbrain, striatum, anterior insula, dorsolateral PFC, and ACC/medial frontal cortex [89]. Moreover, in healthy controls, striatal dopamine D2-type receptor binding potential is correlated positively with modulation of activity in the ventral striatum when participants decide to cash out (take reward), but negatively with modulation of dorsolateral PFC activation during pumping (risk-taking) [90]. Moreover, fractional anisotropy of the white-matter pathways connecting the PFC, insula, and midbrain to the striatum is positively correlated with risk-taking and task performance, and with parametric modulation of activation in the anterior insula, putamen, ACC, and right medial frontal gyrus by risk [91]. These results demonstrate the importance of optimal striatal dopaminergic function and efficient mesocorticolimbic circuitry in modulating striatal and prefrontal activity for advantageous decision-making on the BART.

The BART has also been used to investigate corticostriatal circuitry in individuals who use methamphetamine. Compared to control participants, individuals with Methamphetamine

Dependence exhibit greater modulation of ventral striatal activation, but less modulation of dorsolateral PFC activation, by risk and reward [86]. They also exhibit stronger resting-state functional connectivity (RSFC) of the midbrain with the putamen, amygdala, and hippocampus, and midbrain connectivity is inversely related to dorsolateral PFC sensitivity to risk during the BART [86]. This enhanced connectivity of mesostriatal and mesolimbic pathways associated with diminished sensitivity of the dorsolateral PFC is not observed in control participants. However, modulation of dorsolateral PFC activation by risk is positively related to RSFC of the dorsolateral PFC with the striatum in control participants, a pattern that is not observed in Methamphetamine Dependence [86]. In contrast, RSFC of the midbrain with the striatum, OFC, and insula is negatively related to striatal dopamine D2-type receptor availability in participants with Methamphetamine Dependence, a pattern opposite to that seen in control participants [92]. RSFC of the midbrain and ventral striatum also is positively related to cognitive impulsivity in those with Methamphetamine Dependence, but negatively related in control participants [92]. Thus, mesostriatal and mesolimbic circuitry may function adaptively in control participants, but maladaptively in those with Methamphetamine Dependence.

In sum, converging evidence from the IGT and BART suggests that impaired brain function in mesolimbic-frontal regions in substance abuse contributes to aberrant decision-making under uncertainty. IGT performance points to dysregulated reward sensitivity in the striatum and ventromedial PFC/OFC and hypofunction of the dorsolateral PFC, which is less active during choice, compared to activity in healthy controls [78-80]. Findings obtained with the BART reveal hypersensitivity to risk and reward in the ventral striatum and hyposensitivity in the dorsolateral PFC of individuals with substance abuse disorders; these sensitivities are associated with baseline function of mesocorticostriatal striatal circuitry, which functions adaptively in healthy controls and

exhibits abnormalities in those who misuse drugs [86]. The associations between striatal dopamine D2-type receptor availability, mesocorticostriatal circuitry, and measures of impulsivity [92-94] underscore the crucial role of dopamine D2-type receptor signaling in advantageous decision-making and the importance of dopamine functions in dysregulated mesocorticostriatal circuitry to influence choice under ambiguity.

1.4.2 Decision-making under risk, without ambiguity

Tasks in which outcome probabilities are known typically take the form of probabilistic gambling tasks, such as lottery choice tasks that present choices between options with different probabilities of gains and/or losses. As trials are independent, there is no opportunity for learning, and other confounding functions, such as cognitive flexibility, working memory, reinforcement, and loss and gain sensitivity [69,95], can be avoided. These types of procedures can be based on economic theory and decomposed into specific constructs, such as risk, which can be parametrically varied to isolate their influence on decision-making.

It can be beneficial to investigate the neurological markers of specific risk preferences for their role in the development and maintenance of addiction. In particular, the ACC and insula have been implicated in risk tendencies that depart from classical risk neutrality. That ACC error-likelihood and expected risk signals are seen in risk-averse, but not risk-tolerant individuals, suggests that people more tolerant to risk may be less sensitive to error predictors [96]. Risk-takers may also be less motivated by safer options than risk-averters, as neural activity in frontal, medial temporal, and striatal areas is positively correlated with risk in risk-seekers, but with expected value in risk-averters [97]. A role of the ACC and insula in non-normative decision-making is further supported by the tracking of activity in these regions with reward probabilities, and also the

correlation of activity in these regions with specific "irrational" risk tendencies. Specifically, activity in the ACC and insula correlates with the nonlinear transformation of probabilities [98], which refers to larger risk-seeking in situations with a low probability of success and risk-avoidance in situations with a high probability of success [9].

Neural activity in the ACC and insula is associated with avoiding loss and risk [36,99,100], and activation in these regions during decision-making under risk in is impaired substance users. While playing a monetary game called "Chicken," in which trials offer either guaranteed reward or conflict between increasing reward and risk of penalty, patients diagnosed with both alcohol and cocaine dependence exhibit less ACC activity than controls on trials that include risk [101]. Young adults who occasionally use stimulants, and who therefore may be at risk for future substance abuse, exhibit less activity in the ACC, PFC, insula, and dorsal striatum during a risky gambling task compared to control participants, and the attenuation in ACC activity is inversely related to past drug use [102].

Activity in the ACC and insula may play a role in thwarting maladaptive risky behavior, and these signals may malfunction in substance abuse. Findings from a study of current and former users of both opiates and amphetamines show that lower ACC activity is related to greater risk propensity during performance of the Cambridge Risk Task [103]; this is true as well for abstinent polydrug users performing the Rogers Decision-Making Task [104]. During the Risky Gains Task, individuals with Methamphetamine Dependence exhibit less ACC activity and are more likely to make risky decisions following losses compared to controls [105]. Activity in the ACC and insula is related to propensity to avoid risk following loss in healthy controls during the Cambridge Risk Task, but this relationship is absent in those who use opiates, who also show abnormal OFC activity associated with risk preferences [106]. These studies demonstrate potentially deficient

signaling, especially in the ACC, to inhibit risk in substance abuse. Such signaling may be necessary to prevent disadvantageous behavior by biasing choices to minimize cost and maximize gain [107].

Findings from longitudinal studies suggest that individuals with Methamphetamine Dependence have an impaired ability to discriminate between safe and risky decisions, which may reflect altered insula signaling. For example, participants with Methamphetamine Dependence who later relapsed displayed lower activation in the bilateral striatum, bilateral insula, left inferior frontal gyrus, and left ACC in response to winning and negative feedback on a reinforcement learning task, compared to their non-relapsing counterparts [108]. Those with Methamphetamine Dependence who remained abstinent 1 year after testing displayed lower insula activation during safe decisions compared to risky decisions on the Risky Gains Task, whereas those participants who relapsed displayed similar insula activation during both safe and risky choices [109].

1.4.3 Risk versus ambiguity

Certain studies have directly compared the neural circuitry involved in decisions under ambiguity and risk. Preference for choices containing ambiguity can be predicted by lateral PFC activity [4], and greater activity in the OFC and amygdala is exhibited during ambiguous decisions than decisions with only risk [110]. In contrast, activity in the posterior parietal cortex predicts preference for choices involving risk [4], and activity in the dorsal striatum is higher for these choices than for ambiguous choice trials [110]. Whether ambiguous choices are just a more complicated version of risky choices, or whether these two forms of uncertainty reflect distinct processes, is still an open question. However, subjective value is correlated with activation in the striatum, medial PFC, posterior parietal cortex, and amygdala during ambiguous as well as during risk trials

(although the trend in the posterior parietal cortex did not reach significance for risk trials) [111]. These findings suggest that, at least at the level of value representation, both types of uncertainty are represented by a unified system.

There is evidence that individual with substance abuse disorders have dysregulated circuitry involved in mediating between uncertainty due to risk and ambiguity. The learning of reward contingencies necessary to transition from ambiguous to risky choice on the IGT is delayed in alcohol-dependent patients, and this effect may be due to an impairment in properly estimating the probability distributions of alternative choices [112]. Individuals who chronically use marijuana and were deprived of marijuana value uncertain rewards less than healthy controls on the Reward Uncertainty Decision-Making Task, and this uncertainty aversion is positively correlated with marijuana use [113]. That participants with Methamphetamine Dependence have also been shown to be risk averse on the BART [86] implicates uncertainty aversion as a potential factor in decision-making abnormalities exhibited in addiction.

1.5 Intertemporal Choice

The delay to receipt is a consistent modulator of reward value [114]. Options received sooner in time are naturally valued more than those that are delayed, and the extent of such delay discounting differs among individuals [3]. Contrary to predictions from traditional exponential discounting models [115], people tend to overvalue immediate rewards (Kahneman & Tversky, 1979) and reverse their preferences depending on the specific temporal dynamics [116]. Asked to choose between $15 immediately or $16 tomorrow, most people would choose $15; asked to choose between $15 in 99 days or $16 in 100 days, most would change their answer to the later option [117,118]. This time inconsistency may arise from competition between two distinct decision-making systems, an

"impulsive" limbic and "executive" prefrontal system [119,120], although evidence points to a unified system [44,121-123], in which inputs that differentially contribute to valuation feed into a final estimate of value [2,124]. Preference reversals are especially relevant for addictions, which feature the breaking of resolutions to abstain from addictive behaviors [125].

1.5.1 Delay discounting in addictions

Discounting is exaggerated in individuals with addictions, whether to alcohol, drugs, food, or gambling [126]. The ventral striatum and frontoparietal regions, specifically the medial PFC and posterior cingulate cortex, have been consistently implicated in intertemporal choice [123,127]. Notably, brain function differs between healthy control participants and those with substance abuse during delay discounting tasks. In sober alcoholics, discounting correlates negatively with activity in the lateral OFC and positively with activity in the dorsal PFC and posterior parietal cortex [128]. Alcohol use severity, however, correlates with steepness of discounting and activity in the supplementary motor cortex, insula, OFC, inferior frontal gyrus, and precuneus [129]. Participants with Methamphetamine Dependence exhibit less activity than control participants in the precuneus, right caudate, ACC, and dorsolateral PFC during decision-making on a delay discounting task, and exhibit a positive correlation between discounting and activity in the dorsolateral PFC, posterior parietal cortex, posterior cingulate cortex, and amygdala [130]. Control participants show significantly greater activation in the left dorsolateral PFC and right intraparietal sulcus on hard trials than on easy trials (i.e. large versus small differences in subjective value of alternatives), but participants with Methamphetamine Dependence show as much activation on easy trials as on hard trials, suggesting that cortical processing related to intertemporal choice may be less efficient in participants with Methamphetamine Dependence than controls [131]. Activity in

the dorsolateral PFC may thus be crucial for mediating decisions between more difficult alternatives, and may be impaired in individuals with addictions. Indeed, in what can be assumed to be a difficult choice, participants who chronically use cocaine exhibit greater activity in the dorsolateral PFC when choosing future monetary reward over immediate cocaine [67].

Differences in delay discounting are also related to indices of dopaminergic function. Both discounting behavior and dorsal PFC and posterior parietal cortex activation during task performance can be predicted by variation in the Val158Met polymorphism of the catechol-*O*-methyltransferase gene, which influences dopamine metabolism [128]. In addition, lower striatal D2-type receptor availability, measured with PET, is related to steeper discounting in participants with Methamphetamine Dependence [132] and pathological gamblers [133]. These findings demonstrate that, in controls, greater dopamine metabolism by COMT, which should reduce dopamine levels primarily in the PFC [134], and low striatal D2-type receptor availability in Methamphetamine Dependence contribute to steeper delay discounting. Thus, optimal dopamine function is likely necessary for maintaining value in the face of delay cost.

1.5.2 Vulnerability to addiction and therapeutic outcome

That delay discounting is a common feature across addictions suggests that it may represent an intrinsic feature of addiction and thus be a tractable therapeutic target—although, imprecisions in how delay discounting is estimated raises questions as to the motivations behind heightened preferences for immediacy. For instance, the uncertainty inherent to the delay is often not taken into account and can substantially alter interpretation of results [135-139].

A natural question that arises is whether steep discounting precedes or results from addiction. Chronic drug use likely affects the rate of discounting [e.g., Yi, Johnson, Giordano,

Landes, Badger and Bickel (140)], but converging evidence indicates that individual differences in delay discounting also predict subsequent drug use [e.g., Sheffer, Christensen, Landes, Carter, Jackson and Bickel (141)]. Notably, various behavioral approaches [142], including working memory training [143], visualization of near future episodic events [144], and orientation to the future by forward planning [145], reduce preference for immediate rewards. It would be important to continue investigating the extent to which reduction of delay discounting by such methods can alter therapeutic outcome.

1.6 Internal Influences on Choice

Internal signals, including autonomic, affective, and self-reflective processes, can alter valuation and thereby influence choice. Autonomic responses exert reciprocal influences on decision-making; cognitive processes influence bodily states, which in turn alter cognitive processes and generate interoceptive signals that contribute to affective feeling states and decision-making [5]. These internal signals are necessary for self-monitoring and self-awareness, which are crucial for adaptive decision-making [146]. As discussed below, the integration of autonomic and affective processes with cognitive factors to influence decision-making is disrupted in individuals with addictions.

1.6.1 Bodily states

Physiological responses to emotional signals are necessary for adaptive choice [147]. They are likely integrated with cognitive information through the insula, ACC, amygdala, and somatosensory cortex [40], and integration in all these areas relies on activity in the ventromedial PFC [72]. During decision-making, abstinent drug users perform below control levels on gambling

and decision-making tasks, and have lower skin conductance and smaller heart rate responses while performing both tasks [148].

Indeed, individuals who use substances have been characterized on the basis of physiological responses while performing the IGT. Some are unimpaired on the task, while others display deficits as severe as those of patients with ventromedial PFC lesions [76]. Of those with deficits, some seem insensitive to positive as well as negative outcomes, as they exhibit blunted anticipatory skin conductance responses to both reward and punishment [149]; others seem hypersensitive to reward, as they perform normally with regard to punishment, but display heightened physiological responses to reward magnitude [150]. These results demonstrate that faulty physiological responses, associated with dysfunction in the ventromedial PFC, are related to aberrant decision-making by individuals who use drugs.

Integration of visceral experiences also relies on amygdala function [151]. Abstinent alcoholics with diminished IGT performance have smaller amygdala volume than controls [152], and adolescents at risk for substance abuse have less amygdala, insula, and ACC activation on the BART compared to controls [153]. These differences in activity may reflect emotional responses to the visceral motivations of the task. Integration of somatic and visceral states into the decision-making process could thus be altered and may underlie decision-making impairments seen in addiction, from reductions in sensing risk [147] to overvaluation of visceral motivations [154].

The insula has been implicated in interoception and the influence of autonomic functions on cognition [39]. Disruption of interoceptive signals is considered central to decision-making deficits observed in addictions [155,156], especially in relation to approach and avoidance behaviors [157]. It has been proposed that an insula-dependent system integrates experience and recall of

conscious pleasure derived from the interoceptive effects of drug use into the decision-making process [158].

Studies of individuals with Methamphetamine Dependence have provided supporting data. When making decisions on a task with a positive interoceptive component, participants with Methamphetamine Dependence exhibit less anterior insula, dorsal striatum, and thalamus activity than controls, and the correlation between anterior insula activity and reaction time is positive in controls, but negative in Methamphetamine Dependence [159]. Those with Methamphetamine Dependence also exhibit less posterior insula and ACC activity than controls during a choice task with an aversive interoceptive experience (breathing load); that attenuation of neural activity is exhibited across trials, regardless of error and reward rates, suggests that they are related to the interoceptive component of decision-making on the task [160]. Thus, ineffective processing of interception, particularly in regions of the insula, may underlie an inability to integrate interoceptive information into decisions, especially in response to negative experiences.

1.6.2 Affective states and emotion regulation

Affective states are widely considered to be linked with addictive behavior, both for conferring risk and for contributing to the maintenance of drug use [161]. Emotionally biased decisions represent one of the "irrationalities" observed in behavioral economics [154] and may be exaggerated in addictions through impairment of neural circuitry that mediates emotional contributions to choice. For instance, choice behaviors can be associated with specific affective states, such as sadness, which enhances preference for risk [162]. The influence of affect could thus be enhanced in addictions.

Individuals who use drugs display difficulties with emotion regulation, which relies on activity in the dorsal inferior frontal gyrus and amygdala [163]. Compared to control participants, those with Methamphetamine Dependence exhibit higher trait anxiety and attenuated anterior insula and inferior frontal gyrus activity during a choice task, and attenuation in the anterior insula and inferior frontal gyrus is negatively correlated with trait anxiety [160]. Thus, anxiety in Methamphetamine Dependence seems related to a diminished allocation of cognitive resources to the decision-making process. If executive functions related to emotional choices are disrupted, the impact of moods, emotions, or an immediate affective state on decision-making could be strengthened. Participants with Methamphetamine Dependence also have impaired emotional recognition and processing that is linked to dopamine D2-type receptor availability in the ACC and anterior insula [164]. Further, emotion dysregulation is related to dopamine D2-type receptor availability in the amygdala of both control participants and those with Methamphetamine Dependence [165]. This association suggests that dopaminergic function contributes to individual differences in susceptibility to emotional influences during decision-making.

1.6.3 Insight

The disconnection between perception and reality frequently observed in addiction, perhaps most clear in the tendency to underestimate addiction severity, negative consequences, and the need for treatment, can bias choices towards the maintenance of destructive behaviors [166,167]. Insight necessitates an awareness of cognitive processes and involves functions such as behavior monitoring and error recognition, which are crucial for appropriate decision-making and are impaired in those who use drugs [168-170]. These processes are intrinsically linked with bodily

states and interoceptive awareness, as autonomic responses must be integrated with conscious self-monitoring for relevant functions, such as error recognition [5].

Converging evidence indicates that dysfunction in the ACC of individuals with substance use disorders contributes to poor insight. Activity in the ACC and insula related to error recognition is absent in participants who chronically use opiates [169] and cannabis [168]. Compared to control participants and those with Cocaine Use Disorder with intact insight, participants with Cocaine Use Disorder who have difficulty in self-monitoring also have less emotional awareness, less error-induced activity in the rostral ACC during an inhibitory control task, and less gray matter within the rostral ACC [171]. Denial, measured by the precontemplation scale of the University of Rhode Island Change Assessment Scale (URICA), which assesses the degree to which an individual is ready to change problematic behavior, is inversely related to the strength of connectivity between the rostral ACC and frontal, limbic, and occipital areas in Methamphetamine Dependence [167]. Thus, impairment in a network of brain areas, including the ACC, may contribute to impairment of insight in substance abuse.

1.7 External Influences on Choice

Context has a powerful and ubiquitous impact on decision-making [172]. Context dependence produces violations of rational economic models, in which preferences should be independent, regardless of irrelevant alternatives [173] or how they are framed [174]. Instead, preferences change depending on the availability of other options and past options, and on the framing of options [175,176]. Contextual appraisal also applies to cues in the immediate environment and the social domain, and a rich body of literature has explored both in relation to addiction.

1.7.1 Reference dependence

Contrary to the principles of rational choice theories, preferences for options that present risk change according to whether options are framed as gains or losses, even when the subjective values remain constant [9]. This phenomenon arises from decisions being considered in relation to a reference point and leads to systematic and predictable biases [177]. In studies in which value changes as a function of alternative options and distractors [178], context-dependent neural activity related to reward valuation has been observed in the ventral striatum and parietal cortex [179].

Certain tasks compare choices consistent and inconsistent with the effects of framing put forth by prospect theory [9], and find that activity in the amygdala is related to decisions consistent with framing effects and ACC activity is related to decisions that are inconsistent with framing effects [180]. Risk signals observed in the anterior insula during positively-framed messages on the IGT also have been correlated with how much the message improves choice behavior [181]. While previously hypothesized to result from emotional biases [180,182], framing effects may also be related to cognitive control and engagement [183]. Supporting this view is the observation that activity in the dorsolateral PFC correlates with advantageous decision-making on the framing version of the IGT [181].

The gain/loss asymmetry of framing and the reference dependence of normalizing to the *status quo* could represent biologically separate systems of approach and withdrawal [184], which could influence vulnerability for addiction [81]. Susceptibility to framing effects correlates with activity in the medial and orbital PFC [180] and the ACC [185], and is linked with emotions [186]. Moreover, a study using the IGT indicated that better performance in the positively-framed condition is associated with activity in the ACC and insula in both healthy control participants and those who use substances, whereas substance users perform worse than controls during negatively

framed IGT conditions. Their performance also reflects lower risk-aversion signals in the anterior insula, and a correlation between advantageous decision-making and risk-related activity in the ACC across decisions is only observed in healthy controls [187]. Thus, impaired risk signals in the ACC and insula of participants who use substances, especially related to negatively-framed messages, appear to contribute to disadvantageous decision-making.

The susceptibility to framing effects has therapeutic applications. For instance, conscious perspective shifts can alter value-related neural activity, as evidenced by the modification of cortical activations related to reward value and choice selection by instruction to frame food choices in terms of health or taste [188]. Similarly, framing effects can bias preferences on delay discounting tasks [144,189]. Neural activity in the medial PFC also can predict behavioral changes in the week following persuasive messages [190]. Framing effects and reference dependence warrant further investigation as related to addictions, especially considering that the *status quo* in addictions can be constantly shifting, causing inconsistency in decisions [191].

1.7.2 Environmental cues

Contextual cues can have major effects on drug-related choices [192-194]. For instance, conditioned stimuli with enhanced salience can bias towards drug-seeking behavior [195]. Thus, environmental stimuli can alter the value of certain options and induce a state of craving that heightens the value of drug-related choices compared to alternatives. Studies on the neural basis of cue-induced craving have shown greater activity in mesocorticolimbic regions [7,196,197] in response to drug-related compared to neutral cues. A role of the insula has been emphasized; insula activity correlates with cue-induced drug craving in individuals who smoke cigarettes [198], use cocaine [199], and use opiates [200], and RSFC of the right insula with prefrontal networks is greater in those who use cocaine than controls [201]. Smoking addiction is disrupted by changes in cigarette

craving after lesions to the insula, reinforcing its role in conscious cue-induced drug craving and, perhaps, in the pleasure derived from the bodily effects of smoking [158].

Interestingly, suppression of craving during cigarette cues is linked to activations in limbic brain regions, specifically the left dorsal ACC, posterior cingulate cortex, and precuneus, and deactivations in primary sensory and motor cortices, specifically the cuneus, left lateral occipital gyrus, and right postcentral gyrus [198]. Individuals who use cocaine also exhibit decreases in right ventral striatum and right OFC activity when instructed to inhibit cravings, compared to trials with no instruction to inhibit craving, and the decreases in activity are linked to increased activity in the lateral PFC [202]. Similar results have been found in smokers [203]. Thus, modulation by the lateral PFC appears to be crucial for resisting craving, which is likely mediated by activity in the ventral striatum and OFC, as well as limbic areas.

1.7.3 Social factors and peer influence

Decisions made in a social environment integrate personal goals with the well-being of others, while taking into account drives such as conformity, altruism, and punishment [204,205]. These drives affect the value of different options [206]. Specific economic tasks, such as game theory tasks [207], developed to investigate social decision-making have revealed that social decision-making processes share many neural substrates with reinforcement learning and reward valuation [208,209] and are associated with dopamine signaling [210].

Addiction often is accompanied by disruptions in processes necessary for social decision-making, from understanding the self [170] to recognizing the emotions of others [211] and social functioning [212,213]. Compared to healthy control participants, those with Methamphetamine Dependence exhibit abnormal frontoparietal activity that may reflect difficulty integrating the

emotional components of social information [163,214]. Indeed, affective responses, which are impaired in those with addictions [149], can influence social decision-making [215]. All of these factors could contribute to the development and maintenance of addictions, especially during adolescence, the most common time for the onset of addiction [216], when social functioning is of particular significance [217,218]. While peer influences on performance in delay discounting tasks have been demonstrated [219], the authors are aware of no studies that have yet investigated brain function during game theory tasks in participants with substance use disorders.

Neural activity during decision-making tasks with a social component have demonstrated different patterns of striatal activity in young adults who use marijuana compared to healthy controls when participants are integrating social information into decisions [220]. The neural underpinnings of social conformity are particularly relevant, especially considering the impact of peer influences on addictions, risk-taking, and decision-making [221,222]. Young adults who use marijuana take more time than controls to resist group choices, and reaction times are correlated with greater frontal activation [223]. Self-reported susceptibility to group influence is associated with caudate activity in both groups, with the marijuana group exhibiting greater caudate activation than controls when presented with social influence [223]. Both groups exhibit activation in the ventral ACC, PFC, and insula during social exclusion, but young adults who use marijuana have lower insula signaling [224]. This result is in line with evidence that insula activity is related to group conformity [225]. These studies suggest that, during decision-making, individuals who use drugs may process social information differently in striatal and frontal regions, especially in the insula.

1.8 Conclusions and Future Directions

Maladaptive decision-making may arise from disruptions in the effective computation of reward values. Clarification of how factors such as temporal delay, uncertainty, and internal and external states influence reward valuation, and how subjective value guides choice, can help explain suboptimal choice selection in addiction. “Irrational” choice behavior can reflect inconsistent judgement of delays [117,118] and uncertainty [70], or the influence of emotion [154] and reference [9] on evaluating utility. These biases may be exaggerated in addictions, providing a mechanism by which the underlying neurobiological processes can be better understood.

Consistent with the general consensus of a central role for dopamine in choice and in addictions, many of the findings previously covered are related to the dopaminergic system [56,57,62,90,92,128,132,164,165]. The complexity of the dopaminergic system with respect to localization and function of different dopamine receptor subtypes and mechanisms of dopamine release, and the inconsistency of results [226], necessitates clarification of how dopamine functions to modulate decision-making, especially in addictions. Undoubtedly, while not presently covered, the roles of other neurotransmitter systems warrant further investigation [227].

Limitations in the study of decision-making and addiction can arise from methodological variation. As choice behavior likely varies as a function of reward type, the use of different types of rewards complicate generalization across studies [228]. Decision-making impairments and neural activity can also differ according to the type of addiction [106,229], although there is evidence of consistency across addictions to different types of drugs [103]. Further, that it can be difficult to determine whether neural responses interpreted as value signals are not related instead to other cognitive functions, such as attention or coding of outcome identity [230], can potentially confound results. Similarly, the imprecise definitions of constructs such as risk and impulsivity necessitate caution in the generalization of results [69,231]. For instance, delay discounting tasks capture an

underlying and constant feature of addictive disorders, and still resist generalization past the quantification of the preference for an immediate over a larger delayed reward.

The present chapter is by no means comprehensive and focuses on findings in humans related to the neurobiology of valuation in addictions. Components that alter subjective value are explored in the subsequent chapters.

CHAPTER TWO

Behavioral Methods

2.1 Behavioral Tasks

2.1.1 One-balloon version of the Balloon Analogue Risk Task (BART)

The Balloon Analogue Risk Task (BART) is a risky-decision-making task that provides a naturalistic assessment of risk-taking [73]. A virtual balloon appeared on a computer screen and the participant was told that they would receive $0.25 for each pump of the balloon, which they selected by pressing a key (**Fig. 2.1**). With each pump, the balloon either increased in size or exploded, and the probability of explosion increased as the balloon inflated. Participants were told that pumping was associated with reward ($0.25), but were not told that the number of pumps before explosion was predetermined from a uniform probability distribution. Thus, the participant made a series of choices ─ to pump (taking risk) or to cash out and retain the earnings up to that point in the trial. If the balloon exploded before the participant cashed out, the earnings from that trial were lost. The precise number of trials varied between participants based on their pace of pumping, but the one-balloon version of the BART was faster in than the fMRI version explained below. The mean (SD) of total trials across groups was 28.98 (0.755), with 27.19 (1.512) for the healthy control (HC) and 30.0 (0.772) for the Stimulant Use Disorder (SUD) group.

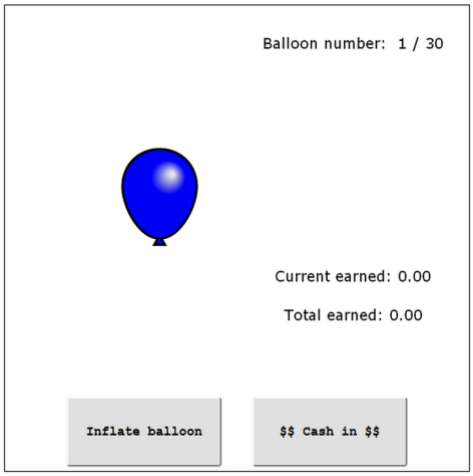

Figure 2.1 One-balloon version of the Balloon Analogue Risk Task. Example view of the task screen.

After testing completed, participants received their earnings from the task in the form of cash, gift cards, or vouchers. The traditional outcome measure of the BART is known as *adjusted pumps*: the average number of pumps before cashing out (i.e., on non-explosion trials). In addition

to this measure, a cognitive parameterization model was used to decompose decision-making into precise parameters.

2.1.2 Two-balloon version of the Balloon Analogue Risk Task (BART)

Participants performed two 10-min runs of an event-related fMRI version of the BART [86,232,233]. Each pump was followed either by an image of the balloon increasing in size, or a 2-second video of the of the balloon exploding and the message "Total = $0.00," at which point the balloon was reset and another trial began (**Fig. 2.2)**. A trial included each pump before either explosion or cashing out and earnings were displayed for 2 seconds after each trial. Three types of balloons were presented: blue, red, and white. Participants were told that red and blue balloons were associated with reward ($0.25), but were not told that the number of pumps before explosion was predetermined from a uniform probability distribution (1-8 for red and 1-12 for blue balloons). Participants received the instruction to pump the white balloons until the trial ended, but that this activity would not be associated with any monetary reward. The number of white control balloons varied from 1-12 based on a uniform distribution. The precise number of trials varied between participants based on their pace of pumping. The mean (SD) of total trials across groups was 33.07 (5.962), with 33.31 (5.734) for the HC group and 32.49 (6.443) for the SUD group. The interstimulus interval

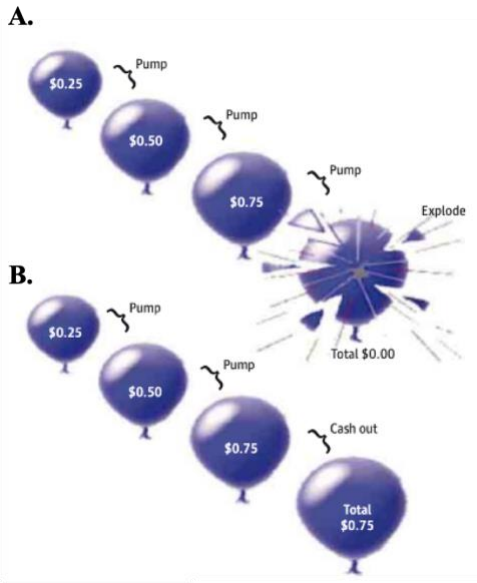

Figure 2.2 Two-balloon version of the Balloon Analogue Risk Task. Example trials ending in either explode (**A**) or cash out (**B**).

between balloons was 1-3 seconds and the intertrial interval was 1-14 seconds, with a mean of 4 seconds.

2.1.3 Loss Aversion Task (LAT)

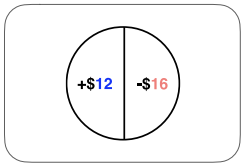

Figure 2.3 Loss Aversion Task. Example trial.

The Loss Aversion Task (LAT) consisted of 128 sequential monetary choices to accept or reject a mixed gamble offering a 50/50 chance of winning a certain amount of money and losing a different amount of money (e.g., gaining $30 or losing $7) [234]. On each trial, an image representing a 50/50 choice was presented on the screen, and the participants indicated whether they strongly accepted, weakly accepted, weakly rejected, or strongly rejected the choice (**Fig. 2.3**). Four options were provided instead of two (i.e., accept or reject) to discourage reliance on rule-based choice (e.g., always accepting when the loss exceeded $5). The probability of winning or losing was kept constant at 50%, and the alternative to accepting the gamble was always to remain at the status quo (i.e., win and lose nothing). The gains ranged from $10-$40 in increments of $2, and the losses ranged from $5-$20 in increments of $1. Once the participant decided, the next choice was presented without showing the outcome of the previous choice; if no selection was made within 3 seconds, the next gamble appeared on the screen. The task was presented using MATLAB (Mathworks, Natick, MA) and the Psychtoolbox (www.psychtoolbox.org) on an Apple PowerMac laptop computer running Mac OSX (Apple Computers, Cupertino, CA), with most of the code the same as used previously [234]. Participants responded using the 1, 2, 3, and 4 keys on the keyboard. A subset of participants also performed 22 extra "gain-only" trials that presented choices between a sure win of $5 or a 50% chance of winning a variable amount that varied from $4-$50.

Before testing, participants received thorough instruction on how to perform the task. Instructions were read aloud, and the participant was encouraged to ask questions while viewing training slides and performing 5-10 practice trials. To ensure that participants were motivated on the task, they were told that one of their choices would be randomly selected to be paid out at the end of testing. This incentive-compatible technique tried to ensure that participants were making choices that reflect their "true" preferences. They also were told that losses would be deducted from their earnings from participation in the study, but losses were not actually deducted.

2.1.4 Choice under Risk and Ambiguity Task

The Choice Under Risk and Ambiguity (CRA) Task was administered to isolate and measure risk-taking under ambiguous and unambiguous conditions [111]. Participants choose between accepting a sure amount of money ($5) or gambling on a lottery for the chance to win more than $5, with reward amounts and probabilities systematically varied. Participants were told that each visual stimulus (**Fig. 2.4A**) represented a stack of poker chips and were shown 6 physical bags that contained the number of red/blue chips corresponding to all 6 visual stimuli (3 levels of risk + 3 levels of ambiguity = 6 bags). They were told that each trial represented picking from the corresponding bag, with the potential to win the amount of money written next to the appropriate color (i.e., in Fig. 2.4A., picking a red chip results in winning $66, and picking a blue chip in winning nothing). In half of the trials, the entire stack of chips was visible and thus the probability of drawing each color was known (*risk*, **Fig. 2.4B**). These proportions were obscured to a varying degree by

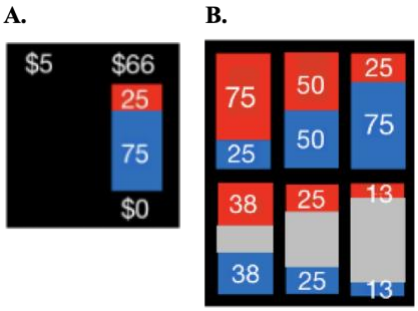

Figure 2.4 The Choice Under Risk and Ambiguity Task. **A**. Example stimulus. **B**. All possible stimuli for risk trials (top row) and ambiguity trials (bottom row).

a grey box in ambiguous trials so that the exact probability of picking each color was unknown (*ambiguity*, **Fig. 2.4B**). The task did not involve "betting" on a red or blue chip, but rather deciding whether to accept the gamble (i.e., pick from the bag) or receive $5.

At the end of the experiment, one of the trials was randomly chosen and played out for real money. The possible rewards ranged from $5 to $50 and the three outcome probabilities for unambiguous risk trials were 0.25, 0.50, and 0.75. Throughout the task, participants were reminded of the $5 sure option, which was held constant so that unambiguous and ambiguous trials were comparable. Trials were presented in 4 blocks of 30, with rest periods in between (120 total trials). The task included checks for active attention/participation, choice consistency/randomness, and rule-based choosing [235]. The outcome measures of the task wre parameters for risk-taking under ambiguous and unambiguous conditions, which were calculated by fitting models that are described below.

2.1.5 Delay Discounting Task (DDT)

Each trial of the delay discounting task presented a choice between monetary rewards that varied in magnitude and delay [236]. The task was incentivized, with one trial selected for payout, and all transaction costs related to receiving the money were minimized. Participants indicated their preference between a smaller reward available in the near future and a larger reward available with a longer delay. The reward magnitudes ranged from $6 to $50. The amount and delay of reward were varied to construct the participant's discount function, and the steepness of the discount function described how strongly a participant discounted future rewards.

2.2 Computational Modeling

2.2.1 Balloon Analogue Risk Task

Decision-making on the BART was decomposed using a re-parameterized model of the 4-parameter model described in detail in Wallsten, Pleskac and Lejuez (237) and reparameterized by Park, Yang, Vassileva and Ahn (238). Briefly, the model assumes that the participant begins the task with a prior belief about the probability of the balloon bursting (p_{belief}). This prior belief is updated as the participant pumps on each trial:

$$p_k^{belief} = 1 - \frac{\phi + \eta * \sum_{i=0}^{k-1} n_i^{success}}{1 + \eta * \sum_{i=0}^{k-1} n_i^{pumps}}, \quad 0 < \phi < 1, \;\; \eta > 0,$$

where $\sum_{i=0}^{k-1} n_i^{success}$ refers to the sum of all successful (non-bursting) pumps up until trial $k-1$ and $\sum_{i=0}^{k-1} n_i^{pumps}$ to the sum of the total number of pumps up to trial $k-1$. The value of ϕ represents the prior belief that pumping the balloon will not make it explode, and η represents the updating rate of the participant. At the beginning of the task, the prior belief about the probability of the balloon bursting (p_k^{belief}) is equal to $1-\phi$. As the participant progresses through the trials, the rate at which they update their belief based on observed data is given by the updating rate η. Lower values of η indicate that more data is needed to update the participant's belief: when $\eta = 0$, the belief about the balloon bursting (p_{belief}) is unaffected by observed data and equals $1-\phi$, or the prior belief. At large values of η, p_{belief} approaches the observed probabilities.

The probability that the participant will pump the balloon was calculated using prospect theory [9], and elaborated by Park, Yang, Vassileva and Ahn (238). The formula for expected utility is given by U_{kl}, where *l* is the number of pumps on trial *k*:

$$U_{kl} = (1 - p_k^{belief})^l (lr)^\gamma, \qquad \gamma \geq 0,$$

where *r* is the amount of reward for each pump, and γ represents the risk-taking parameter. Setting the first derivative of U_{kl} for *l* equal to zero can then be used to calculate the optimal number of pumps, v_k:

$$v_k = \frac{-\gamma}{\log\left(1 - p_k^{belief}\right)}, \qquad \gamma \geq 0,$$

Thus, the probability that the participant will pump on trial *k* for pump *l* is:

$$p_{kl}^{pump} = \frac{-\gamma}{1 + e^{\tau(l - v_k)}}, \qquad \tau \geq 0$$

where τ is the inverse temperature that represents the consistency of participants' choices. Now the probability of the data given the parameters can be represented by the likelihood function:

$$p(D|\phi, \eta, \gamma, \tau) = \prod_{k=1}^{k^{last}} \prod_{l=1}^{l_k^{last}} p_{kl}^{pump} \left(1 - p_{k,l_k^{last}+1}^{pump}\right)^{d_k},$$

where k^{last} is the final number of trials, l_k^{last} is the final number of pumps taken on that last trial *k*, and d_k is the outcome of that last trial *k* ($d_k = 0$ if balloon explodes, $d_k = 1$ if the participant cashes out).

The cognitive parameters of risk-taking (γ), updating rate (η), and consistency (τ) were estimated using hierarchical Bayesian analysis as described below.

2.2.2 Loss Aversion Task

Data from the Loss Aversion Task were estimated in two ways. First, a logistic regression was fit to each participant's data with the amounts of gain and loss as independent variables and the participant's choice as the dependent variable. The responses "strongly accept" and "weakly accept" were both treated as accepting the gamble, and both "strongly reject" and "weakly reject"

were treated as rejecting the gamble. Loss aversion (λ) was then taken as the ratio of the coefficient for the loss amount to the coefficient of the gain amount ($\lambda = \beta_{loss}/\beta_{gain}$).

Full utility functions were fit to choices of the subset of participants who also performed the Choice under Risk and Ambiguity task (*see next section*). The trials that presented a 50% probability level and no ambiguity were included as "gain-only" trials to isolate risk preferences from loss aversion. This second analysis was performed using a multi-parameter utility function [239] that represents subjective value (Equation 1) based on original prospect theory [9,240]:

$$SV(x) = \begin{cases} x^{\rho}, x \geq 0 \\ \lambda * (-x)^{\rho}, x < 0 \end{cases}$$

The subjective value (SV) of the gamble is estimated using the objective magnitudes of gain (x) and loss ($-x$) given in each choice and the parameters of loss aversion (lambda; λ) and risk attitude (rho; ρ). The sensitivity to potential loss relative to potential gain is represented by λ. If $\lambda = 1$, the participant values gains and losses equally. When $\lambda > 1$, the participant is considered loss averse and assigns more weight to losses than to gains of equal magnitude. When $\lambda < 1$, the participant is considered gain-seeking, and overvalues gains compared to losses. Rho (ρ) describes the curvature of the utility function and represents attitude towards risk. If $\rho = 1$, the participant's preferences can be modeled by a linear utility function, which signifies that each incremental increase in reward has equal utility. Values for ρ other than 1 indicate that the preferences of the participant can be described by a utility function that shows diminishing marginal utility. When $\rho < 1$, the participant is risk-seeking for losses (more likely to take a gamble over a sure loss) and risk-averse for gains (more likely to choose a sure gain over a riskier prospect). The opposite is true when $\rho > 1$. The subjective values were then inserted into a logit (softmax) function that estimates the probability of accepting the gamble based on the difference in subjective values between the lottery (50/50 choice or SV_{gamble}) and the fixed amount (\$0 or $SV_{certain}$):

$$p(Accept\ Gamble) = [1 + \exp(-\tau * SV_{gamble} - SV_{certain})]^{-1}$$

Tau (τ) is the logit sensitivity or inverse temperature and represents choice consistency, or the sensitivity of the participant to the difference in utility between the certain amount and the gamble. When $\tau = 0$, choices would be completely random, whereas an infinite τ would be a step function and participants would be changing their behavior completely as if based on a calculation.

To determine whether parameter values were misestimated when the task did not include trials to isolate risk from loss, the full utility was also fit to the larger subset of participants who performed the LAT without an explicit measurement of risk attitudes.

2.2.3 Choice Under Risk and Ambiguity Task

To estimate the parameters of risk (α) and ambiguity (β) for each individual, the subjective value of each option was modeled, while taking into account the reward magnitude, outcome probability, level of ambiguity, and individual attitudes towards risk/ambiguity. This was achieved using a power function [9] that incorporated the influence of ambiguity [241]:

$$SV = \left[p - \beta\left(\frac{A}{2}\right)\right] * M^{\alpha}$$

where *SV* is the subjective value, *p* is the objective reward probability, *A* is the level of ambiguity, and *M* is the reward magnitude.

When $\alpha = 1$, the objective and subjective values of the reward are the same (risk-neutral, $M^{\alpha} = M^{1} = M$). As α increases, the participant is considered more risk-seeking, as they value money more; as α decreases, the participant is less risk-seeking, or more risk-averse, as they value money less. When $\beta = 0$, that component of the equation above disappears and the participant is considered ambiguity-neutral ($SV = \left[p - 0 * \left(\frac{A}{2}\right)\right] * M^{\alpha} \rightarrow SV = [p] * M^{\alpha}$). As β increases, the

effect of ambiguity becomes stronger and the subjective value is considered less than the objective probability, so the participant is considered ambiguity-averse; as β decreases, the effect of ambiguity becomes weaker, the subjective value is considered higher, and the participant more ambiguity-tolerant.

To model the probability of each participant choosing the lottery over the safe option, the choice data of each participant was fit to a logistic function. This model assumes that task performance depends on the difference in subjective values of the sure bet and the risky option (either risk or ambiguity, depending on trial type), as well as an identically distributed error term.

$$\Pr(ChooseRisky) = \frac{1}{1 + e^{\gamma(SV_S - SV_L)}}$$

with SV_S as the subjective value of the safe option, SV_L as that of the lottery, and γ as the slope of the logistic function, a subject-specific parameter.

2.2.4 Delay Discounting Task

Delay discounting was assessed using two approaches for comparison. For an option that presents a reward of magnitude *M* at a delay *(d)*, the subjective value (*SV*) is a function of the discount factor (*D*) and the utility of the reward magnitude, *U(M):*

$$SV = D(d) * U(M)$$

The discount factor (*D*) is a function of the delay (*d*) and the discount rate parameter (*k*), which represents the rate at which utility (or the SV of the reward) is discounted by time:

$$D = \frac{1}{1 + kd}$$

Based on the choices of each subject, the point at which each participant is indifferent between the sooner and later amount (*indifference point*) was used to estimate the best-fit *k* value. A higher *k*

value signified that rewards were devalued fairly quickly as they moved farther into the future, resulting in a greater preference for smaller-sooner rewards.

A hyperbolic model [242] was fit to the data twice. The first model assumed linear utility, meaning that utility was equal to the reward magnitude ($U = M$). This assumption means that individuals are assumed to be risk-neutral. When $U = M$, the model becomes the classic delay discounting equation:

$$SV = \frac{M}{1 + kd}$$

The second model included a separate estimate of utility curvature, obtained from the Choice under Risk and Ambiguity Task. Instead of estimating *k* values through calculating the point at which a participant is indifferent between a sooner and later *amount*, this model calculates the point at which the *utility* of receiving the sooner and later amounts, given by $U(M)$, would be equal. This is accomplished by raising the magnitude of the reward M to the power of the risk aversion parameter (α):

$$U(M) = \frac{M^{\alpha}}{1 + kd}$$

Models were fit using the hierarchical Bayesian modeling described in the following section.

2.2.5 Hierarchical Bayesian Analysis

Parameter values were estimated using hierarchical Bayesian analysis implemented in the "hBayesDM" package in R [243], which allows the joint estimation of individual and group parameters and robustly identifies individual differences in decision-making [244]. Posterior

inference was performed with Markov Chain Monte Carlo (MCMC) sampling using Stan [245] and RStan (http://mc-stan.org/interfaces/rstan).

The healthy control and Stimulant Use Disorder groups were modeled separately, as groups are assumed to be homogeneous in Bayesian analysis [246,247]. The models specified 2000 samples drawn after 1000 burn-on samples for 4 chains for a total of 8000 samples.

2.2.6 Model Quality Assessment

Convergence of Markov Chain Monte Carlo (MCMC) chains was assessed using the Gelman-Rubin test [248] by examining the rhat ($\hat{R}$) values. $\hat{R}$ values close to 1.00 indicate that chains converged to stationary target distributions. $\hat{R}$ statistics for all models were at or below 1.00, with one $\hat{R} = 1.01$. Trace plots were also visually inspected to determine whether MCMC samples were mixed and converged well. Models were validated by using the posterior distribution to generate data and visually inspecting whether the generated data corresponded to the underlying distribution.

2.2.7 Data Quality Assessment

The data were assessed for quality and cleaned in three ways: (1) trials with implausible reaction times (i.e., < 200 ms) were excluded; (2) data were excluded for any participant whose preferences were random, erratic, or inconsistent with trends predicted by our structural models (i.e., they were not more likely to accept the gamble for increasing magnitude of gain, decreasing magnitude of loss, or increasing expected value); (3) Simulated data generated by the models were fit to the data and then visually inspected to determine whether they were similar to the original data (known as "posterior predictive checks" [246]).

2.3 Behavioral Statistics

Statistical analyses were performed using RStudio version 1.1.456. Analysis of variance (ANOVA) or correlation, as appropriate, was used to determine whether SUD and HC groups significantly differed in age, biological sex, race/ethnicity, estimated IQ [using the Wechsler Test of Adult Reading (WTAR) [249]], years of education of the participant's mother (as a proxy for socioeconomic status), or cigarette smoking status. The same potential variables were analyzed for association with choice parameters when controlling for group.

To assess trial-by-trial behavior on the BART, we used a linear mixed model with trial number, outcome of the previous trial, and group as fixed effects, subject as the random effect, and number of pumps per trial as the dependent variable. The mean number of pumps on trials where the participant chose to cash out (non-explode trials) was calculated and this measure of *mean adjusted pumps* was tested for association with the demographic measures listed above as well as for group differences. Trial-by-trial behavior on choice tasks was assessed by visual inspection of the probability of choosing to gamble based on the expected value, reward magnitude, and/or loss magnitude of options.

For computational parameters, two analysis methods were used. As is recommended in Bayesian analysis [246], the posterior distribution of group mean differences were compared by computing the 95% Highest Density Interval (HDI) using the hBayesDM package [250]. For this method, if the HDI does not include a value of zero, the groups can be considered to be statistically different. However, in order to account for group differences in covariates and/or association between dependent variables and covariates, the posterior means of choice parameters from each task were used in generalized linear models (GLMs) to test for group differences. GLMs were used

to test for association between outcome measures and stimulant use (cocaine or methamphetamine) in 30 days prior to entering treatment.

CHAPTER THREE

Naturalistic Decision-Making under Uncertainty

3.1 Introduction

Real-world behavior [251-256] and performance on laboratory tests [10-12] indicate that individuals with Methamphetamine Use Disorder (MUD) exhibit maladaptive decision-making. Decision-making is a complex process by which an individual must calculate and compare different alternatives to determine which options are worth pursuing, while taking into account the possible rewards and costs [1]. Feedback from the environment after choice selection is then integrated to guide future decisions [257,258]. Most situations present incomplete information about the probabilities of possible rewards, and this uncertainty can causes distortions in choice [9,259]. Individuals with addictions may be especially susceptible to distortions related to uncertainty [10,193,260], and clarifying the cognitive and neural processes involved in decision-making under uncertainty is thus a logical goal.

The Balloon Analogue Risk Task (BART) is a risky-decision-making task that has been employed in the study of addictions [86-88,261-264]. Participants must decide between pumping a virtual balloon for reward or "cashing out" to receive the earnings accrued on the trial. After a certain number of pumps, the balloon explodes and the earnings from that trial are lost. Some studies have shown that individuals with addictions take less risk (i.e., pump less) on the task than healthy control participants [86,87,263,265]. Although the BART provides a naturalistic assessment of risk-taking during uncertainty [73], interpretation of performance is complicated by overlapping cognitive processes, including risk-taking, attitude toward ambiguity, reaction to loss, and learning [69,75,95,266].

Using a computational model to decompose behavior on the BART can help identify the underlying cognitive and neural processes, including those that may drive differences between healthy control (HC) volunteers and those with MUD [267,268]. The cognitive model used here to analyze performance of the BART enabled the distinct analysis of risk-taking and behavioral

updating (Section 2.3). Formulized by Wallsten, Pleskac and Lejuez (237) and re-parameterized by Park, Yang, Vassileva and Ahn (238), the model assumes that the participant begins the task with a prior belief about the probability of the balloon bursting, and that the prior belief is updated as the participant pumps and receives feedback on each trial. Prospect theory calculations of expected utility were used to evaluate the probability that the participant would pump the balloon [9].

The updating rate is of particular relevance to addiction, which is characterized by persisting in actions with negative consequences, even if the positive outcomes of those actions have all but ceased [23,195,269]. This phenomenon may reflect deficits in estimating and updating outcome contingencies and cause individuals to revert to actions that were rewarding in the past [23,260]. Since individuals diagnosed with Stimulant Dependence show impairments in cognitive flexibility and learning [45,270-273], we hypothesized that MUD participants would show an impairment in updating rate on the BART.

Decision-making on the BART produces activation in a network of striatal and cortical brain regions, including the dorsolateral prefrontal cortex (DLPFC) and anterior insula [86,89,90,232,233,274]. The DLPFC also shows functional differences during decision-making on the BART between healthy control and MUD participants, as well as between adolescents who do and do not smoke cigarettes [86,232]. DLPFC activations have also been related to the updating of value [275,276]. Level of risk on the BART modulated activation in the anterior insula [93], and insula activity can act as a risk-aversion signal [99,277-279] and encode risk prediction errors [35]. Risk aversion signals in the anterior insula may influence performance by MUD participants, in whom risk-related signaling in the insula is impaired [102,105,106,109,280]. The anterior insula participates in integrating arousal and interoceptive inputs into choice processes [25,39], and a major component of risk-taking on the BART

is the visceral sensation associated with pumping the balloon. Thus, we hypothesized that updating rate would be related to risk-related activity in the DLPFC and anterior insula that would differ between HC and MUD groups.

Goal-directed behavior and reward-related learning rely on striatal and cortical dopaminergic function [281-286]. We therefore questioned whether striatal and cortical dopamine D2-type (D2-type) receptors play a role in risk-taking and behavioral updating on the BART. Striatal dopamine D2-type receptors have long been implicated in risk-taking in studies of primates [273,287-291] and rodents [292-295]. Dopamine D2-type receptors in the medial and lateral OFC and the insula mediate reward-related decision-making, learning, and behavioral flexibility [29,286,296-298]. The insula and OFC receive dopaminergic innervation and are reciprocally connected [299,300], and activation in both regions was modulated by risk (and reward) on the BART [93]. We therefore hypothesized that behavioral updating would be related to D2-type receptors in these regions.

Participants were tested on the two-balloon version of the BART [73] during fMRI. Parametric modulation of activation in the DLPFC and anterior insula by risk and reward (indexed by pump number) was assessed. Since sensitivity to loss plays a role in performance but is not explicitly measured on the BART, a subset of participants also performed the Loss Aversion Task (LAT) to elucidate motivations for continuing to pump (i.e., take risk) versus cashing out (i.e., take reward).

The version of the BART with one balloon was given to a different sample of participants who had [^{18}F]fallypride positron emission tomography (PET) scans to measure dopamine D2-type availability (binding potential, BP_{ND}). D2-type BP_{ND} was analyzed in striatal subregions and the midbrain for association with risk-taking, and the medial and lateral OFC and insula for association with updating rate. The complexity and antagonistic nature of the dopaminergic system suggests that nonlinear relationships between D1 and D2-type dopamine receptors and cognitive functions

may be more common than strictly linear associations [93,297,301-305]. Thus, we tested for nonlinear associations between dopamine receptor binding and updating rate on the BART.

3.2 Methods

3.2.1 Participants

All participants provided written informed consent, as approved by the UCLA Institutional Review Board. They were fluent in English and in good physical and neurological health, as assessed by clinical history and physical examination. All Axis I psychiatric diagnoses were exclusionary, other than Methamphetamine Dependence in the MUD participants and Tobacco Dependence in both groups, as determined by the Structured Clinical Interview for DSM-IV [306].

The two-balloon version of the BART was performed during fMRI by 69 HC (31 women) and 30 MUD (15 women) participants (**Table 3.1**). The LAT was also performed by 17 HC and 18 MUD volunteers (**Table 3.2**). In the MUD group (aged 22-52 years), 15 participants were not seeking or receiving treatment for their addiction, and had abstained from methamphetamine use for a mean (SD) of 7.82 (4.35) days before testing. Fifteen volunteers participated while receiving behavioral residential treatment and were abstinent from methamphetamine use for a mean (SD) of 7.25 (0.96) days before scanning. MRI and behavioral data from these participants have been published in other reports [86,90,91,93,307].

The one-balloon version of the BART was performed by 16 HC and 28 MUD participants (**Table 3.3**) who also received [^{18}F]fallypride PET scans. MUD participants participated while receiving behavioral residential treatment and were abstinent from methamphetamine use for a mean (SD) of 11.75 (1.71) days.

On all study days, participants provided a urine sample that was negative for cocaine, methamphetamine, benzodiazepines, opiates, and cannabinoids. Participants who smoked cigarettes were allowed to smoke until 15 min before testing to avoid effects of nicotine withdrawal. They were compensated with cash, gift cards, or vouchers.

Variable	Healthy Controls (HC; n=69)	Participants with Methamphetamine Use Disorder (MUD; n=30)	Statistics
Age, years[a]	25.67 (1.28)	36.50 (1.51)	$t(97) = -4.97$, $p < 0.001$***
Biological sex female/male (n)	31/39	15/15	$c^2(1) = 0.094$, $p > 0.05$
IQ estimate standard score[a]	109.0 (2.57)	101.4 (2.61)	$t(33) = -2.03$, $p > 0.05$
Mother's Education, years[a]	3.957 (0.179)	3.481 (0.322)	$t(94) = 1.36$, $p > 0.05$
Race/Ethnicity (n)			$H(5) = 4.78$, $p > 0.05$
White	22	13	
African American	7	1	
Hispanic/Latinx	17	7	
Asian/Pacific Islander	15	4	
Other	8	5	
Cigarette smoking, n	36	19	$c^2(1) = 6.79$, $p < 0.01$**
Days of substance use in the previous 30 days			
Alcohol	4.875 (0.795)	3.593 (1.23)	$t(89) = 0.878$, $p > 0.05$
Marijuana	0.4878 (0.175)	1.926 (0.667)	$t(29.62) = -2.09$, $p < 0.046$*
Tobacco	20.69 (2.10)	22.81 (2.36)	$t(66) = -0.651$, $p > 0.05$
No. who smoked	36	55	$t(89) = -2.96$, $p < 0.005$**
Methamphetamine		22.5 (1.59)	

[a]Values are means (SE)
IQ estimate = Weschler Test of Adult Reading

Table 3.1. Demographics of participants who performed the two-balloon BART during fMRI

Variable	Healthy Controls (HC; n=17)	Participants with Methamphetamine Use Disorder (MUD; n=18)	Statistics
Age, years[a]	37.38 (2.45)	34.50 (1.49)	$t(33) = 1.28$, $p > 0.05$
Biological sex female/male (n)	4/13	7/11	$c^2(1) = 0.377$, $p > 0.05$
IQ estimate standard score[a]	109.6 (2.54)	102.5 (2.88)	$t(24) = 1.81$, $p > 0.05$
Mother's Education, years[a]	13.18 (0.73)	12.59 (0.80)	$t(32) = 0.544$, $p > 0.05$
Race/Ethnicity (n)			$H(4) = 4.62$, $p > 0.05$
White	10	5	
African American	0	1	
Hispanic/Latinx	4	5	
Asian/Pacific Islander	1	4	
Other	2	3	
Days of substance use in the previous 30 days			
Alcohol	4.56 (1.43)	2.07 (0.67)	$t(32) = 0.447$, $p > 0.05$
Marijuana	0.0 (0.0)	1.87 (0.99)	$t(26) = 1.29$, $p > 0.05$
Tobacco	22.45 (3.79)	19.53 (3.40)	$t(31) = -0.310$, $p > 0.05$
No. who smoked	12	13	$c^2(1) = 0.448$, $p > 0.05$
Methamphetamine		22.33 (1.96)	

[a]Values are means (SE)
IQ estimate = Weschler Test of Adult Reading

Table 3.2. Demographics of participants who performed the Loss Aversion Task and the two-balloon BART

Variable	Healthy Controls (HC; n=16)	Participants with Methamphetamine Use Disorder (MUD; n=28)	Statistics
Age, years[a]	31.44 (2.14)	35.43 (1.87)	$t(42) = -1.35$, $p > 0.05$
Biological sex female/male (n)	10/6	14/14	$c^2(1) = 0.237$, $p > 0.05$
IQ estimate[a]	108 (9)	102.3 (3.90)	$t(4) = 0.715$, $p > 0.05$
Mother's Education, years[a]	14 (0.606)	12.75 (0.623)	$t(38) = 1.37$, $p > 0.05$
Race/Ethnicity (n)			$H(5) = 1.12$, $p > 0.05$
White	10	15	
African American	0	1	
Hispanic/Latinx	3	6	
Asian/Pacific Islander	1	2	
American Indian/Alaska Native	1	1	
Other	1	3	
Days of substance use in the previous 30 days			
Alcohol	7.4 (2.42)	5.964 (1.41)	$t(41) = 0.550$, $p > 0.05$
Marijuana	5.583 (3.02)	2.423 (1.25)	$t(14.9) = 0.966$, $p > 0.05$
Tobacco	21 (3.94)	24.37 (2.23)	$t(37) = -0.793$, $p > 0.05$
No. who smoked	6	27	$c^2(1) = 14.4$, $p < 0.001$ ***
Methamphetamine		20.93 (1.50)	

[a]Values are means (SE)
IQ estimate = Weschler Test of Adult Reading

Table 3.3. Demographics of participants who performed the one-balloon BART

3.2.2 fMRI methods

3.2.2.1 MRI data acquisition

Imaging was performed on a 3-T Siemens Trio MRI system, with 302 functional task-based and 152 resting-state T2*-weighted echoplanar images (EPI) acquired (slice thickness = 4 mm; 34 slices; repetition time = 2 seconds; echo time = 30 milliseconds; flip angle = 90°; matrix = 64 × 64; field of view = 200 mm). High-resolution, T2- weighted matched-bandwidth scans were collected in the same plane as the EPI data. The orientation for these scans were oblique axial to maximize brain coverage and optimize signal from ventromedial prefrontal cortex (PFC). T1-

weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scans were also acquired.

3.2.2.2 MRI data pre-processing

ROIs were selected based on prior literature showing the role of the dorsolateral prefrontal cortex (DLPFC) and anterior insula in BART performance [89,233], as well as differences between MUD and HC groups [86]. The DLPFC ROI was defined from a contrast of parametric modulation of pumps for HC vs. MUD groups, as shown in [86]. To define the right anterior insula (**Fig. 3.1**), we compared anatomical landmarks from a probabilistic atlas [308] to functional connectivity-based parcellations of the insula [309,310]. Based on these studies, we used the precentral sulcus to segment the anterior from the posterior insula. Using this landmark, we manually determined the anterior/posterior insula subdivisions from the MNI152 template.

Image analysis was performed using FSL 5.0.2.1 (http://www.fmrib.ox.ac.uk/fsl). Images were realigned to compensate for motion [311] and high-pass temporal filtering was applied (100 s cut-off). Data were skull stripped and spatially smoothed (5-mm full-width-at-half-maximum gaussian kernel). The echoplanar images were registered to the matched-bandwidth image, then to the high-resolution MPRAGE image, and finally into standard Montreal Neurological Institute space using 12-parameter affine transformation and FMRIB's nonlinear image registration tool [312].

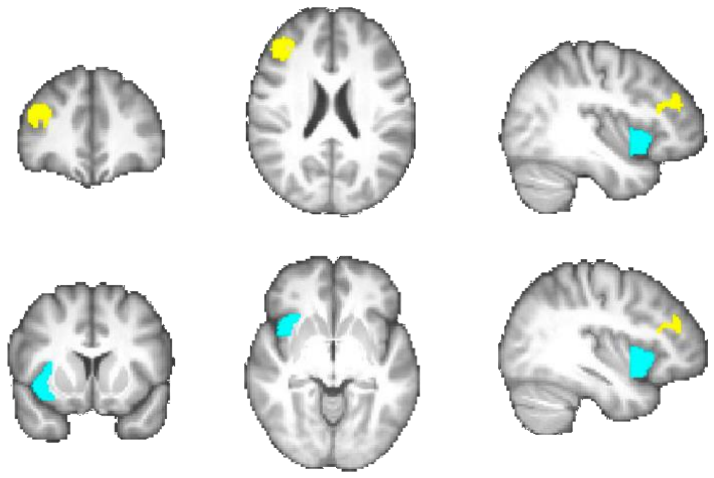

Figure 3.1. Dorsolateral prefrontal cortex and anterior insula regions of interest. *A priori*-defined regions of interest (ROIs) for the fMRI BART analysis. The right dorsal lateral prefrontal cortex (rDLPFC) ROI (yellow) was defined through a contrast of parametric modulation of activation by pump number for HC vs. MUD groups, as shown in Kohno, Morales, Ghahremani, Hellemann and London (86). Shown are slices that intersect MNI coordinates x=40, y=38, z=22. The right anterior insula ROI (teal) was anatomically defined as described in the methods. Shown are slices that intersect MNI coordinates x=38, y=12, z=-6.

3.2.2.3 Task-based fMRI data analysis

Parametric modulation of activation was tested as the linear relationship between pump number and activation, as described in previous reports [86]. Pump number reflects the increasing risk and reward of each pump. Four types of events were included in the general linear model: pumps on active balloons, cash outs, balloon explosions, and pumps on control balloons. Two regressors for each of the 4 types of events were included to obtain estimates of parametric modulation [313] of activation by pump number and of mean activation for each event type. Regressors estimating the mean activation for each event did not include increasing risk by pump. The contrast of interest to check for modulation of activation with risk and reward levels was parametric pump events.

Regressors were created by convolving a set of delta functions, representing onset times of each event with a canonical (double-gamma) hemodynamic response function. The first temporal derivatives of the 8 task-related regressors were included to capture variance associated with the temporal lag of the hemodynamic response along with 6 motion parameters estimated during motion correction. Fixed-effects analyses were conducted for each imaging run of data from each participant and again to combine contrast images across both runs. All analyses included sex and age as nuisance covariates.

Parameter estimates (average of β values) corresponding to modulation of activation by pump number were extracted from each ROI and used as dependent variables in Generalized Linear Models (GLMs) with dependent variables of age, biological sex, and computational parameters of risk-taking (γ) or updating rate (η). First, the interaction of participant group with the associations between computational parameters and modulation of activation was tested. Subsequently, the relationship between computational parameters and modulation of activation during decision making was examined within each group.

3.2.3. PET procedures and analysis

3.2.3.1.PET acquisition

PET scans were acquired by the 16 HC and 28 MUD participants who performed the one-balloon version of the BART. PET scanning was conducted using [^{18}F]fallypride, which was prepared as reported, using [^{18}F]fluoride ion [314]. [^{18}F]Fallypride is not selective for D2 receptors and has approximately equal affinity for D2 and D3 receptors [315], but its affinity for D2-type receptors is adequate for imaging in extrastriatal as well as striatal regions [314].

Scans were acquired on a Siemens EXACT HR+ scanner with in-plane resolution full-width at half-maximum (FWHM) 4.6 mm, axial FWHM = 3.5 mm, axial field of view = 15.52 cm, in 3D mode. After a 7-min transmission scan acquired using a rotating ^{68}Ge/^{68}Ga rod source for attenuation correction, PET dynamic data acquisition was initiated. Participants were free to open and shut their eyes. [^{18}F]fallypride (5 mCi ± 10%) was injected as an intravenous bolus. Dynamic scanning was conducted in two 80-min blocks separated by a 10-20 min break. Data were corrected for decay, attenuation, and scatter, and were reconstructed using ordered subset expectation maximum (OSEM; 3 iterations, 16 subsets) with ECAT v7.3 software (CTI PET Systems Inc.).

3.2.3.2.PET data analysis

Reconstructed PET data were corrected for head motion using FSL MCFLIRT. MRI-to-PET coregistration was performed using FSL FLIRT (FMRIB Software Library) [311]. Volumes of interest (VOIs) were the bilateral midbrain, bilateral medial and lateral OFC, bilateral insula, and striatal subdivisions of the nucleus accumbens, caudate, and putamen (all bilateral). VOIs were defined on each MPRAGE scan from the Harvard-Oxford atlases transformed into individual native space, or using FSL FIRST [316]. VOIs of striatal functional divisions [317] were transformed to native space using FSL FNIRT. Cerebellar VOIs were manually drawn bilaterally in MNI152 space and transformed to the corresponding individual structural MRI.

Time-radioactivity data were extracted and imported into PMOD 3.2 for kinetic modeling (PMOD Technologies Ltd.). Time-radioactivity curves were fit using the simplified reference-tissue model (SRTM) [318] to estimate k2′, the rate constant for transfer of the tracer from the reference region to plasma. A cerebellar VOI was used as a reference region, and a volume-weighted average of k2′ estimates from high-radioactivity regions (caudate + putamen) computed.

The time-radioactivity curves were refit using the SRTM2 model [319]. BP_{ND} was calculated by subtracting 1.0 from the product of tracer delivery (R1) and tracer washout (k2′/k2a).

Separate independent t-tests were used to check for group differences in BP_{ND} of all VOIs, as well as their relationship to covariates when accounting for group. BP_{ND} in the ventral tegmental area/substantia nigra (VTA/SN) and the whole nucleus accumbens, caudate, and putamen were analyzed for their association with the risk-taking parameter from the BART cognitive model. Cortical D2-type BP_{ND} was analyzed in the medial and lateral orbitofrontal cortex (OFC) and insula for association with the updating rate parameter. We tested for quadratic associations between cortical BP_{ND} and behavioral parameters because prior research had demonstrated nonlinear relationships between dopamine function and cognitive function and decision-making [93,297,301-305].

3.3. Results

3.3.1. Demographic factors

Demographics for participants who performed the one-balloon version of the BART are shown in **Table 3.1**. Cigarette smoking status was the only variable that differed significantly between groups and was thus included in statistical analyses. All regions aside from the VTA/SN and insula showed group differences in binding potential (*ps* < 0.0001). Age was correlated with dopamine D2-type BP_{ND} in the putamen, caudate nucleus, and all cortical regions. There were significant differences in dopamine D2-type BP_{ND} in the VTA/SN and medial OFC by biological sex. No demographic variables were significant when accounting for group.

For the cohort that performed the two-balloon version of the BART during fMRI (**Table 3.2)**, age and smoking status significantly differed between HC and MUD groups. The HC group

(aged 17-54 years) included 36 and the MUD group (aged 22-52 years) included 19 participants who smoked cigarettes.

Characteristics of the participants who performed both the two-balloon BART and the LAT are shown in **Table 3.3**. There were no significant group differences in any demographic variables.

3.3.2. Traditional analysis of the BART

On both versions of the task, HC and MUD groups pumped significantly more as the task progressed, and there were no interactions between group and trial number or outcome of the previous trial. When controlling for group, mean adjusted pumps (i.e., the number of pumps on trials that did not end in an explosion) was not significantly associated with any demographic variable. There were no group differences in mean adjusted pumps, whether or not smoking status was controlled.

3.3.3. Computational analysis of behavior of the BART

One-balloon BART. When controlling for group, updating rate (η) was not significantly associated with any demographic variable. The parameter of risk-taking (γ), however, differed significantly by biological sex, as women look less risk than men [$\beta - 0.385\,, t(41) = -3.37, p < 0.01$]. When controlling for group, the parameter η was not associated with γ or with mean adjusted pumps, but γ was significantly associated with mean adjusted pumps [$\beta = 0.018, t(41) = 4.4, p < 0.0001$].

Posterior distributions of computational parameters are shown in **Fig. 3.2A** and **Fig. 3.2C**. The posterior distribution of group mean differences is shown in **Fig. 3.2E**. MUD participants were very close to displaying credibly lower updating rates than HC participants, with 92.7% of

posterior samples below zero (95% HDI of group difference: -0.0047 – 0.0004). When accounting for the group difference in smoking status, a GLM revealed that MUD participants were significantly slower to update their behavior $[\beta = -0.00275, t(40) = -5.195, p < 0.0001]$ than the HC group, but there were no differences in the risk-taking parameter, including when controlling for biological sex and/or smoking status (**Fig. 3.3A**). There were no group differences in τ.

Two-balloon BART. The parameter of risk-taking (γ) was associated with ethnicity, age, and smoking status. Updating rate (η) was associated with IQ. Just as on the one-balloon task, the parameter γ was significantly associated with mean adjusted pumps $[\beta = 0.015, t(97) = 10.1, p < 0.0001]$. However, when controlling for group, η also was associated with both γ and mean adjusted pumps. Due to the large group difference in η, Pearson's correlations were calculated separately for each group. In HC participants, there were significant negative correlations for η with γ $[r(68) = -0.50, p < 0.0001]$ and mean adjusted pumps $[r(68) = -0.39, p = 0.00078]$. In MUD participants, there was only a correlation between η with γ $[r(28) = -0.45, p = 0.01]$.

Posterior distributions of computational parameters are shown in **Fig. 3.2B** and **Fig. 3.2D**. MUD participants were very close to displaying credibly lower updating rates than HC participants, with 92.7% of posterior samples below zero (95% HDI of group difference: -0.0064 – 0.0008) (**Fig. 3.2F**). MUD participants also were close to displaying credibly lower risk-taking parameters than HC participants, with 95.4% of posterior samples below zero (95% HDI of group difference: -0.29-0.018).

When accounting for the group difference in age and smoking status, a GLM revealed that the MUD group had a lower propensity towards risk-taking $[\beta = -0.227, t(86) = -4.02, p =$

0.0124] and were slower to learn from their behavior [$\beta = -0.00292, t(86) = -16.5, p < 0.0001$] than the HC group (**Fig. 3.3B**). There were no group differences in τ.

Drug Use Measures. There were no associations between any of the behavioral measures from either task and drug use in the 30 days prior to testing.

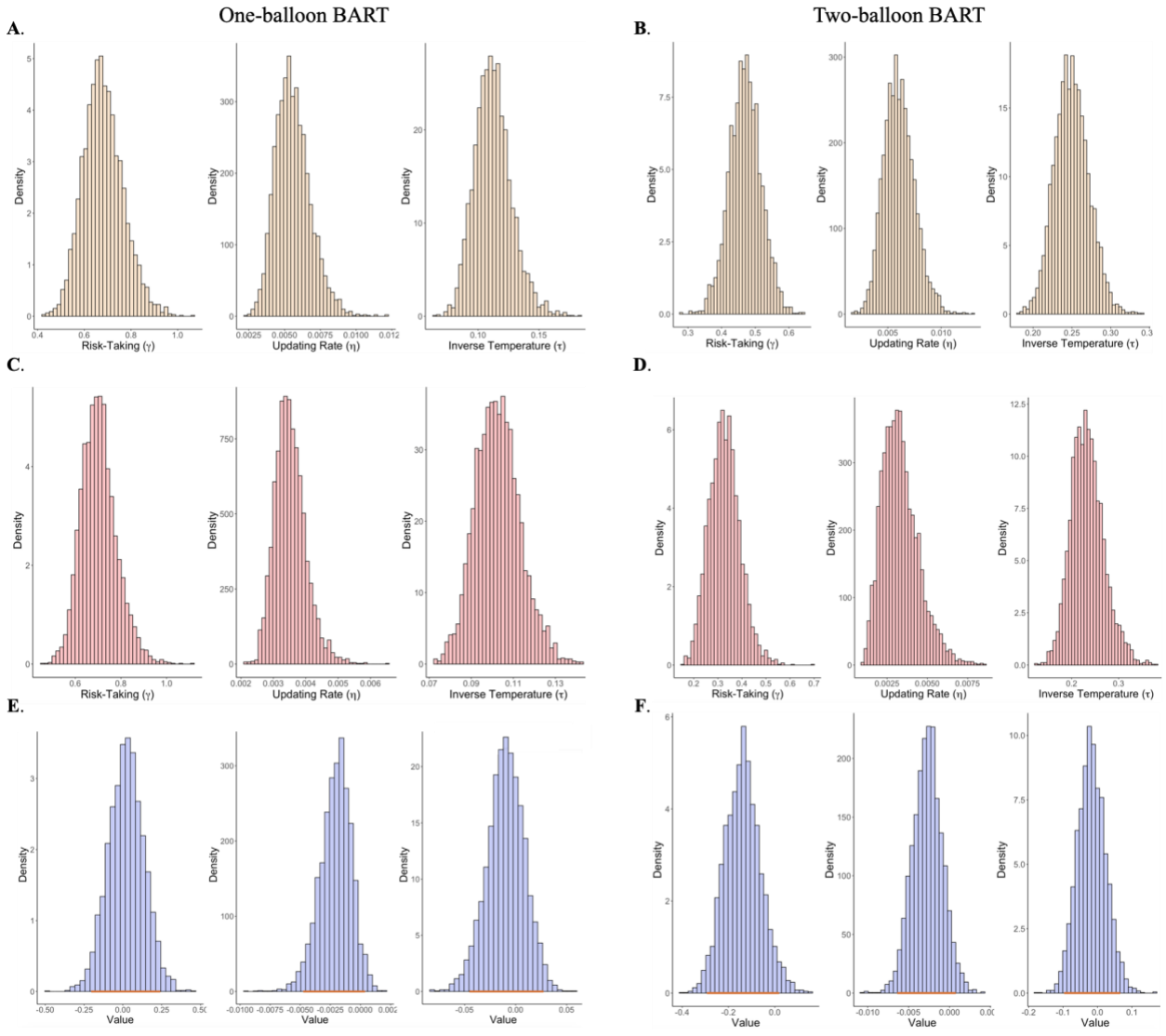

Figure 3.2. Posterior distributions of computational parameters from the BART. Parameters were estimated using hierarchical Bayesian analysis separately for healthy control (HC) (*yellow*) and Methamphetamine Use Disorder (MUD) (*red*) groups who performed the one-balloon (left

column; **A**, **C**, **E**) or two-balloon (right column; **B**, **D**, **F**) versions of the BART (**A**, **B**, **C**, **D**) The posterior distributions (i.e., group parameter estimates) of each parameter are plotted. Higher values of γ and η indicate higher risk-taking and updating rate, respectively. The inverse temperature τ represents choice consistency. (**E**) Posterior distributions of group mean differences are plotted with the 95% Highest Density Interval (HDI) indicated in red for γ $(-0.20 - 0.24)$, η $(-0.0047 - 0.0004)$, and τ $(-0.045 - 0.027)$. Group differences are considered credible if the HDI does not contain zero. For the updating rate (η), 92.7% of posterior samples were below zero. (**F**) Posterior distributions of group mean differences were plotted with 95% Highest Density Interval (HDI) is indicated in red for γ $(-0.29 - 0.018)$, η $(-0.0064 - 0.0008)$, and τ $(-0.097 - 0.065)$. For the updating rate (η), 92.7% of posterior samples were below zero. For the risk-taking parameter (γ), 95.4% of posterior samples were below zero.

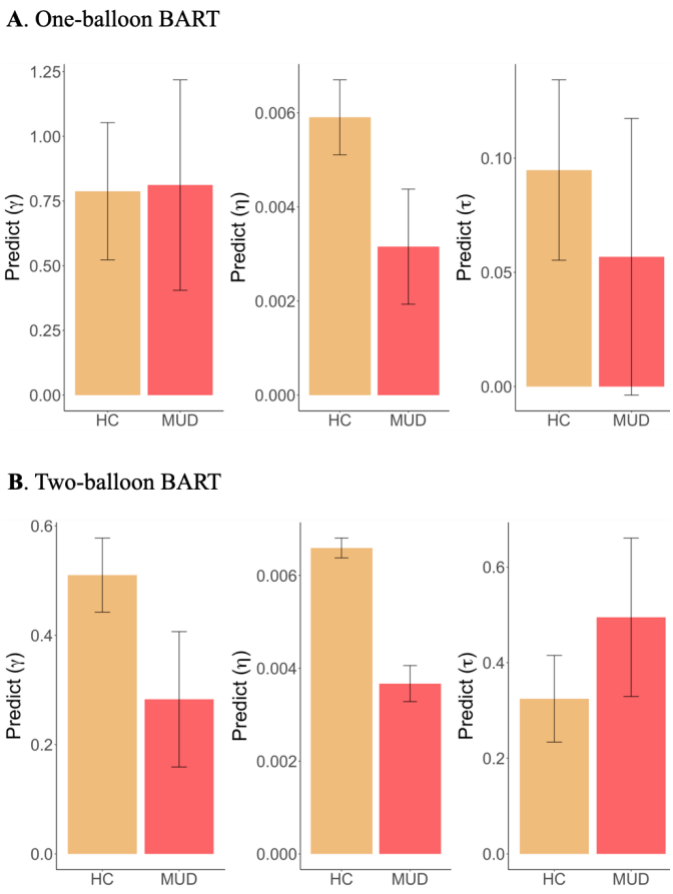

Figure 3.3. Estimated marginal effects of group on computational parameters from the BART. The posterior means of choices parameters were used in generalized linear models (GLMs) to account for group differences and covariates. (**A**) Estimated marginal effects of parameters from the one-balloon BART on group are plotted while accounting for smoking status and biological sex. The MUD group was significantly slower to learn from their behavior than the HC group ($p < 0.0001$), but there were no differences in the risk-taking parameter or inverse temperature. (**B**) The posterior means of choices parameters from the two-balloon BART performed during fMRI were used in generalized linear models (GLMs) to account for group differences in smoking status and age. Estimated marginal effects of parameters on group are plotted while accounting for smoking status and age. The MUD group had a lower proclivity towards risk-taking ($p = 0.0124$) and were slower to learn from their behavior ($p < 0.0001$) than the HC group.

3.3.4. Relationships between risk-taking on the BART and loss aversion on the LAT

In the subsample that performed both the LAT and BART, the interaction of group and age on loss aversion (λ) was significant [$\beta = 0.146, t(31) = 3.465, p = 0.00172$]. The updating rate parameter from the BART (η) was negatively associated with estimated IQ in MUD participants [$\beta = -0.0000298, t(10) = -2.353, p = 0.0404$]. Age was thus included as a covariate in analyses of loss aversion and estimated IQ in analyses of updating rate.

There were no significant associations between parameters from the BART and loss aversion. Results were unchanged when the interaction term was included.

3.3.5. Associations between updating rate and parametric modulation of activation in the DLPFC and anterior insula by level of risk

There were main effects of group and updating rate (η) on parametric modulation of the right DLPFC activation by risk (indexed by pump number). MUD participants showed less modulation compared to the HC group [$\beta = 55.6, t(85) = 3.87, p = 0.000212$] and updating rate was negatively correlated with rDLPFC sensitivity to risk in both groups [$\beta = -13200, t(85) = -3.08, p = 0.00276$] (**Fig. 3.4A**). There was no interaction between group and modulation of DLPFC activation by risk on updating rate.

In the right anterior insula, the interaction of group and modulation of activation by risk showed a nonsignificant trend [$\beta = 22700, t(85) = 1.67, p = 0.0986$], and the simple effect of updating rate was significant [$\beta = -26200, t(85) = -2.027, p = 0.0459$] (**Fig. 3.4B**). Thus, only the MUD group exhibited a negative correlation between updating rate and parametric modulation of the right anterior insula during the decision to take risk; there was no relationship in HC participants.

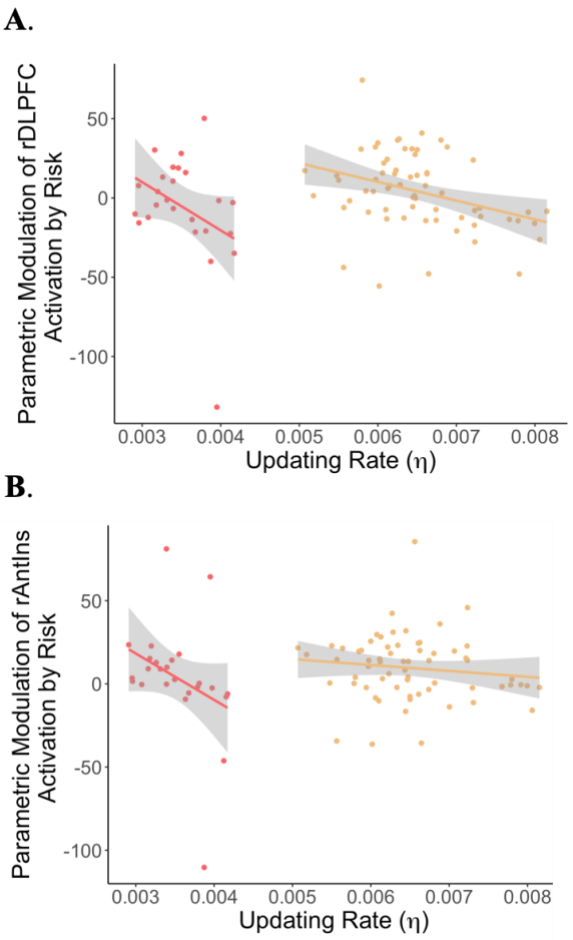

Figure 3.4. Updating rate and parametric modulation of activation in the right DLPFC and right anterior insula by risk during decision-making on the BART.(**A**) There was a main effect of group on parametric modulation of the right dorsolateral prefrontal cortex (rDLPFC) activation by risk (indexed by pump number), where HC participants had greater rDLPFC sensitivity to risk (p = 0.00021). Both groups exhibited a negative relationship between updating rate and parametric modulation of the rDLPFC activation by risk (p = 0.0028). (**B**) However, the interaction between group and modulation on updating rate was trending in the right anterior insula (rAntIns) (p = 0.099), where only the MUD group exhibited a negative correlation between updating rate and parametric modulation of the rAntIns during the decision to take risk; there was no relationship in HC participants. Age and biological sex were included as covariates. Shaded grey regions indicate standard errors.

3.3.6. Relationship between risk-taking on the BART and striatal dopamine D2-type BP_{ND}

Individual GLMs were used to determine whether the risk-taking parameter γ was related to dopamine D2-type BP_{ND} and the interaction of group and BP_{ND} on γ. Dopamine D2-type BP_{ND} in striatal subregions and the VTA/SN were significantly associated with risk-taking on the BART, where there was a negative relationship in the HC but not the MUD group (**Fig. 3.5A-D**). Because the results differed when smoking status (**Table 3.4**) and/or biological sex (**Table 3.5**) were included in the model, both are presented. There were no associations between γ and BP_{ND} in cortical regions.

3.3.7. Relationships between updating rate on the BART and dopamine D2-type BP_{ND} in the insula and medial OFC

Dopamine D2-type BP_{ND} was not related linearly to the updating rate parameter η in any of the cortical or striatal ROIs. However, there was a U-shaped relationship between η and BP_{ND} in the insula, and an inverted U-shaped relationship between η and BP_{ND} in the medial OFC (**Table 3.6**; **Fig. 3.5E-F**).

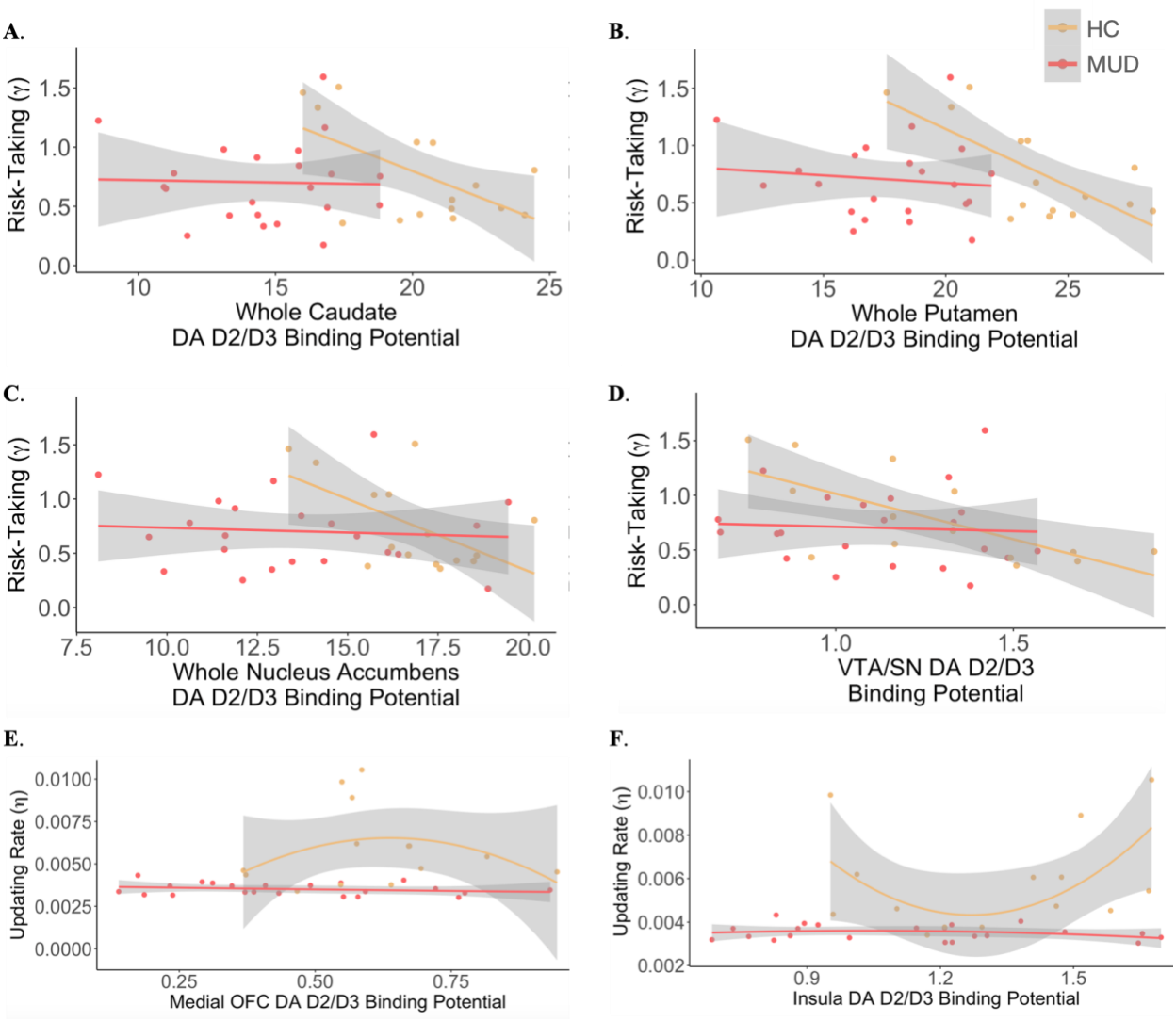

Figure 3.5. Striatal and cortical dopamine D2/D3 BPND and computational BART parameters. (**A**, **B**, **C**, **D**) Main effects of group and region were significant for all regions. Depending on the covariates, the interaction of group and region on the risk-taking parameter were significant in the putamen and ventral tegmental area/substantia nigra (VTA/SN). Full statistics are presented in Table 3.3 and 3.4. (**E**, **F**) Dopamine D2-type (D2/D3) receptor binding potential (BPND) was not related linearly to η in any of the cortical or striatal ROIs. However, when the quadratic of region was tested, there were simple effects region and region^2 in the medial orbitofrontal cortex (OFC), lateral OFC, and insula. The interaction between group and region was significant in the medial OFC and insula, where there was a U-shaped relationship between η and BPND in the insula, and an inverted U-shaped relationship between η and BPND in the medial OFC. Full statistics are presented in Table 3.5. Grey shading indicates standard error of the mean.

	Region	*Group*	*Smoking Status*	*Region * Group*
Putamen	0.0045***	0.023**	0.80	0.048**
Caudate	0.019**	0.04**	0.55	0.072
Nucleus Accumbens	0.026**	0.04**	0.67	0.057
VTA/SN	0.0082***	0.04**	0.48	0.079

*Values denote beta estimates determined using Generalized Linear Models. Asterisks denote statistical significance. ****p < 0.0001 ***p < 0.001 **p < 0.01 *p < 0.05.*

Table 3.4. Association between risk-taking from the one-balloon BART and dopamine D2-type BPND with the covariate of smoking status

	Region	*Group*	*Smoking Status*	*Biological Sex*	*Region * Group*
Putamen	0.014**	0.032**	0.61	0.045**	0.072
Caudate	0.032**	0.028**	0.74	0.021**	0.053
Nucleus Accumbens	0.082	0.086	0.69	0.042**	0.13
VTA/SN	0.017**	0.013**	0.18	0.03**	0.035**

*Values denote beta estimates determined using Generalized Linear Models. Asterisks denote statistical significance. ****p < 0.0001 ***p < 0.001 **p < 0.01 *p < 0.05.*

Table 3.5. Association between risk-taking from the one-balloon BART and dopamine D2-type BPND with the covariates of smoking status and biological sex

	Region	*Region^2*	*Group*	*Smoking Status*	*Region * Group*	*Region^2 * Group*
Medial OFC	0.032*	-0.026**	0.0069	0.00018	-0.033*	0.026*
Lateral OFC	0.039*	-0.040*	0.0062	0.00014	-0.038	0.039
Insula	-0.057***	0.022***	-0.038***	0.000088	0.059***	-0.023***

*Values denote beta estimates determined using Generalized Linear Models. Asterisks denote statistical significance. ****p < 0.0001 ***p < 0.001 **p < 0.01 *p < 0.05.*

Table 3.6. Association between updating rate from the one-balloon BART and dopamine D2-type BPND

3.4. Discussion

We used a computational model to leverage the naturalistic elements of the Balloon Analogue Risk Task (BART) and elucidate differences in choice behavior between MUD and HC participants. The MUD group showed a marked deficiency in behavioral updating and advantageous risk-taking compared to the control group. When paired with neuroimaging,

dopamine D2-type receptor availability in the striatum and midbrain was associated with risk-taking; dopamine D2-type receptor availability in the insula and medial orbitofrontal cortex (OFC) was associated with behavioral updating. These findings demonstrate the advantages of pairing naturalistic risk tasks with computational modeling and neuroimaging to identify deficits in decision-making.

3.4.1. Risk-taking on the BART

While real-world examples suggest that individuals who suffer from substance use disorders engage in risky behaviors, studies of propensity towards "risk" in the laboratory largely depend on which definitions and tasks are used [69,266]. The BART is a complex task that presents circumstances in which taking risk is adaptive: mean adjusted pumps is directly correlated with total earnings on the task, and increased pumping secures more earnings overall. Thus, through feedback on the task, participants should update their estimation that the balloon will burst and learn that pumping is the optimal strategy.

That the risk-taking parameter (γ) from the BART was correlated with mean adjusted pumps confirms the accuracy of our model in capturing risk-seeking on the task. Risk-taking was lower in participants with MUD—a phenomenon also found in alcohol dependence [263] and adolescents who smoke cigarettes [87]. Women also took less risk than men, in line with previous findings [320-323]. Since MUD participants had slower updating rates than controls, their lower risk-taking may reflect impairments in estimating and updating outcome contingencies in uncertain circumstances [112]. Outcomes are more ambiguous in early trials of the BART when the participant has not yet received adequate feedback [75], and MUD participants may have particular difficulty estimating the probability of outcomes under uncertain conditions.

Although beyond the scope of the current analyses, control participants also may have taken a more broad frame of sequential choices [324]; since pumping over time resulted in net gains, and they had significantly higher updating rates than MUD participants, control participants may have learned that taking risk yielded greater reward [325]. MUD participants, on the other hand, may have had a more myopic perspective [326,327], viewing each pump as a potential reward that could be lost by risking an explosion [325]. Thus, the smaller immediate reward earned by cashing out may have more value than the larger but uncertain reward [132,150,328].

This valuation process may have been biased in part by the visceral responses to the balloon bursting [154,329], as individuals with addictions can have exaggerated responses to arousal [157,330]. Individuals with MUD also may be more sensitive to reward [132,150,328], but the rewards on the BART are also probabilistic, adding complexity to the computational process. Differing attitudes towards uncertainty in healthy control participants and those with substance use disorders [113,331-334] could manifest as an increased preference for taking the smaller immediate reward on the BART (*see Chapter 5*).

3.4.2. The dopaminergic system and goal-directed behaviors

Markers of dopamine in the brain, including striatal D2-type receptor availability [307] and polymorphisms in genes related to dopamine function [93,291], have been related to behavior on the BART. Here, dopamine D2-type BP_{ND} in the striatum and midbrain was associated with risk-taking but not behavioral updating. The relationship between updating rate and dopamine D2-type BP_{ND} in the insula followed a U-shaped function, and an inverted U-shaped function in the medial OFC. None of the associations were exhibited by MUD participants.

The ways in which dopamine receptors mediate goal-directed behavior is complex due to both cooperative and antagonistic activity [281,283]. Dopaminergic cell bodies in the midbrain innervate the brain through three main pathways: nigrostriatal projections from the substantia nigra (SN) pars compacta to the caudate nucleus and putamen, mesolimbic projections from the ventral tegmental area (VTA) to the nucleus accumbens and the olfactory tubercle, and mesocortical connections from the VTA to prefrontal cortical areas. Dopaminergic neurons have two patterns of firing: phasic burst activation in response to stimuli, and tonic spontaneous release [335,336]. At rest, the baseline activity of dopaminergic neurons causes small concentrations of dopamine to leak from the synapse into the extracellular space [337]. Such tonic dopamine release is thought to reflect the total number of active VTA neurons and responsiveness of the system to dopamine [293,337,338].

While tonic dopamine can activate high-affinity presynaptic D2-type receptors that inhibit the amplitude of phasic burst firing [339,340], postsynaptic D2-type receptors are associated with signaling via the indirect pathway through the basal ganglia and thalamus to the cortex [341,342]. Phasic burst firing releases large concentrations of dopamine that act on excitatory D1 receptors [337,343] to signal through the direct pathway [341,342]. Phasic and tonic release are regulated by different inputs, namely glutamatergic and cholinergic inputs into the VTA and presynaptic limbic and PFC glutamatergic connections, respectively [344].

Signaling at D1 receptors is associated with reward and salience, including reward prediction error and other aspects of reinforcement learning and decision-making [49,285], whereas D2-type receptor signaling is associated with behavioral inhibition and negative reinforcement [297,345,346]. In addition to dopamine D1 and D2 receptors, dopamine D3 receptors are hypothesized to be involved in cognition and motivation, including related to drug-seeking [347]. In contrast to the

deficiency in signaling at D2 receptors observed across addictions [348], individuals who use stimulants show upregulation of D3 receptors [349], particularly in the substantia nigra, where D3 receptor availability was correlated risky decision-making and behavioral impulsivity in individuals with Cocaine Dependence [350].

3.4.3. Striatal and midbrain dopamine D2-type receptors and risk-taking

Dopamine D2-type BP_{ND} in the striatum and midbrain was associated negatively with risk-taking in HC participants. Risk-taking propensity has been negatively associated with dopamine D2-type signaling in rodents [292-295]. Humans also show this association [273,288,289], and carriers of polymorphisms in the dopamine transporter gene (DAT1) that is thought to cause lower striatal dopamine availability took more risk on the BART [291]. The inverse relationship of risk-taking with striatal and midbrain dopamine D2-type BP_{ND} may reflect enhanced behavioral inhibition through the indirect pathway, perhaps in response to aversive outcomes on the task [341,342].

Aside from postsynaptic effects, higher concentrations of D2-type autoreceptors could result in greater dopamine tone and/or more inhibition of phasic release [64]. With higher dopamine tone, the influence of inputs into the striatum, including corticostriatal circuitry that directs reward-seeking [282,283,345,351,352], may be diminished [293]. Presynaptic D2-type receptors on corticostriatal terminals inhibit glutamate release [353] and preferentially modulate corticostriatal inputs [282]. Since HC participants with higher D2-type BP_{ND} took less risk, it may be through inhibition of corticostriatal afferents necessary for goal-directed behavior.

Healthy control participants with higher D2-type BP_{ND} also may be more sensitive to the option for immediate reward on the BART and thus take less risk in favor of the immediate reward. In HC participants, striatal D2-type BP_{ND} was correlated positively with task-based activation in

the ventral striatum when participants were choosing to take reward on the BART (i.e., cash out), and with risk-taking following cash-out choices [90]. Increases in risk-taking in participants administered dopamine D2-type receptor antagonists stemmed from increased sensitivity to reward magnitude [288], and animals administered D2-type antagonists or agonists had increased and decreased reward sensitivity on a probabilistic discounting task, respectively [354]. Thus, the negative association of risk-taking with striatal and midbrain D2-type receptor availability may be related to a sensitivity to reward.

If cashing out on the BART is compared to taking a smaller, sooner reward on a delay discounting task, then a relationship between higher D2-type BP_{ND} and a preference for cashing out seemingly goes against prior findings [126]. However, studies testing the direct relationship between dopamine receptors and delay discounting have found mixed results [355-357], and many suggest nonlinear relationship between delay discounting and dopamine function [260,302,358].

3.4.4. Updating rate and cortical activity

That participants with MUD have lower updating rates on the BART may reflect a deficit in estimating ambiguous risk as well as somewhat rigid decision tendencies characteristic of addiction [23,195,260]. The updating rate is not a learning parameter but describes how beliefs about the probability of the balloon bursting change from experience on the task. Behavioral updating drives behavioral change through the integration of distinct and overlapping cognitive processes, from behavioral flexibility to reward-related learning. Previous research from our lab and others have demonstrated impairments in reversal learning [270,271] and compromised reward learning circuits [271,359-363] in people with addictions, including MUD. It may be that chronic stimulant use disrupts learning and updating signals related to corticostriatal dopamine function [361-364].

The relationship between updating rate and modulation of activation in the anterior insula by risk and potential reward differed by group and may be related to impairments in updating rate in MUD. Insula activity is associated with aversion to and prediction of risk [35,99,277-279], and risk sensitivity of the anterior insula was negatively correlated with updating rate in MUD in the present study. Thus, activity in the insula may be biasing MUD participants away from taking adaptive risk on the BART by integrating arousal and the affective components of choice [25,39], including interoceptive sensations provoked by pumping (i.e., taking risk), with past perceptions of risk [365]. Such inputs may bias MUD participants by assigning too much value to the visceral loss provoked by the balloon exploding [158] and thus overestimating the probability of the balloon bursting.

Contrary to our hypothesis, there was no group difference in the association between updating rate and modulation of DLPFC activation by risk and potential reward (indexed by pump number). That the HC group did have greater modulation of DLPFC activation by risk than the SUD group, as reported previously [86], suggests that there are group differences in DLPFC function during risk-taking but not in the relationship of that function to behavioral updating. Aside from its hypothesized role in self-control [44], the DLPFC is involved in reversal learning [275], and neurons in primate DLPFC reflect the updating of value [276]. Together with the BP_{ND} results, these findings suggest an abnormality in MUD related to how the insula, DLPFC, and medial orbitofrontal cortex (OFC) work together to update behavior on the BART. The DLPFC shares reciprocal connections with the medial OFC [366] and both regions were associated with inflexible and habitual responding in MUD [367]. Repetitive transcranial magnetic stimulation (rTMS) of the DLPFC caused dopamine release in the medial OFC [368], where dopamine D2-type receptor availability was correlated with updating rate in the present study. Thus, activity in the DLPFC may modulate medial OFC dopaminergic signaling [369] related to behavioral updating.

3.4.5. Updating rate, cortical dopamine D2-type receptors, and nonlinear relationships

The current finding of nonlinear relationships between updating rate and dopamine D2-type BP_{ND} in the insula and medial orbitofrontal cortex (OFC) follow decades of research demonstrating quadratic relationships between measures of dopamine function and behavior [93,297,301-305]. Early studies demonstrated inverted U-shaped functions between cortical D1 dopamine receptors and cognitive functions, where performance was improved in those with lower baseline dopamine levels but impaired in those with higher baseline levels (see Cools and D'Esposito (304) for review). Quadratic relationships have been found between dopamine and risk-taking and flexibility, which may be mediated by striatal as opposed to cortical dopamine [304] or D2-type as opposed to D1 receptors [351,370]. This research suggests an optimal dopamine level of that is highly dependent on individual differences and basal dopamine levels. With particular relevance to the present studies, converging research has indicated that optimal levels of striatal and cortical D2-receptors maintain behavioral flexibility [297,302,370,371].

The inverted U-shaped relationship between medial OFC D2-type BP_{ND} and updating rate in the HC group suggests that more or less D2-type receptor density is associated with lower rates of behavioral updating [372,373], similar to findings of probabilistic reversals in rodents [374]. The medial OFC could influence behavioral updating through its role in the integration of changing outcome expectancies [296,298]. It has also long been implicated in addiction [29,375] due to its direct innervation from the VTA and dense projections to the nucleus accumbens [376], which also projects back to the OFC through the mediodorsal nucleus of the thalamus [377].

D2-type signaling and/or dopamine tone in the medial OFC may maintain flexibility [286,295,354,374,378] by responding to changing contingencies in probabilistic environments [379-381] and updating incentive values of response outcomes [382-385]. The medial OFC may be especially

sensitive to devaluation [378,386,387] during updating of values [388], and dysregulation related to D2-type receptors in the medial OFC of MUD participants may hinder responses to negative feedback on the BART and bias towards more rigid choices.

Compared to updating rate and dopamine D2-type BP_{ND} in the medial OFC, the relationship was the opposite direction in the insula, suggesting that dopamine in these two regions differentially impacts behavioral updating during risky decision-making. Diverging influences of dopamine receptors in the OFC and insula of rodents was shown for risky choices, whereby preference for risky choices was increased by pharmacological blockade of dopamine D2-type and serotonergic 5-HT_{1A} receptors in the anterior insula, but increased by blocking 5-HT_{1A} receptors in the OFC [389]. The U-shaped curve in the HC group suggests that deviation from the optimal level of D2-type receptors in the insula is associated with an impairment of behavioral updating. Von Economo neurons in the insula express dopamine D3 receptors and are related to arousal and incorporating visceral feelings into decision-making [390,391]. Since the BART is a visceral task and the insula has shown both increases and decreases in activity in response to changes in value [25], optimal dopamine tone may thus be necessary to respond efficiently.

3.4.6. Limitations and final remarks

These findings demonstrate a marked impairment in behavioral updating on the BART in MUD. Updating rate was correlated with sensitivity of the DLPFC and anterior insula to risk. Dopamine D2-type receptors in the striatum and midbrain were associated with risk-taking, and those in the insula and medial OFC were associated nonlinearly with updating rate, but only in HC participants. The lack of relationships between striatal or cortical dopamine D2-type receptors and behavioral measures in MUD participants suggests that dopaminergic signaling related to

behavioral updating are disrupted in MUD. Such findings demonstrate the advantage of pairing a visceral, naturalistic risk-taking task with a computational model capable of decomposing behavior. Combining with brain imaging can provide insights into the neural substrates of complex behavior, including risky behaviors that drive addictions.

The major limitation of this study was the small sample size. We also were unable to compare behavior on the two versions of the BART, as only 14 participants (5 HC and 9 MUD) performed both tasks (while visualization suggests similarities in pumping behavior, we cannot draw any firm conclusions). Our results regarding dopamine D2-type receptors are also not specific to D2 receptors, as the radiotracer we used has affinity for dopamine D2 and D3 receptors. While MUD participants took less risk on the BART, it is not known why. A deficit in updating rate was shown, but other factors may influence performance, including aversion to potential loss [88,392] and attitudes towards risk and uncertainty [393]. If MUD participants prefer the immediate reward of cashing out, they may be oversensitive to reward or they may prefer the certainty of cashing out to the uncertainty of continuing to pump. Chapters 4 and 5 address such questions.

CHAPTER FOUR

Loss Aversion

4.1 Loss aversion in healthy control participants: Age and posterior cingulate cortical thickness

4.1.1 Introduction

The proportion of the global population that is 65 years or older is increasing faster than those of other age groups; it is estimated that by 2050, one in four people in North America and Europe, and one in six people worldwide, will be over 65 [394]. As older adults face a myriad of choices that involve uncertainty and loss across multiple domains, changes in decision-making can substantially impact their quality of life [395,396]. Accordingly, the impact of aging on decision-making is of substantial interest [397,398]. Some reports have shown worsening in some aspects, particularly in more deliberative domains, such as applying decision rules [399]. Yet, older adults can show more advantageous decision-making than their younger counterparts, especially for choices that rely on life experience and acquired knowledge [400].

Many everyday decisions present a potential for loss, which increases in salience with age [397,401-403]. When making a choice that balances the chance of gain against the risk of loss, people of all ages tend to be risk averse and to accept a gamble only if the magnitude of the win vastly outweighs that of the loss. This phenomenon has been explained by loss aversion, which reflects the overweighing of losses compared to equivalent gains [240,404]. Despite reports of greater loss aversion in adults over compared to under 40 [405-407], some studies find no differences [400,408-410]. This discrepancy could be due to nonlinear effects of age on loss aversion, the exclusion of middle-aged participants in comparisons of older and younger groups [400], or differences in methods of measuring loss aversion [408,409].

Although aversions to risk and loss are presumably evolutionarily adaptive mechanisms [411-414], extreme sensitivity to potential loss can impair decision-making in laboratory tests [415,416]

and real-world choices [417-419]. Loss sensitivity also affects choices by people with psychiatric pathologies, such as affective disorders [420,421]. Notably, a curvilinear relationship exists between age and both real-world financial choices [422] and risky decision-making in the laboratory [423-425], with better performance by middle-aged adults than their younger and older counterparts.

The goal of this study was to determine whether loss aversion followed a curvilinear relationship with age, and whether such a relationship is mediated by thickness of the insula, ventromedial prefrontal/orbitofrontal cortex, and/or anterior and posterior cingulate cortices, all of which are particularly vulnerable to age-related atrophy [426-428], and are implicated in loss aversion [234,429,430]. Because risky decision-making [424,425] and associated cognitive functions [431-433] follow curvilinear trajectories with age, we hypothesized that age and loss aversion would be related by a quadratic function, and that cortical thickness would influence this relationship. Considering reports that the cortical regions selected for study exhibit linear age-related thinning [426-428], we hypothesized that cortical thickness would influence loss aversion after a threshold of atrophy had been reached. Loss aversion was measured using the Loss Aversion Task, and structural MRI was performed on participants from young adulthood through middle age.

4.1.2 Methods

4.1.2.1 Participants

Data presented here are from healthy, right-handed volunteers (40 women) between the ages of 17 and 54 who participated in studies that were approved by the University of California, Los Angeles Institutional Review Board. Of 130 participants (40 women) who performed the Loss Aversion Task, data from 24 were excluded during data analysis (*see Section 2.2.7*), leaving a final

sample of 106. Behavioral data from these participants, other than performance on the Loss Aversion Task, and corresponding MRI findings have been reported [86,167,434-452].

Participants were recruited using online and print advertisements. After initial screening, they received detailed information about the study and gave written informed consent before further screening for eligibility by physical examination, medical history, and psychiatric evaluation. Drug use history and demographic information were collected using questionnaires. Participants were excluded for medical or neurological disorders or any current Axis I psychiatric disorder except Nicotine Dependence, determined by the Structured Clinical Interview for DSM-IV [306]. After intake, participants returned on a different day to perform the Loss Aversion Task, which was administered using identical procedures for all studies. A subset of participants (n = 83) also received structural magnetic resonance imaging (sMRI) scans on a different day. Data from 5 of those participants were excluded during preprocessing, leaving 78 for analysis. The average time between behavioral testing and the MRI scan was 7 days. At intake and on each test day, participants were required to provide a urine sample that was negative for amphetamine, cocaine, methamphetamine, benzodiazepines, opioids, and cannabis. They were compensated in the form of cash, gift cards, or vouchers.

4.1.2.2 Structural MRI

Structural T1-weighted magnetic resonance images of the brain were acquired from 83 participants using a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence. Images were collected from 31 participants on Scanner 1: a 1.5-Tesla Siemens Sonata MRI scanner (Erlangen, Germany) with a standard quadrature head coil (TR = 1900 ms, TE = 4.38 ms, flip angle = 15°, FOV = 160 × 256 × 256 mm^2, 176 slices, resolution: 1x1x1 mm^3). Images from 33

participants were collected on Scanner 2: a 3-Tesla Trio TIM Siemens MRI scanner (Erlangen, Germany) using parameters of TR = 2530 ms, TE = 3.31 ms, flip angle = 7°, FOV = 176 × 256 × 256 mm^2, 176 slices, resolution: 1x1x1 mm^3. Data from the remaining 14 participants were acquired on Scanner 3: a different 3-Tesla Trio TIM Siemens scanner using the same parameters.

4.1.2.3 MRI processing

Anatomical MRI images were processed using FreeSurfer 6.0.0 (http://surfer.nmr.mgh.harvard.edu), which generates a three-dimensional model of the cortical surface and provides measurements of local cortical thickness [453]. Mean thickness within 72 automatically defined cortical parcels for each hemisphere were extracted from this model [454,455]. Data quality was evaluated using the Qoala-T supervised learning quality control tool [456], which identified data from 5 participants for exclusion, leaving data from the remaining 78 for the final analyses. As scans were acquired on different scanners, the ComBat procedure was used to harmonize the data and remove variability due to scanner type. ComBat has been validated on cortical thickness data and has been shown to robustly correct for scanner differences [457]. To preserve the variability due to age, we specified age as a biological variable for the ComBat model.

4.1.2.4 Statistical analysis

Statistical analyses were performed using RStudio version 1.1.456. Analysis of variance (ANOVA) or correlation, as appropriate, was used to determine whether λ was significantly associated with biological sex, race/ethnicity, estimated IQ [using the Wechsler Test of Adult Reading (WTAR) [249]], mother's years of education (as a proxy for socioeconomic status), or

cigarette smoking status. As shown below, only race/ethnicity was associated with λ and was therefore included as a covariate in subsequent analyses.

A generalized linear model (GLM) was used to assess the effect of age on loss aversion. The parameter estimate (λ) from the behavioral choice model was used as the dependent variable in a GLM with the independent variable of age. Based on previous research demonstrating a curvilinear relationship between age and economic decision-making under risk [424], a hierarchical regression analysis was used to test for a quadratic relationship between λ and age, with age^2 added as an independent variable for the second step of the model. On an exploratory basis, the same associations were tested with the risk attitude parameter, ρ.

The average of the mean cortical thickness of both hemispheres, weighted by cortical volume, was calculated to determine whether λ was related to whole-brain cortical thickness. Based on prior research indicating brain regions important for loss aversion [234,429,430] and cortical thinning of the cortex with age [426-428], a region of interest (ROI) analysis was performed, including the insula, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and posterior cingulate cortex (PCC). ROIs were created by calculating a weighted average of both hemispheres for each region. A weighted average was also used to combine the rostral and caudal ACC to create one ACC ROI, and the medial and lateral OFC to create one OFC ROI.

To assess the main effect of cortical thickness on λ, a GLM was used for each region with λ as the dependent variable and the linear and quadratic components of cortical thickness (cortical thickness and the square of cortical thickness) as independent variables. Estimated intracranial volume was included as a covariate. Results were corrected for multiple comparisons using the Holm-Bonferroni method.

For brain regions showing significant relationships of structure with λ, a mediation analysis was performed to test whether cortical thickness mediated the relationship between age and λ. Age-related cortical thinning was confirmed using a GLM with cortical thickness as the dependent variable, age as the independent variable, and biological sex, race/ethnicity, and estimated intracranial volume tested as covariates. Age^2 was then added as an independent variable for the second step of the model to check for any nonlinear effects of age.

The mediation model tested whether cortical thickness mediated the effect of age on λ. Because of the quadratic relationship between age and λ, age^2 was specified as the independent variable, with age and estimated total intracranial volume as covariates. To account for any nonlinearities, the square of cortical thickness was also included as a covariate. The mediation analysis used the "mediations" specification of the "mediation" package in R, which enables nonparametric causal mediation analysis [458,459]. Indirect effects, given by the Average Causal Mediation Effects (ACME), were computed using Monte Carlo simulations, and the 95% confidence intervals were computed by determining the effects at the 2.5^{th} and 97.5^{th} percentiles.

4.1.3 Results

4.1.3.1 Participant characteristics and covariates

Data presented are from 130 healthy, right-handed volunteers (40 women) between the ages of 17 and 54 (**Table 4.1**). Only race/ethnicity was associated with λ and was therefore included as a covariate in subsequent analyses. Biological sex, estimated IQ, cigarette smoking status, and years of mother's education had no significant effects on λ (ps > 0.05), and, therefore, were not included in subsequent analyses (results were consistent when measures of socioeconomic status, such as father's education, were used instead of mother's education). An

ANOVA revealed differences in λ based on race/ethnicity [$F(4,101) = 5.78$, $p < 0.01$], with post-hoc t-tests illustrating that Caucasians had higher λ than all other groups ($ps < 0.05$), and Hispanic/Latinx had higher λ than African Americans ($p < 0.05$); all other pairwise comparisons were nonsignificant ($ps > 0.05$). Based on these findings, subsequent analyses used race/ethnicity as a covariate which was coded as 1=Caucasian, 2=Hispanic/Latinx, 3=African American, and 4=Other.

Variable	Scanner 1 (1.5 T Siemens Sonata; n = 31)	Scanner 2 (3 T Trio TIN Siemens; n = 33)	Scanner 3 (3 T Trio TIM Siemens; n = 14)	Omnibus Statistics
Age, years[a]	32.8 (1.14)	19.9 (0.193)	38.0 (2.76)	F(2,75) = 61.1, p < 0.001***
Biological sex female/male (n)	18/13	8/25	4/10	$c^2(2) = 8.38$, p = 0.015*
IQ estimate standard score[a]	105.5 (2.153)	110.9 (1.843)	108.4 (2.408)	F(2,62) = 1.635, p = 0.203
Mother's Education, years[a]	12.3 (0.656)	14.8 (0.690)	13.3 (1.06)	F(2,72) = 3.16, p = 0.0482*
Race/Ethnicity (n)				$c^2(8) = 28.8$, p < 0.001***
White	9	27	9	
African American	6	1	0	
Hispanic/Latinx	13	2	3	
Asian/Pacific Islander	0	3	1	
Other	3	0	1	
Cigarette smoking, n	13	14	10	$c^2(2) = 3.94$, p = 0.139

[a]Unless otherwise indicated, values are means (SE)
IQ estimate = Weschler Test of Adult Reading.
* p < 0.05; ** p < 0.01; *** p < 0.001.

Table 4.1. Demographics of healthy control participants who performed the Loss Aversion Task and had MRI scans

4.1.3.2 Quadratic relationship between loss aversion and age

In data from the full sample, parameter estimates of the behavioral choice model, estimated using hierarchical Bayesian analysis, were consistent with published values [234,239,460]. Posterior distributions of the parameters are shown in **Fig. 4.1**. Means with standard errors and ranges were: $\lambda = 1.58$ (0.04; 0.76 – 2.61; loss aversion), $\rho = 0.60$ (0.0036; 0.44 – 0.70; risk attitudes), $\tau = 3.07$

(0.09; 0.96 – 6.74; choice consistency) and reaction time = 1.45 (0.0059; 0.206 – 4.49). When the quadratic variable of age was added to the model, both age [β = -0.067, t(97) = -2.24, p = 0.028] and age^2 [β = 0.0010, t(97) = 2.309, p = 0.023] had significant effects, and the model fit the data better than the linear model [ANOVA; F(97,98) = 5.33, p = 0.02, change in $R^2 = 0.0433$; **Fig. 4.2A**].

The curvilinear association between λ and age persisted in the subsample from which sMRI data were acquired (n = 78); when the quadratic variable of age was added to the model, both age [β = -0.0722, t(75) = -2.36, p = 0.021] and age^2 [β = 0.0011, t(75) = 2.46, p = 0.016] were significantly related to λ. The quadratic model provided a significantly better fit for the data than the linear model [ANOVA; F(75,76) = 6.074, p = 0.016; change in $R^2 = 0.070$].

4.1.3.3 Mediation by posterior cingulate cortical thickness of the age effect on loss aversion

Main effects: Mean overall cortical thickness was not significantly related to loss aversion (β = 0.072, t(77) = 0.152, p = 0.88) and was therefore excluded from subsequent analyses. There were no linear or quadratic main effects of cortical thickness on λ in the insula [linear: β = 1.71, t(71) = 0.111, p = 0.878; quadratic: β = -0.244, t(71) = -0.134, p = 0.894], OFC [linear: β = 0.169, t(71) = 1.56, p = 0.123; quadratic: : β = -3.18, t(71) = -1.57, p = 0.122], or ACC [linear: β = -1.257, t(71) = -0.124, p = 0.902; quadratic: β = 0.139, t(71) = 0.076, p = 0.939]. Although there were effects of both the linear and quadratic components of PCC thickness on λ [linear: β = -0.200, t(71) = -2.28, p = 0.026; quadratic: β = 3.82, t(71) = 2.20, p = 0.031], neither survived Holm-Bonferroni correction for multiple comparisons.

To determine whether there was a confounding effect of scanner, particularly given demographic differences between participants scanned on the different machines (**Table 4.1**), we

tested whether brain structure differed by scanner. There was a significant difference due to scanner [$F(2,75) = 10.53$, $p < 0.001$]. Post-hoc analyses revealed that PCC thickness measured on Scanner 2 was larger than on Scanners 1 and 3 ($p < 0.0001$), whereas data from Scanners 1 and 3 did not differ; ps > 0.05). Therefore, the aforementioned analyses of main effects were performed twice: both with scanner as a covariate and excluding data from Scanner 2. The results were unchanged: linear and quadratic components of PCC thickness affected λ ($p < 0.05$), but neither survived multiple comparison correction.

Mediation analysis: Age-related cortical thinning of the PCC followed a linear course [β = -0.00471, $t(73) = -2.22$, $p = 0.0294$; **Fig. 4.2B**], with no quadratic component [β = -0.000123, $t(72) = -0.546$, $p = 0.59$]. Due to the confounding effect of scanner, the mediation analysis was performed twice: once without the covariate of scanner, and once with data from Scanner 2 removed. The results were comparable, and results without those from Scanner 2 are reported here. PCC thickness significantly mediated the age-loss aversion relationship, as quantified by the Average Causal Mediation Effects (ACME; $p = 0.018$; **Fig. 4.2C**). To account for any nonlinearities, the mediation model was repeated with the square of PCC thickness as a covariate. Results were comparable (ACME; $p < 0.05$). Since linear age-related change in the PCC was confirmed, but age and λ were quadratically related, we examined which component of the λ-age relationship was mediated by PCC thickness. To visualize the relationship between λ and PCC cortical thickness for different ages, we plotted the relationship between PCC thickness and λ by age for younger (<35) and older (>35) participants (**Fig. 4.2D**). We split the data at the age of 35 as this was the inflection point of the age-loss aversion quadratic. The plot suggests that the mediation analysis captures an effect of PCC thickness on loss aversion that shifts throughout the

lifespan, potentially mediating the increase in loss aversion in later life as opposed to the decrease in young adulthood.

4.1.3.4 Exploratory analyses: risk aversion (ρ) and brain structure

The risk aversion parameter (ρ) was not significantly correlated with age [β = -0.000520, $t(98) = 0.83$, $p = 0.408$] or the quadratic variable of age [$\beta = 0.0000266$, $t(97) = 0.494$, $p = 0.622$]. There were no main effects for cortical thickness or the cortical thickness^2 on risk attitudes in any of the four ROIs: insula [linear: $\beta = -0.0557$, $t(72) = -0.050$, $p = 0.960$; quadratic: $\beta = 0.0142$, $t(72) = 0.077$, $p = 0.939$]; OFC [linear: $\beta = -1.08$, $t(72) = -0.980$, $p = 0.330$; quadratic: $\beta = 0.203$, $t(72) = 0.987$, $p = 0.327$]; ACC [linear: $\beta = -1.22$, $t(72) = -1.22$, $p = 0.228$; quadratic: $\beta = 0.219$, $t(72) = 1.214$, $p = 0.229$]; PCC [linear: $\beta = 0.911$, $t(72) = 0.993$, $p = 0.324$; quadratic: $\beta = -0.177$, $t(72) = -0.972$, $p = 0.334$].

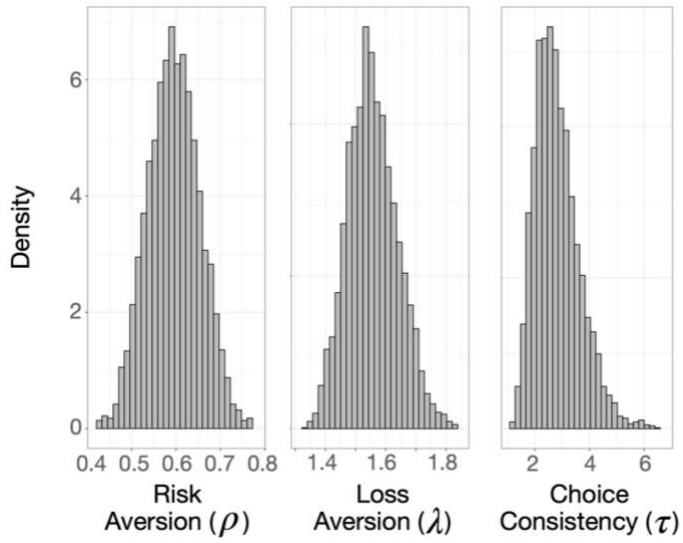

Figure 4.1. Posterior distributions of computational parameters from the Loss Aversion Task in healthy control participants. The distribution densities of each parameter are plotted. Higher values of λ indicate higher loss aversion and that the participant assigns more weight to losses than to gains of equal magnitude. When $\rho < 1$, the participant is risk-seeking for losses (more likely to take a gamble over a sure loss) and risk-averse for gains (more likely to choose a sure gain over a riskier prospect). The opposite is true when $\rho > 1$. Tau (τ) is the logit sensitivity and represents choice consistency, or the sensitivity of the participant to the difference between the certain amount and the gamble.

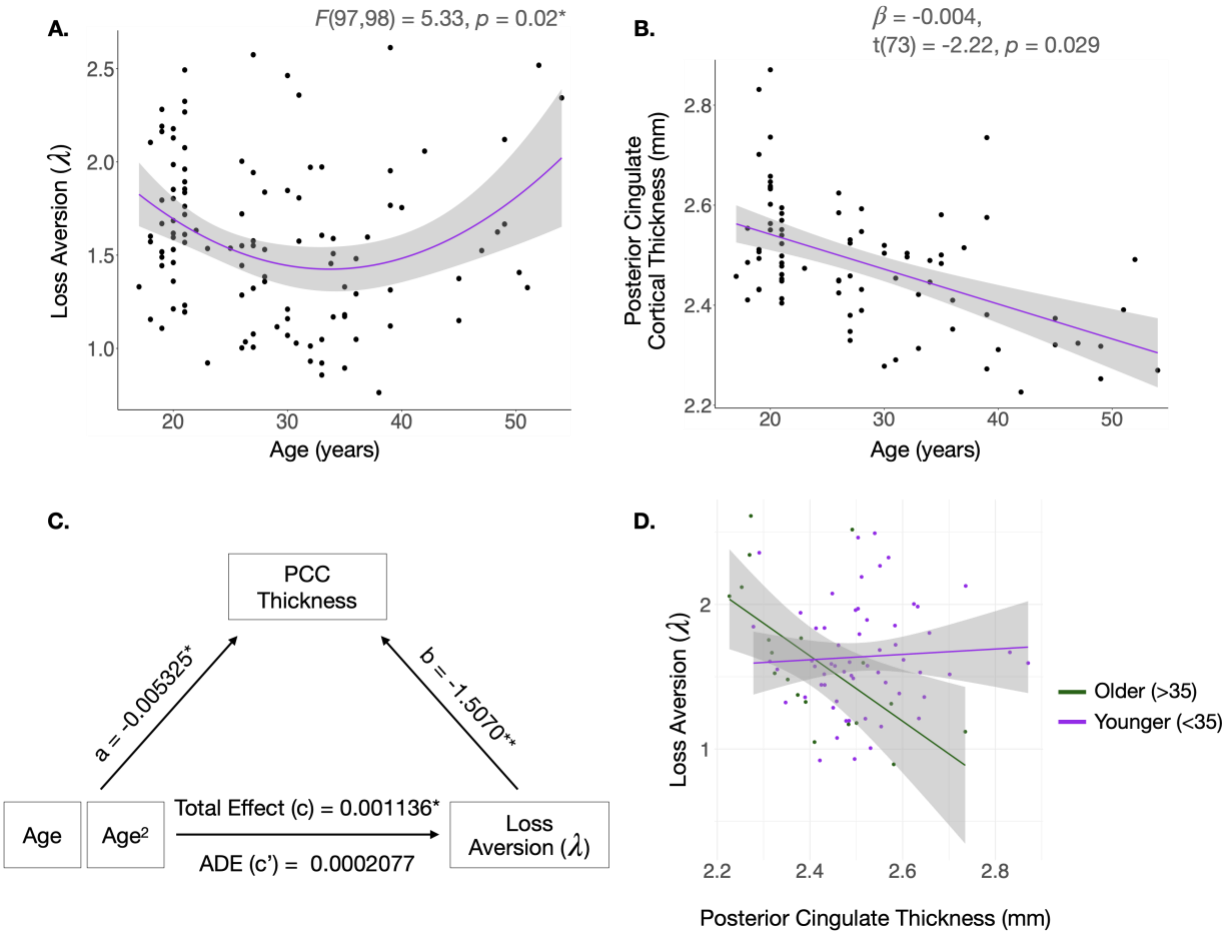

Figure 4.2. Relationships between age, loss aversion, and cortical thickness. **A and B.** Loss aversion (λ) follows a quadratic trajectory with age, whereas cortical thickness of the posterior cingulate cortex (PCC) declines linearly with time. Shading indicates standard error confidence intervals. **C.** Cortical thickness of the PCC mediates age-related changes in λ. The effect of age on PCC thickness is given by "a". The effect of PCC thickness on λ is given by "b". The Average Direct Effect (ADE; c') is the effect of age on λ when controlling for the mediator of PCC thickness. To calculate the Total Effect (c) of age on λ, without accounting for the mediator, both age and age^2 were included in the model and the regression coefficient for age^2 was taken as the strength of the effect. The causal mediation analysis was performed using nonparametric bootstrap confidence intervals and Monte Carlo simulations. The model included age, age^2, race/ethnicity, scanner, and estimated intracranial volume, as well as PCC thickness as the mediator. Age^2 was specified as the variable of interest. The measure of significance was given by the Average Causal Mediation Effect (ACME; p = 0.018*). Asterisks denote statistically significant results. * $p < 0.05$. ** $p < 0.01$. **D.** A negative relationship between PCC thickness and λ exists in older participants, but no relationship is present in participants under 35 years. The age of 35 was used to split the data into younger and older groups as it approximates the inflection point of the age-λ quadratic.

4.1.4 Discussion

With the global population of those 65 years and older growing faster than all other age groups [394], an understanding of the trajectory of decision-making over the lifespan may help people make better choices as they age [395,422]. Providing unique insight into the relationship between aging and decision-making, this study found an association between age and loss aversion that followed a quadratic function, declining across young adulthood and reaching a minimum around age 35 before increasing in middle-age. We also showed that PCC thickness mediates the relationship between age and loss aversion, suggesting that cortical thinning of the PCC is likely one of several factors that contribute to changes in decision-making throughout the lifespan. Because we also confirmed that PCC thickness declines linearly with age [426-428], PCC thinning may emerge as an important factor in loss aversion when a certain threshold of atrophy begins in middle age.

A nonlinear relationship between age and loss aversion could unify seemingly-conflicting results in the literature. Previous studies may have captured components of the quadratic relationship: participants aged 25-40 were less loss averse than those aged 41-55 [405], and participants ~18-28 were less loss averse than those aged ~60-86 years [406,407]. Others may have missed differences due to the nonlinearities observed here [400,410]. Our findings conflict with certain studies that did not find a quadratic relationship between age and loss aversion [408,409,461], which may be accounted for by the use of different tasks and methods to measure loss aversion [408,409,461]. Nevertheless, the loss aversion and risk preference parameters were very similar to those recently reported in a study that fit a prospect theory utility function to choice data from 146 participants [462].

The quadratic relationship between loss aversion and age mirrors the developmental trajectory of the cortex, during which the neurobiological mechanisms of cortical thinning differ

in development and aging [463]. Cortical maturation includes thinning in sensory and eventually fronto-cortical areas, and may extend beyond the mid-twenties [428], whereas cortical thinning approaching middle-age could be considered the onset of senescence [464]. Thus, PCC thickness may be unrelated to loss aversion during cortical maturation but may arise as a contributing factor once cortical thinning is underway.

With normal aging, functional changes include the reduction of the integration of coordinated activity between brain regions and increases in the localization of function within regions [465]. Such reorganization can contribute to shifts in the mechanisms underlying decision-making, perhaps increasing reliance on certain regions and not others. The PCC has been linked to the representation of subjective value during probabilistic choice tasks [111,123], reward signaling [466], attentional focus [467], and the dynamic adaptation of behavior [468]. Beyond a threshold of cortical thinning of the PCC, such functions may be impeded, rendering the most adaptive strategy that which is the least cognitively demanding [469]. Such adaptations could manifest in the use of an automatic or default heuristic, such as loss aversion, as shown by older adults using less cognitively taxing strategies in paradigms that involve risk [470]. The plasticity of the brain coupled with an adaptive response to shifting cognitive resources [471] may result in older adults opting for choices that are "good enough" instead of searching to maximize outcomes [i.e., using "satisficing" instead of maximizing strategies [407]]. During probabilistic choices involving loss, older adults are more likely to use such strategies when making decisions related to finances [472] and health [473]. Satisficing strategies are related selectively to loss aversion and not to risk preferences; those who have greater loss aversion tend to stop searching for an optimal solution sooner [474].

Notably, the Loss Aversion Task does not measure adaptive decision-making, and a loss-aversion strategy is not necessarily disadvantageous. Older individuals do not indiscriminately

make worse decisions [400,475-477], and heightened loss aversion may reflect naturally occurring shifts in values and motivations [401,478]. Changes in cognitive faculties with age are not linear across time nor uniform across domains; the age-related decline of certain cognitive faculties, such as processing speed, episodic memory, and executive functions [479,480], may lead older adults to revert to a previously learned response, such as loss aversion, that requires less cognitive effort. Meanwhile, prioritizing the use of abilities that remain intact or even improve with age, such as those that depend on experience, emotional intelligence, and crystallized intelligence, may improve efficiency [433,478,481,482]. While young adults can take more risk than older adults, risk-seeking as measured in the laboratory is separable from loss aversion [483]. Thus, it is possible for a participant to display a certain level of loss aversion in the face of uncertain gambles but still be seek risk when presented different options.

The PCC also is implicated in emotional processing, as it is activated by emotional words [484] and attending to emotional states [485]. Emotional processing is necessary for adaptive decision-making [154,486,487], and loss aversion is linked to the ability to regulate [239,460] and process [488] emotions. Such faculties peak around age 45-60 [433], and emotional content is particularly salient for older adults [489,490]. Since reliance on emotional information can compensate for age-related declines in cognitively challenging situations [481,491], increases in loss aversion with age may reflect greater focus on emotional or experiential dimensions of decision-making. Related to emotional processing is interoception, which is also involves PCC function [492,493] and tied to loss aversion [494]. Thus, age-related cortical thinning in the PCC may hinder the ability to efficiently integrate affective responses into complex choices, especially those that include loss.

As the present moment also gains salience with age, and prioritizing immediate or emotional wellbeing may intensify as time horizons constrict [495,496]. Converging evidence,

including self-reported goal orientations and performance on a probabilistic gambling task [401-403], indicates a shift later in life towards avoiding losses instead of seeking gains. In fact, loss orientation in later adulthood is correlated with subjective well-being [403]. When motivations shift towards optimizing immediate, emotional wellbeing and processing power becomes limited with age, perhaps partly because cortical thinning of the PCC impedes probabilistic assessments, loss aversion may naturally emerge as a low-effort response when facing choices with uncertainty.

Greater loss aversion in younger participants and its subsequent decline across young adulthood may similarly reflect the underdevelopment of complex probabilistic decision-making [470,497]. The Loss Aversion Task requires the time-limited integration of the magnitude and probability of both reward and loss to decide whether the chance of reward is worth the risk of loss; this estimation of subjective value is critical to adaptive choice behavior. Sensitivity to the difference in expected value between options follows an inverted U-shaped function, suggesting that the ability to distinguish appropriately between reward-based options may not fully develop until the mid-20s [470].

While the age range of 17 to 54 covered in the current study does not represent the entire lifespan, prior studies point to the trajectory of the quadratic relationship observed here. Loss aversion was a main driver of behavior in children as young as 5-8 years old [498], and adults older than those examined here (aged 61-86) exhibited greater loss aversion than young adults [406,407], consistent with the upward trend we observed from ages 35-54. Another limitation of this study is imbalance and relatively small samples of men and women; therefore, conclusive statements about effects of biological sex on loss aversion were not possible. That race/ethnicity was a significant factor in loss aversion also merits further investigation. The lack of an effect of age on risk-taking may reflect the type of task used, as the Loss Aversion Task is not necessarily designed to

comprehensively elicit risk preferences. Finally, the lack of significance when testing for the linear association between loss aversion and PCC thickness when correcting for multiple comparisons was likely due to nonlinearities in the relationship not captured in the statistical model – a negative correlation of loss aversion with PCC thickness in older participants, who had smaller PCC thickness, but not in participants whose PCC thickness crossed the inflection point on the U-shaped curve.

We conclude that cortical thickness of the PCC may supplement other cognitive and neurobiological age-related changes and arise as an important factor for loss aversion around the onset of age-related atrophy. Tracking age-related changes in the influence of decision-making biases, such as loss aversion, can inform policies that are tailored to the aging population [396]. Moreover, determining the age at which changes begin can introduce opportunities for early intervention, such as services, education, or incentives that could better inform important life decisions, such as those related to health and finances [395,422,499]. Identification of brain regions that affect such choices when altered with age provides the opportunity to forecast – and perhaps forestall – future decision-making impairments. To this end, future longitudinal studies may go beyond cross-sectional investigations to use measurements from key brain regions (e.g., PCC) at mid-life to predict changes in decision making biases later in life.

4.2 Loss aversion in Stimulant Use Disorder: Loss aversion and striatal dopamine D2-type receptors availability

4.2.1 Introduction

Individuals with substance use disorders persist in the use of drugs despite negative outcomes [23,195,500,501]. As such behavior may reflect insensitivity to negative consequences [82,102,105,106,108,109,160], individuals with these disorders may be less loss averse than healthy control (HC) participants. However, findings regarding sensitivity to loss of those with addictive disorders are mixed, with some showing greater, some showing lower, and some showing no difference in loss aversion than HC groups [82,105,106,502-512].

Sensitivity to loss is related to affective components of choice [239,420,460,488,494,513], and arousal may have an exaggerated impact in those with drug addictions [154,329]. Thus, whether loss aversion differs between HC and participants with Stimulant Use Disorder (SUD) remains unclear. These individuals also may perceive the discontinuation of drug use as a loss, and thus heightened sensitivity to loss may motivate continued drug use [500].

While many tasks involve potential loss, attitudes towards loss can be specifically assessed using the Loss Aversion Task (LAT) [234,460]. Loss aversion describes the overweighing of losses compared to equivalent gains [240,404] and has been used to explain the pervasive phenomenon of forgoing larger amounts of money to avoid potential loss (although see Gal and Rucker (514). For instance, when making a choice that balances the chance of gain against the risk of loss, people tend to accept the gamble only if the magnitude of the win outweighs that of the loss (e.g., flipping a coin to win $200 if it lands on heads and lose $100 if it lands on tails, versus winning $150 for heads and losing $100 for tails).

Studies have tested for differences in loss aversion between HC participants and individuals with addictive disorders [508-512], and the few studies that assessed neural function related to loss aversion in these groups demonstrated activations in areas of the prefrontal cortex, striatum, and amygdala [502,507]. These results mirror findings of brain activity during loss aversion in HC participants [234,429,430,460,513,515-517].

The striatum and amygdala both receive dopaminergic innervation and are implicated in addiction [12,330,518]. Since signaling at striatal dopamine D2-type (D2 and D3) receptors can mediate responses to negative or aversive outcomes [519,520], we hypothesized that striatal and/or amygdala dopamine D2-type receptor availability (binding potential, BP_{ND}) would be related to loss aversion. We also sought to determine whether HC participants differ in risky choices involving loss from those with SUD.

4.2.2 Methods

4.2.2.1 Participants

Data presented here are from 189 participants (112 HC and 77 SUD) who performed the Loss Aversion Task (LAT) across three studies (**Table 4.2**). All participants provided informed consent, as approved by the UCLA Institutional Review Board. They were fluent in English and in good physical and neurological health, as assessed by history and physical examination. All Axis I psychiatric diagnoses were excluded, other than Methamphetamine Use Disorder or Cocaine Use Disorder in the SUD group, and Tobacco Use Disorder, mild Alcohol Use Disorder, and mild Cannabis Use Disorder in both groups, determined by the Structured Clinical Interview for DSM-IV [306].

After intake, participants returned on a different day to perform a cognitive battery that included the LAT. A subset of participants (14 HC and 39 SUD) also performed trials specifically designed to elicit risk preferences. These 22 "gain-only" trials presented choices between a sure win of $5 or a 50% chance of winning a variable amount that varied from $4-$50 (*see Chapter 2 for task details*). On each study day, participants provided a urine sample that was negative for cocaine, methamphetamine, benzodiazepines, opiates, and cannabinoids. Individuals who smoked cigarettes were allowed to smoke until 15 min before testing to avoid effects of nicotine withdrawal. They were compensated with cash, gift cards, or vouchers.

The HC participants were recruited as part of a study of individuals who smoked cigarettes (N = 41) or as control participants for studies of stimulant dependence (N = 71). For the SUD group, one cohort comprised participants (N = 44) who met DSM-IV criteria for Methamphetamine Dependence, were not seeking or receiving treatment, and reported abstinence from methamphetamine for a mean (SD) of 6.80 (5.86) days, confirmed by negative urine test. Participants in the second cohort (N = 33) met DSM-5 criteria for SUD (cocaine type or amphetamine type), were recruited following ≈1 week of supervised abstinence in a residential substance use disorder treatment program, and reported abstinence from their drug of choice (cocaine or methamphetamine) for a mean (SD) of 7.00 (1.26) days before testing. A subset of participants who met DSM-5 criteria for Methamphetamine Use Disorder (MUD) received [^{18}F]fallypride PET scans (22 HC and 18 SUD).

4.2.2.2 PET data acquisition, processing, and analysis

PET scanning was conducted using [^{18}F]fallypride, which was prepared using [^{18}F]fluoride ion as reported [314]. [^{18}F]Fallypride has sufficient affinity to allow measurement extrastriatal regions

as well as striatal regions [314]. Scans were acquired on a Philips Gemini TF PET-CT scanner and reconstructed with the row action maximum likelihood algorithm (RAMLA). Participants were free to open and shut their eyes during the PET scan. A CT transmission scan was used for attenuation correction. [^{18}F]fallypride (5 mCi) was injected as a bolus, and emission data were acquired dynamically scanning was conducted in two 80-min blocks separated by a 10-20 min break.

Processing of decay-corrected, attenuation-corrected data was the same as described in Section 3.2.3. Separate independent t-tests were used to assess group differences in BP_{ND} of the striatum and amygdala, and GLMs to test the relationship of BP_{ND} to demographic covariates when accounting for group.

4.2.3 Results

4.2.3.1 Participant characteristics and demographics

Demographics of participants who performed the LAT are presented in **Table 4.2**. Data from 19 subjects were excluded on the basis of data quality (e.g., displaying implausible choices, as described in Section 2.2.7). The SUD group was slightly older, had fewer years of mothers' education, and included more participants who smoked cigarettes than the HC group. When group was included in the model, ethnicity, age, and the variable of study were significantly related to loss aversion (λ). Loss aversion was higher in younger participants and those who identified as Caucasian and Hispanic than in older participants and those who identified as belonging to other ethnic groups. The interaction of group and estimated IQ on loss aversion was also significant, whereby where was a positive relationship in participants with SUD but a negative relationship in control participants.

In the SUD group, there was no relationship between behavioral parameters and days since the last use of the drug of choice or days in the last month in which the participant smoked cigarettes, drank alcohol, or used marijuana. However, loss aversion differed by treatment status—participants who were not in treatment were more loss averse. Because the variables of study and inpatient status were both significant but described overlapping variance (i.e., three different studies, two of which included participants receiving inpatient treatment), the variable of study was included as a covariate in analyses.

HC and MUD participants who performed trials specifically designed to elicit risk preferences differed only on biological sex: there were more men than women in the SUD group $[\chi^2(1) = 4.6761, p = 0.0306]$. When accounting for group, ethnicity was associated with λ. When full utility functions were fit to these participants, ethnicity was associated with both λ and ρ and age only with ρ.

In subset of participants who received PET scans, there were no group differences in any demographic variables, and no variable was significantly associated with λ when group was included in the model.

Variable	Healthy Controls (n=112)	Participants with Stimulant Use Disorder (n=77)	Omnibus Statistics
Age, years[a]	28.61 (0.88)	38.03 (1.31)	$t(182) = -6.27$, $p < 0.0001$***
Biological sex female/male (n)	39/71	22/53	$c^2(1) = 0.594$, $p > 0.05$
IQ estimate[a]	105.5 (1.20)	103.28 (1.20)	$t(138) = 1.53$, $p > 0.05$
Mother's Education, years[a]	13.81 (0.26)	12.61 (0.33)	$t(172) = 2.85$, $p < 0.005$**
Study (n)			$H(2) = 45.7$, $p < 0.0001$***
Study 1	41	0	
Study 2	63	52	
Study 3	8	25	
Race/Ethnicity (n)			$H(4) = 6.3576$, $p > 0.05$
White	62	31	
African American	14	16	
Hispanic/Latinx	22	15	
Asian/Pacific Islander	7	5	
Other	7	10	
Days of substance use in the previous 30 days			
Alcohol	3.058 (0.40)	3.169 (0.58)	$t(171) = -0.163$, $p > 0.05$
Marijuana	2.789 (0.78)	4.55 (1.0)	$t(130.96) = -1.37$, $p > 0.05$
Tobacco	18.95 (1.7)	20.07 (1.4)	$t(143) = -0.516$, $p > 0.05$
No. who smoked	55	59	$c^2(1) = 18.3$, $p < 0.0001$***
Stimulants (cocaine or methamphetamine)		21.58 (1.17)	

[a]Values are means (SE)
IQ estimate = Weschler Test of Adult Reading

Table 4.2. Demographics of healthy control and participants with Stimulant Use Disorder who performed the Loss Aversion Task

4.2.3.2 Group differences in loss aversion

Loss aversion analysis. Participants with SUD were less loss averse (M = 1.72, SD = 1.06) than their healthy control counterparts (M = 2.09, SD = 1.18), as assessed by a two-sample t-test ($t(170) = 2.12, p = 0.036$) (**Fig. 4.3A**). However, GLMs with age, mother's education, study, and smoking status did not reach statistical significance. Results were unchanged in the sample that received PET scans (**Fig. 4.3B**).

Full utility model. Full utility functions were fit to the data of participants with SUD who completed trials to explicitly measure tolerance for risk as well as for loss. Posterior distributions

and group mean differences of λ, ρ, and τ are shown in **Figures 4.4A and 4.4C**. The 95% highest density interval (HDI) was used to assess the credibility of group differences in parameter estimates [246], as described in Section 2.3. The analysis revealed that SUD participants were close to displaying credibly lower risk tolerance than HC participants [95% HDI of group difference: $(-0.27 - 0.01)$, with 96.1% of posterior samples below zero] (**Fig. 4.4E**). When GLMs with age, mother's education, study, and smoking status were used to analyze group differences in λ and ρ, the SUD group showed lower risk tolerance than the HC group (p = 0.025) (**Fig. 4.5A**).

The full utility model was also fit to the data of participants who completed just the 50-50 gamble task (i.e., the Loss Aversion Task without risk-only trials) to explore whether the recovered parameter estimates replicated earlier work, despite the fact that accurate parameter recovery is in principle problematic using this approach (**Fig. 4.4B and Fig. 4.4D**). This analysis revealed no credible differences in any parameters (**Fig. 4.4F**), but the GLM revealed higher values of risk tolerance for SUD compared to HC participants $[\beta = 0.0765, t(139) = 3.42, p = 0.000816]$ (**Fig. 4.5B**). This suggests misestimation, as the analysis revealed the opposite association in participants who performed trials designed to accurately calculate risk tolerance and loss aversion. Indeed, when the data of participants who did complete risk-only trials were reanalyzed without the risk-only trials, the analysis replicated the misestimated results.

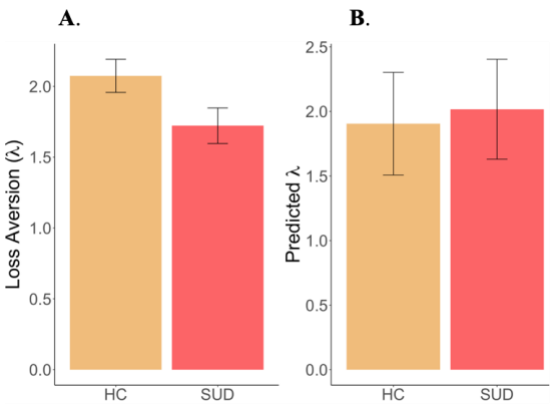

Figure 4.3. Group differences in loss aversion (λ). A logistic regression was fit to each participant's data with the gain and loss amounts as independent variables and the participant's choice as the dependent variable. Loss aversion was taken as the ratio of the coefficient for the loss amount to the coefficient of the gain amount. **(A)** Participants with SUD were less loss averse (M = 1.72, SD = 1.06) than their healthy control counterparts (M = 2.09, SD = 1.18), as assessed by a two-sample t-test ($t(170) = 2.12, p = 0.036$). (**B**) Estimated marginal effects of generalized linear models with age, mother's education, study, and smoking status are plotted. Results did not reach statistical significance.

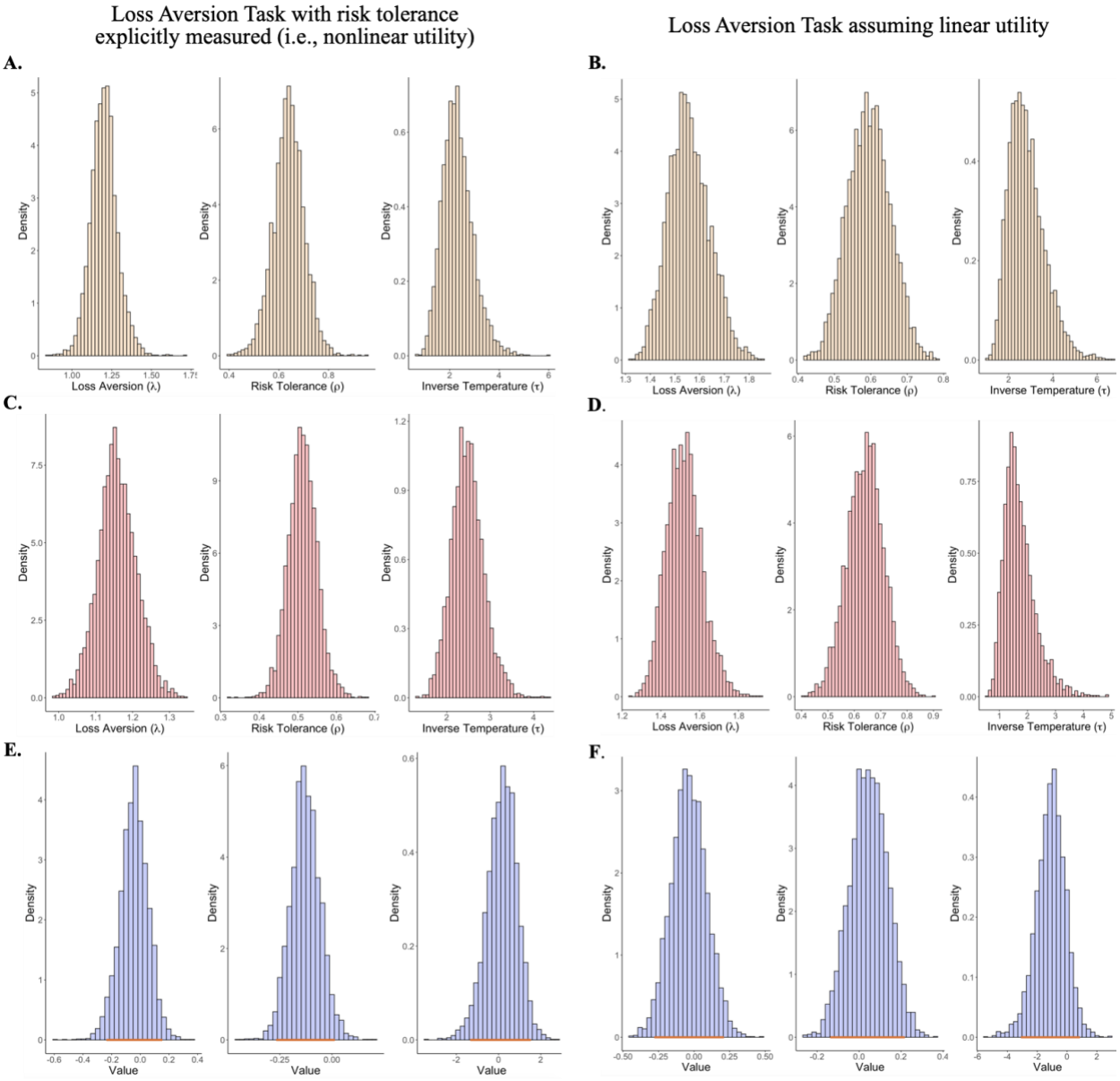

Figure 4.4. Posterior distributions of computational parameters from the Loss Aversion Task analyzed with full utility functions. Parameters were estimated using hierarchical Bayesian analysis separately for healthy control (*yellow*) and Stimulant Use Disorder (*red*) participants who completed the Loss Aversion Task. (**Left column**) Data from participants who completed trials specifically designed to isolate attitude towards loss (i.e., 22 extra trials that presented choices between a sure win of $5 or a 50% chance of winning a variable amount that varied from $4-$50). (**Right column**) Participants who only completed the Loss Aversion Task with 50-50 gambles. (**A-D**) The posterior distributions (i.e., group parameter estimates) of each parameter are plotted. Higher values of λ indicates higher loss aversion, and higher ρ less curvature of the utility function, or in other words higher risk tolerance or less risk aversion. The inverse temperature τ represents choice consistency. (**E**) Posterior distributions of group mean differences were plotted with the

95% Highest Density Interval (HDI) indicated in red for λ $(-0.25 - 0.15)$, ρ $(-0.27 - 0.01)$, and τ $(-1.2 - 1.6)$. Group differences are considered credible if the HDI does not contain zero. For risk tolerance (ρ), 96.1% of posterior samples were below zero. (**F**) Posterior distributions of group mean differences are plotted with the 95% Highest Density Interval (HDI) indicated in red in for λ $(-0.24 - 0.15)$, ρ $(-0.27 - 0.01)$, and τ $(-1.3 - 1.53)$.

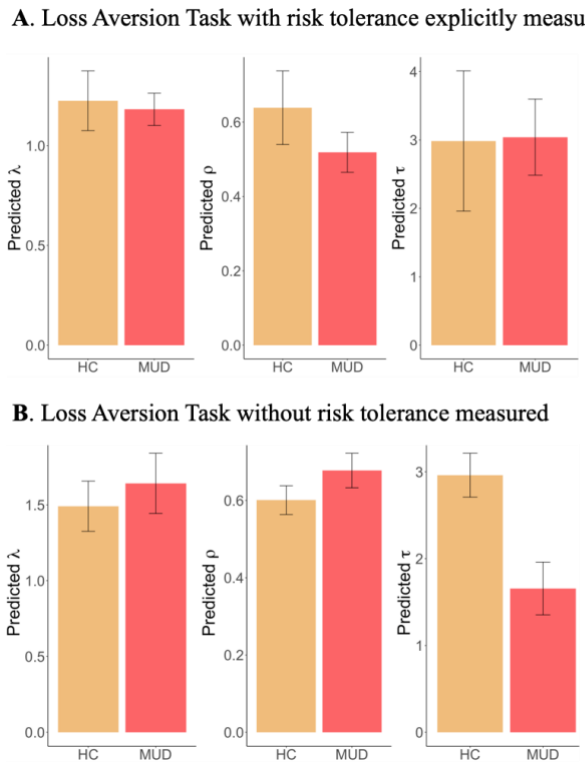

Figure 4.5. Estimated marginal effects of group on computational parameters from the Loss Aversion Task. The posterior means of choices parameters were used in generalized linear models (GLMs) to account for group differences in covariates. Estimated marginal effects of parameters on group are plotted. (**A**) When risk tolerance was measured explicitly and biological sex was included as a covariate, and analysis indicated that participants with Stimulant Use Disorder (SUD) were significantly less risk tolerant (p = 00.025). (**B**) However, when the full utility model was applied to data from the 50-50 gamble Loss Aversion Task without explicitly measuring risk tolerance, parameters were misestimated. With age, smoking status, participant's mother's years of education, and study as covariates, the analysis indicated that participants with SUD had higher risk tolerance (ρ) (i.e., lower risk aversion) than did healthy control participants (p = 0.00082), but no differences in loss aversion (λ). The analysis also indicated a group difference in the inverse temperature parameter (p < 0.0001).

4.2.3.3 Loss aversion, risk tolerance, and dopamine D2-type BPND in the striatum

Loss aversion analysis. The interaction of group and dopamine D2-type BPND in the whole striatum on loss aversion (λ) did not reach significance [interaction: $\beta = -0.155,\ t(27) = -1.97,\ p = 0.060$; simple effect of whole striatal BPND: $\beta = 0.17,\ t(27) = 3.11,\ p = 0.0048$]. MUD participants who were more loss averse had greater striatal BPND than those who

were less loss averse (**Fig. 4.6A**). In HC participants, however, loss aversion was not correlated with dopamine D2-type BPND. There were no main effects or interactions between BPND in the amygdala with group on loss aversion.

Full utility model. In participants with MUD for whom the full utility model was fit, the positive association between λ and striatal receptor availability was trending ($\beta = 0.016,\ t(15) = 1.78,\ p = 0.096$) (**Fig. 4.6B)**. There was also a negative association between the risk tolerance parameter (ρ) and striatal receptor availability ($\beta = -0.014,\ t(14) = -2.95,\ p = 0.012$). There were no associations with BPND in the amygdala (**Fig. 4.6C**).

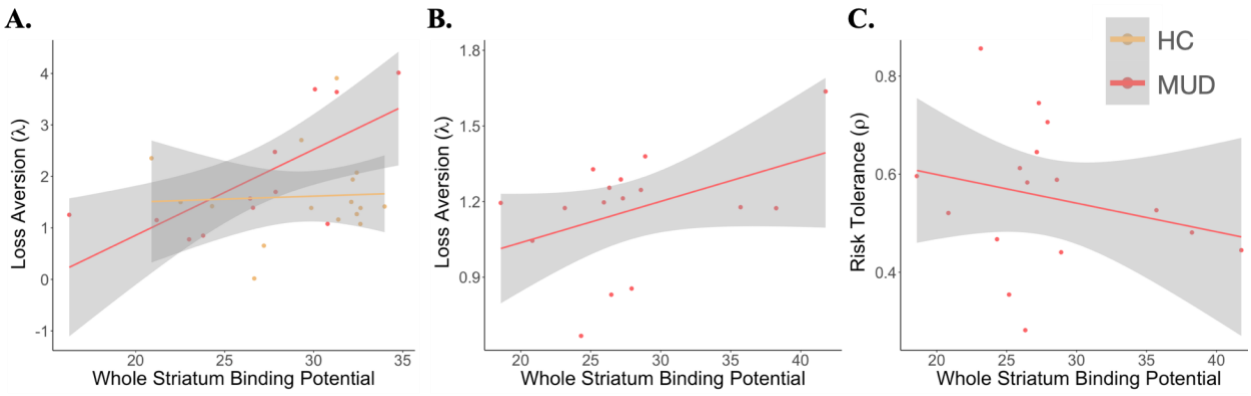

Figure 4.6. Dopamine D2-type receptor availability, loss aversion, and risk tolerance on the Loss Aversion Task. (**A**) In 17 healthy control (HC) volunteers and 13 participants with Methamphetamine Use Disorder (MUD), loss aversion was differentially related to striatal dopamine D2-type receptor (D2/D3) binding potential (BPND) between groups. The interaction of group and striatal D2-type BPND was trending (p = 0.060), and the simple effect of BPND was significant (p = 0.0048). Analyses were performed using generalized linear models (GLMs) including the interaction of group and region. (**B and C**) In participants for whom the full utility model was fit, the positive association between loss aversion and striatal BPND was trending (p = 0.096). The negative association between risk tolerance and BPND was significant (p = 0.012). Grey shading indicates standard error of the mean.

4.2.4 Discussion

These findings demonstrated no difference in loss aversion between Stimulant Use Disorder (SUD) and healthy control groups, although the analysis without covariates indicated lower loss aversion in SUD participants. Results revealed a potential association between striatal dopamine D2-type receptor availability and loss aversion only in Methamphetamine Use Disorder (MUD), and a second analysis reinforced these findings. When full utility functions were fit to a subset of participants with MUD, analysis indicated that MUD participants had lower tolerance for risk than healthy controls, and that risk tolerance was negatively correlated with striatal D2-type BP_{ND}. Taken together, these results suggest that avoiding loss may not be a motivating factor in MUD, but may be modulated by signaling through D2-type receptors only in MUD.

4.2.4.1 Loss aversion and risk tolerance in SUD

Lower tolerance for risk in MUD compared to HC participants is in line with findings from the BART, where participants with SUD took less risk (*see Chapter 2*). These results follow previous studies showing lower risk-taking in individuals with Methamphetamine Dependence and those who heavily use marijuana, alcohol, or cigarettes compared to control participants [86,87,263,265]. Lower tolerance for risk could be related to greater distortion of outcome probability or sensitivity to rewards, both of which have been associated with administration of the D2-type receptor antagonist amisulpride to control participants [288]. Real-world risky choices of individuals with SUD may thus not stem from an indiscriminate tolerance for risk. Such findings reinforce the importance of how risk is assessed and defined across studies [69,231,521].

In the large sample who completed the LAT as assessed using logistic regression, the group difference in loss aversion did not reach statistical significance when covariates were included in

the model. However, the two-sample independent t-test indicated that SUD participants had lower loss aversion than healthy controls. Similar findings have been shown in alcohol dependence [502], cocaine dependence [509,511,512], and opiate dependence [505]. On tasks that do not directly measure loss aversion but that assess sensitivity to loss, participants with addictions have shown attenuated processing in response to loss compared to controls [82,102,105,106,108,160]. Reduced loss aversion may be related to a lower sensitivity to aversive outcomes [82,105,106,160], which may be reflected in the persistence of drug use despite negative consequences [23,195,500,501].

Participants who were in residential treatment were less loss averse than those who were not in residential treatment. Previous research has demonstrated changes in preferences during inpatient treatment [113,332,522]. Since rewards on the LAT are monetary, they may be associated with future drug use for participants who are not in treatment. Thus, participants not in treatment may be more cautious on the task and display higher loss aversion. When in residential treatment, however, the nature of what is valued presumably changes, and the money won on the task may be less valuable as it is no longer associated with potential drug use.

Notably the LAT is not a measure of adaptive risk-taking. Aversions to risk and loss are presumably evolutionarily adaptive mechanisms [411-414,523], but extreme sensitivity to potential loss can impair decision-making during laboratory tasks [415,416] and real-world choices [417-419], as well as by those with psychiatric pathologies [420,421]. Many tasks used clinically and in the laboratory to assess decision-making involve loss although it is not explicitly measured. Thus, understanding whether participants with SUD show differences in tolerance for loss may help clarify decision-making deficits in the disorder.

4.2.4.2 Loss aversion, risk tolerance, and striatal dopamine D2-type availability

The interaction between group and striatal D2-type receptor availability on loss aversion was trending in the large sample, and the simple effect of striatal BP_{ND} reached significance. In the sample of participants with MUD to whose data full utility functions were fit, the association between loss aversion and striatal dopamine BP_{ND} was trending for loss aversion and was significant for risk tolerance. The striatum has been implicated in loss aversion in healthy controls [524]; striatal activity tracked the magnitude of potential losses and was involved in a network displaying bidirectional responses to losses and gains, whereby striatal deactivations in response to loss, compared to activations in response to gain, biased choices towards loss aversion [234,429,460,513,515,517]. A natural question is whether D2-type receptors are related to the striatal response to loss.

HC participants exhibited no relationship between striatal D2-type receptor availability and loss aversion. The lack of association supports previous findings of no change in loss aversion when control participants were administered the dopamine precursor levodopa [287,290] (see Sokol-Hessner and Rutledge (524) for review). In the SUD group, however, the positive correlation between striatal D2-type BP_{ND} and loss aversion was trending. In the subsample to whose data the full model was fit, striatal D2-type BP_{ND} was negatively correlated with risk tolerance and the positive correlation with loss aversion was trending. Taken together, these findings are in line with previous research demonstrating an inverse relationship between D2-type receptor availability and the propensity to gamble [287-290]. For instance, pharmacologically boosting dopamine with levodopa led to riskier choices [287], and similar findings were shown in rodents [293-295].

SUD participants did not show a relationship between striatal dopamine D2-type BP_{ND} and decision-making on the BART. These results suggest that signaling through striatal D2-type

receptors may play a role specific to loss aversion during decision-making in SUD and raises interesting possibilities. The dopamine system may assume control when chronic stimulant use affects function in circuitry involving neurotransmitters other than dopamine [227,525,526], or control over the dopaminergic system may malfunction, perhaps though hypofunction of the PFC [191,269]. Corticostriatal signaling necessary for goal-directed behavior [282,283,342] may be disrupted in SUD [12,269], impairing reward-seeking for losses.

Neuroadaptations related to drug use [191,527] or preexisting individual differences [102,153,528-531] may be related to a role for striatal D2-type receptor signaling in loss-related choices that is absent in nonaddicted individuals. Homeostatic adaptations to dysregulated dopamine tone could alter sensitivity of the dopaminergic system [338] and thereby risk-seeking [293,345]. For instance, imbalances in striatal dopamine tone may alter the threshold for response [338], reducing the ability to devalue stimuli through negative feedback [293]. Lower D2-type BP_{ND} in SUD [12,22] and skewed dopamine tone [532,533] may shift risk-taking behaviors, especially in situations with potential loss [293]. Striatal D2-type receptors also may assume a role in loss sensitivity in situations of dopamine perturbation [534,535]. Indeed, as opposed to boosting dopamine nonselectively with levodopa, administering dopamine D2-type agonists caused changes in the subjective value of losses in HC participants [536] and reduced prediction errors for losses in patients with Parkinson's disease [534,535].

4.2.4.3 Estimation of risk tolerance and loss aversion

Estimating the parameters of loss aversion (λ) and risk tolerance (ρ) without trials that isolated risk resulted in inaccurate parameter estimates. This is because ρ is a measure of the curvature of the utility function, from which risk attitudes naturally arise through diminishing sensitivity to marginal changes in value. Higher values indicate less curvature and therefore less

risk aversion in the domain of gains. But if the LAT contains no trials that present risk without potential for loss, ρ cannot be measured accurately (*see Section 2.2.2*) [537], as was exhibited by parameter estimates that suggested higher instead of lower risk tolerance of participants with SUD.

This misestimation was further confirmed when the data from participants whose risk tolerance was explicitly measured were reanalyzed without separate risk-only trials. Results indicated that the SUD group had greater aversion to loss but not to risk than the HC group. On the surface, greater risk-taking when there is a potential for loss can reflect either lower loss aversion or greater risk tolerance. Thus, attempting to estimate full utility functions using only the 50-50 mixed gamble task (the LAT) resulted in confounded parameters of risk and loss aversion.

4.2.4.4 Concluding remarks and limitations

This study showed lower tolerance for risk and either no difference or potentially lower loss aversion in individuals with SUD compared to control participants. There also were associations between choice behavior and striatal dopamine D2-type receptor availability only in SUD participants. We suggest that signaling at striatal dopamine D2-type receptors is involved in risky decisions that involve loss, and that neuroadaptations arising from substance use or preexisting differences in the balance of D1 and D2-type receptors establish a role for dopamine in loss-related choices not observed in healthy control groups. It is also clear that risk and loss should be isolated on the LAT to provide accurate measures of loss aversion and risk tolerance.

The main limitation of the current analysis was that most participants did not perform trials designed to isolate their preferences towards risk; therefore, the full utility model could not be fit to most of the data. However, we were able to show misestimation using the full model when not accounting for risk tolerance. There were also cohort effects based on study, but the variable of

study was controlled for in all statistical analyses, and the difference in risk and loss aversion between participants who were in treatment and those who were not suggested that loss aversion may change with inpatient treatment.

CHAPTER FIVE

Risk, Ambiguity, and Delay

"*We sail within a vast sphere, ever drifting in uncertainty, driven from end to end.*"

– Blaise Pascal (1623-62), French mathematician, physicist, inventor, philosopher, and theologian

"*Uncertainty! Fell demon of our fears! The human soul that can support despair, supports not thee.*"

– David Mallet (1705-1765), Scottish poet and playwright

"*Neurosis is the inability to tolerate ambiguity.*"

– Sigmund Freud (1856-1939), Austrian neurologist

"*The quest for certainty blocks the search for meaning. Uncertainty is the very condition to impel man to unfold his powers.*"

– Erich Fromm (1900-1980), German psychologist, sociologist, philosopher

"*We demand rigidly defined areas of doubt and uncertainty!*"

– Majikthise and Vroomfondel, *A Hitchiker's Guide to the Galaxy*

"*Johnny's always runnin' around, tryin' to find certainty.*"

– Robert Palmer (1949-2003), English musician and producer

5.1 Introduction

Humans dislike uncertainty—a fact echoed for centuries by scientists, philosophers, and theologians. Since most decisions encountered in everyday life present incomplete information about the probabilities of possible outcomes, such ambiguity is an important but often overlooked factor in decision-making [70,538]. People tend to be particularly averse to ambiguity—which can be compared with pure risk, when the probabilities of possible outcomes are known [539]—and this aversion can lead to disadvantageous choices [70,71,540]. Ambiguity aversion has not been assessed

in individuals with Stimulant Use Disorder (SUD), but individuals who heavily use marijuana were more ambiguity averse than healthy controls [113], and a related measure of intolerance for uncertainty was linked to a variety of substance abuse disorders [541-544]. Decision-making under ambiguity is associated with functional activation in corticolimbic and frontostriatal circuitry [4,110,111,545] that is particularly impaired in addictions [12,22,533]. Yet ambiguity aversion is understudied with respect to addiction, and its neural circuitry has not been studied at all in individuals with SUD.

5.1.1 Ambiguity aversion and addiction

Since ambiguity aversion and drug use are motivated by similar factors, including the desire to avoid and/or alleviate stress and negative affect [546-549], ambiguity aversion may confer vulnerability to and contribute to the maintenance of drug use [550]. The familiar and relatively unambiguous rewarding outcome produced by continued drug use also may be preferable to the pursuit of other, less certain, rewards, especially considering neuroadaptations that occur in addiction [527,551], including decreased responses to non-drug rewards and exaggerated responses to stressors [191,269,552]. In support of this theory, alcohol reduced the stress response to uncertainty [553] and ambiguity aversion was associated with drug use in participants with Opioid Use Disorder [554] and those who heavily uses marijuana [113], as well as addiction severity [331] and inpatient drug abuse treatment outcome [332,333]. Intolerance of uncertainty also was a motivating factor for alcohol use [542,543].

In individuals with substance abuse disorders, brain activity during decision-making under uncertainty (i.e., risk and ambiguity) has shown differences in the striatum, amygdala, and prefrontal regions [78,79,82,86,101-106,109,555]. Ambiguity aversion can be assessed formally using

economic choice tasks that compare risk-taking under ambiguous and unambiguous conditions (i.e., ambiguity vs. pure risk). There has been recent interest in isolating attitudes toward risk and ambiguity in individuals with substance use disorders [113,554,556,557], but few studies have been paired with neuroimaging. In individuals with opioid use disorder, activity in the striatum and vmPFC encoded the value of ambiguous choices and correlated with striatum-vmPFC connectivity at rest [522]. Decision-making under uncertainty also has been related to striatal dopamine release [334], polymorphisms in dopamine receptor genes [558], and striatal D2-type receptor availability [90].

5.1.2 Risk, ambiguity, and delay discounting

Choosing between immediate or delayed reward is common in everyday decisions—deciding between eating a tasty desert now or a healthy meal for long-term health, or smoking a cigarette that provides immediate relief but long-term negative health consequences. People naturally prefer options that reap sooner rewards compared to those available in the future, and the value of the future reward is discounted as a function of its delay. Such delay discounting is not pathological, but when the present vastly outweighs the future in determining value, choices can become maladaptive [559].

Intertemporal choices can be measured using a delay discounting task (DDT), in which participants make a series of choices between smaller, more immediate rewards and larger, more delayed rewards [236]. Delay discounting is exaggerated in various clinical groups, including those with substance use disorders [126,560], and high levels of delay discounting have been associated with predisposition to addiction and treatment outcome [561-566].

However, delay discounting behavior can be altered by various factors, from the framing of options [144,189] and influence of peers [219] to working memory training [143] and orientation to the

future [144,145,567]. Various considerations influence the calculation of value, and motivations and priorities likely differ between clinical groups [568]. Still, delay discounting behavior is frequently taken as a measure of "impulsivity," which is likely overlooking crucial factors and can lead to erroneous conclusions.

A crucial component of decision-making during intertemporal choice is the uncertainty inherent to the delay, and this uncertainty affects choices [569]. Neglecting to account for tolerance for uncertainty has led to inflated measures of discounting [135-139]. The effect of risk on the value of delayed options can be understood when considering how value is modeled in such tasks. Briefly, most models of delay discounting assume that people consider each increment in reward amount to have equal value, represented by a linear utility function, in which utility reflects satisfaction obtained from a reward (i.e., money). However, empirical studies show that most people value such increments in reward proportionally less as the total amount increases: an increase from $1 to $10 provides greater satisfaction than an increase from $1,001 to $1,010 [9]. This effect of diminishing marginal utility can be described by a concave utility function. When discount functions are calculated assuming linear utility, the discounting due to delay can be confounded with the discounting due to change in utility (independent of the delay), and measures of discounting can become inflated [135-139]. This issue is compounded when comparing groups that have different underlying risk preferences, such HC volunteers and those with SUD [22,570]. However, the respective contributions of risk and delay to intertemporal choice have remained underexplored with respect to addiction.

5.1.3 The current study

We evaluated ambiguity aversion in SUD and HC volunteers who performed the Choice under Risk and Ambiguity (CRA) task. Participants with SUD also received an fMRI scan to assess resting-state functional connectivity (RSFC) with seeds in the nucleus accumbens, caudate, and amygdala, as well as [^{18}F]fallypride positron emission tomography (PET) to assess striatal dopamine D2-type BP_{ND}. Based on prior literature [86,113,546], we expected individuals with SUD to be more averse to ambiguity than HC participants. Due to the systematic impairment in corticolimbic and frontostriatal circuitry in SUD [12,22], we also hypothesized that ambiguity aversion would be associated negatively with frontostriatal and positively with corticolimbic circuitry, and that striatal dopamine D2-type BP_{ND} would be associated with aversion.

To determine whether SUD and HC volunteers discounted delayed rewards at different rates when their attitudes towards risk were taken into account (i.e., by measuring the curvature of their utility function), we administered a DDT and hypothesized that group differences would be lessened when risk tolerance was taken into account. Since tolerance for risk, but not ambiguity, was incorporated into the DDT model estimation, we wanted to determine whether ambiguity aversion was correlated with discount factors and whether ambiguity aversion would be accounted for by including risk tolerance in the model.

5.2 Methods

5.2.1 Participants

The CRA task and a DDT were performed by 40 SUD and 13 HC volunteers. All participants provided informed consent, as approved by the UCLA Institutional Review Board. They were fluent in English and in good physical and neurological health, as assessed by history

and physical examination. All psychiatric diagnoses were excluded, other than Cocaine Use Disorder or Methamphetamine Use Disorder in the SUD participants, and Tobacco Use Disorder, mild Alcohol Use Disorder, and mild Cannabis Use Disorder in both groups, determined by the Structured Clinical Interview for DSM-IV [306].

SUD participants were recruited following ≥1 week of supervised abstinence in the residential substance use disorder program at the CLARE | Matrix Foundation. They had at least two weeks abstinence. Only in SUD participants received resting-state fMRI and [^{18}F]fallypride PET. On all study days, participants provided a urine sample that was negative for cocaine, methamphetamine, benzodiazepines, opiates, and cannabinoids. Participants who smoked cigarettes were allowed to smoke until 15 min before testing to avoid effects of nicotine withdrawal. They were compensated with cash, gift cards, or vouchers.

5.2.2 MRI data acquisition

fMRI scans were collected from 35 volunteers with SUD. Images were acquired on a 3-Tesla PRISMA (Siemens) MRI scanner with a 32-channel head coil receiver. Data from 10 participants were excluded. Resting-state data were collected over 13 min. while participants had their eyes open and were viewing a black screen. The protocol consisted of the continuous acquisition of 750 Echo-planar Image (EPI) volumes over 10 minutes. A multi-band accelerated EPI pulse sequences (factor 8) was used to acquire 72 axial slices with a repetition time (TR) of 800 ms with a 104x104 matrix. The resolution was 2x2x2 mm^3, echo time (TE) 37 ms, and flip angle 52 degrees. The structural T1-weighted images were obtained using a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence with parameters of isovoxel 0.8 mm^3, FOV 240 x 256 mm^2, TE 2.24 ms, TR 2400 ms, flip angle 8 degrees, and 208 sagittal slices.

5.2.3 MRI data pre-processing

All analyses were performed on Linux (CentOS release 6.10) using FSL 5.0.9, MATLAB 8.6, R (version 3.6.0). FMRI processing included rigid body realignment to correct for head movements within each scanning run, skull removal, and non-linear registration to the Montreal Neurological Institute (MNI) template. Motion cleaning and noise reduction were performed by first removing variance associated with motion parameters by running a 24-parameter linear regression model that included six motion parameters (3 translational dimensions along X, Y and Z axes and 3 rotational dimensions: "pitch", "roll" and "yaw"), the temporal derivatives of these parameters and the quadratic of all parameters [571]. Next, a censoring procedure was used. Mean frame displacement (FD) and the variance of signal change from the average signal (DVARS) of the raw images were estimated. A null sampling distribution of DVARS was used to identify frames with excessive variance at $p < 0.05$ [572]; frames with FD exceeding 0.45 mm were also flagged. Those frames as well as the one located in time just prior (t-1) and two just after (t+1 and t+2) each were included in a censoring temporal mask for data interpolation: a least-squares spectral decomposition of the uncensored data was performed to reconstitute data of the censored timepoints see methods in [573]. The uncensored data defined the frequency characteristics of signals that then replaced the censored data. This step aimed at minimizing the contamination of the signal from the censored frames during frequency filtering. The interpolated signal was then demeaned, detrended and filtered using an ideal bandpass filter (0.009 – 0.08 Hz). Following band-pass filtering, the interpolated timepoints were finally censored. Participants with more than 50% frames censored (i.e., those with less than 5 minutes of remaining resting state data) were excluded from the analysis. To reduce the contribution from non-neuronal noise in the data, the minimal number of principle components that explained at least 50% of the variance of mean signal

extracted from white matter and cerebrospinal fluid were evaluated and regressed out from the signal aCompCor50, [574]. Volumes were then spatially smoothed with a Gaussian filter using a 5-mm FWHM kernel. Each voxel was normalized to a mean value of 100 (SD=1).

5.2.4 Resting-state functional connectivity analysis

To minimize bias, we used the statistically conservative approach of voxel-wise whole-brain analyses rather than restricting to *a priori*-selected target regions or networks. Seeds were placed in the nucleus accumbens, caudate, and amygdala, as defined by FSL's FIRST—a tool for automated segmentation of subcortical strucutures. The time series from each seed was extracted, and its first normalized eigen vector (mean = 100, SD = 1) used as a regressor in an ordinary least squares linear regression analysis on every voxel (OLS, FEAT). The parameter estimates of the model, corresponding to the Pearson's correlation coefficient (since data were previously normalized), were z-transformed to improve data normality. The resulting z-transformed images were used in separate group models for risk tolerance and ambiguity aversion (using FLAME1 in FSL's FEAT). To account for movement differences between sessions and participants the mean frame displacement value was included as a covariate in all models, in addition to age. Results were cluster-corrected for multiple comparisons using a voxel-height threshold of $p < 0.001$ ($Z > 3.1$) and cluster threshold of $p < 0.05$ as recommended per [575].

5.2.5 PET data acquisition and processing

PET scanning was conducted using [^{18}F]fallypride. Scans were acquired on a Siemens Biograph mCT and reconstructed data were combined into 16 images containing data averaged across 10 minutes and corrected for motion with FSL MCFLIRT, as described in Section 3.2.3.

Separate independent t-tests were used to check for group differences in dopamine D2-type BP_{ND}, as well as their relationship to demographic covariates when accounting for group.

5.3 Results

5.3.1 Participant characteristics and demographics

Data from 4 SUD participants were excluded for data quality, leaving 36 SUD and 13 HC for statistical analysis (**Table 5.1**). The SUD group had slightly older participants than the HC group and more men than woman. When testing for associations between demographic variables and behavioral parameters, while controlling for group, age was the only significant demographic factor, where older individuals in both groups had higher risk aversion [$\beta = -0.00464, t(43) = -2.64, p = 0.0115$].

The DDT was performed by 13 HC and 28 SUD volunteers. When accounting for group, neither *k* nor *k risk* was associated with any demographic factors. Results were the same when the natural log transforms of both parameters were tested. Thus, only HDIs, as is recommended in Bayesian analysis [246], were used to assess differences between groups and no additional GLMs were performed.

Variable	Healthy Controls (HC; n=13)	Participants with Stimulant Use Disorder (SUD; n=36)	Statistics
Age, years[a]	34.94 (2.43)	42.91 (2.08)	$t(46) = -2.15$, $p = 0.037$*
Biological sex female/male (n)	7/6	6/27	$c^2(1) = 4.22$, $p = 0.040$*
IQ estimate standard score[a]	94.54 (7.66)	103 (2.46)	$t(14.53) = -1.05$, $p > 0.05$
Mother's Education, years[a]	14.75 (0.730)	13.53 (0.51)	$t(40) = 0.801$, $p > 0.05$
Race/Ethnicity (n)			$H(5) = 7.60$, $p > 0.05$
White	4	11	
African American	6	10	
Hispanic/Latinx	2	8	
Asian/Pacific Islander	1	0	
American Indian/Alaska Native	0	3	
Other	0	2	
Days of substance use in the previous 30 days			
Alcohol	3.64 (1.14)	2.97 (0.88)	$t(39) = 0.416$, $p > 0.05$
Marijuana	5.75 (2.10)	3.00 (0.91)	$t(31) = 1.07$, $p > 0.05$
Tobacco	19.30 (5.40)	22.38 (1.96)	$t(37) = -0.635$, $p > 0.05$
No. who smoked	5	25	$c^2(1) = 4.11$, $p = 0.043$
Methamphetamine		19.64 (1.96)	

[a]Values are means (SE)
IQ estimate = Weschler Test of Adult Reading

Table 5.1. Demographics of participant who performed the Choice Under Risk and Ambiguity Task

5.3.2 Group differences in risk tolerance and ambiguity aversion

Posterior distributions of parameters and group mean differences for risk tolerance (α), ambiguity aversion (β), and inverse temperature (γ) are shown in **Fig. 5.1A-C**. For risk tolerance, 96.75% of posterior samples were above zero, suggesting that HC participants have credible higher values for risk tolerance than MUD participants. For ambiguity aversion, however, 84.23% of posterior samples were above zero—a less credible difference (**Fig. 5.1C)**.

GLMs with age and biological sex as covariates did not reveal any group differences. However, a chi squared analysis revealed that MUD participants had more extreme values of ambiguity aversion (β), but not risk tolerance (α), when categorized as having low, medium, or

high values of aversion $[\chi^2(2) = 7.042, p = 0.0296]$. As shown in **Table 5.2**, a greater proportion of MUD participants had very low and high levels of ambiguity aversion.

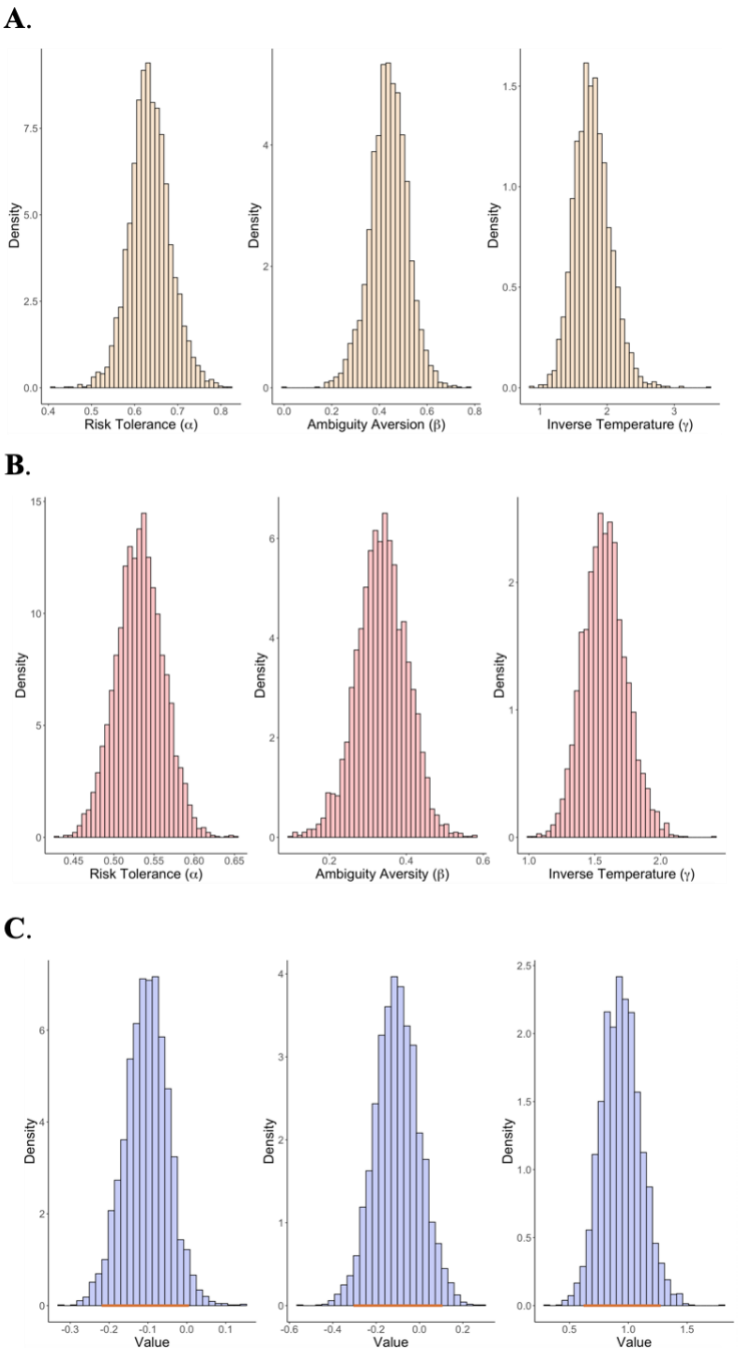

Figure 5.1. Posterior distributions of risk and ambiguity aversion. (**A and B**) Parameters were estimated using hierarchical Bayesian analysis separately for 12 HC (a, yellow) and 35 SUD (b, red) volunteers. The posterior distributions (i.e., group parameter estimates) of each parameter are plotted. Higher values of α indicate higher tolerance for risk (i.e., lower risk aversion) and higher values of β indicate higher ambiguity aversion (i.e., lower tolerance for ambiguity). The inverse temperature (γ) represents choice consistency. (**C**) The posterior distributions of group mean differences are plotted, with the 95% HDI of α (-0.22 - 0.0053), β (-0.30 - 0.11), and γ (0.62 - 1.37) indicated in red. Group differences are considered credible if the HDI does not contain zero. For α, 96.75% of posterior samples were above zero, suggesting higher risk tolerance in the HC group. For β, 84.23% of posterior samples were above zero—a less credible group difference. HDI = Highest Density Interval; SUD = Substance Use Disorder; HC = healthy control.

	Group	Low α	Medium α	High α
Risk aversion (α)	HC	2	8	3
	MUD	17	10	9
Ambiguity aversion (β)	HC	3	10	0
	MUD	16	13	7

Table 5.2. Contingency tables showing participants with low, medium, and high aversion from the Choice Under Risk and Ambiguity Task

5.3.3 Group differences in delay discounting

DDT model fit was assessed using Leave-One-Out Information Criterion (LOOIC) and Widely Applicable Information Criterion (WAIC) [576]. Surprisingly, values were lower for the models that did not include a separate measure of risk tolerance (**Table 5.3**).

Posterior distributions of the discount factor with (*k risk*) and without (*k*) risk tolerance in the model and of the group mean differences are shown in **Fig 5.2A-D**. When risk tolerance was not included in the model, 95.48% of posterior samples were above zero [95% HDI of group difference: $(-0.0071 - 0.0906)$], suggesting a credible group difference in discount factors (**Fig. 5.2E**). However, the group difference was eliminated by including risk tolerance in the estimation process, where only 49.06% of posterior samples were above zero [95% HDI of group difference: $(-0.0317 - 0.0326)$] (**Fig. 5.2F**).

GROUP	MODEL	LOOIC	WAIC
HC	Hyperbolic	193.050	180.786
	Hyperbolic with raised risk	345.477	337.562
MUD	Hyperbolic	478.694	454.773
	Hyperbolic with raised risk	654.228	634.027

Table 5.3. Delay discounting task model fit.

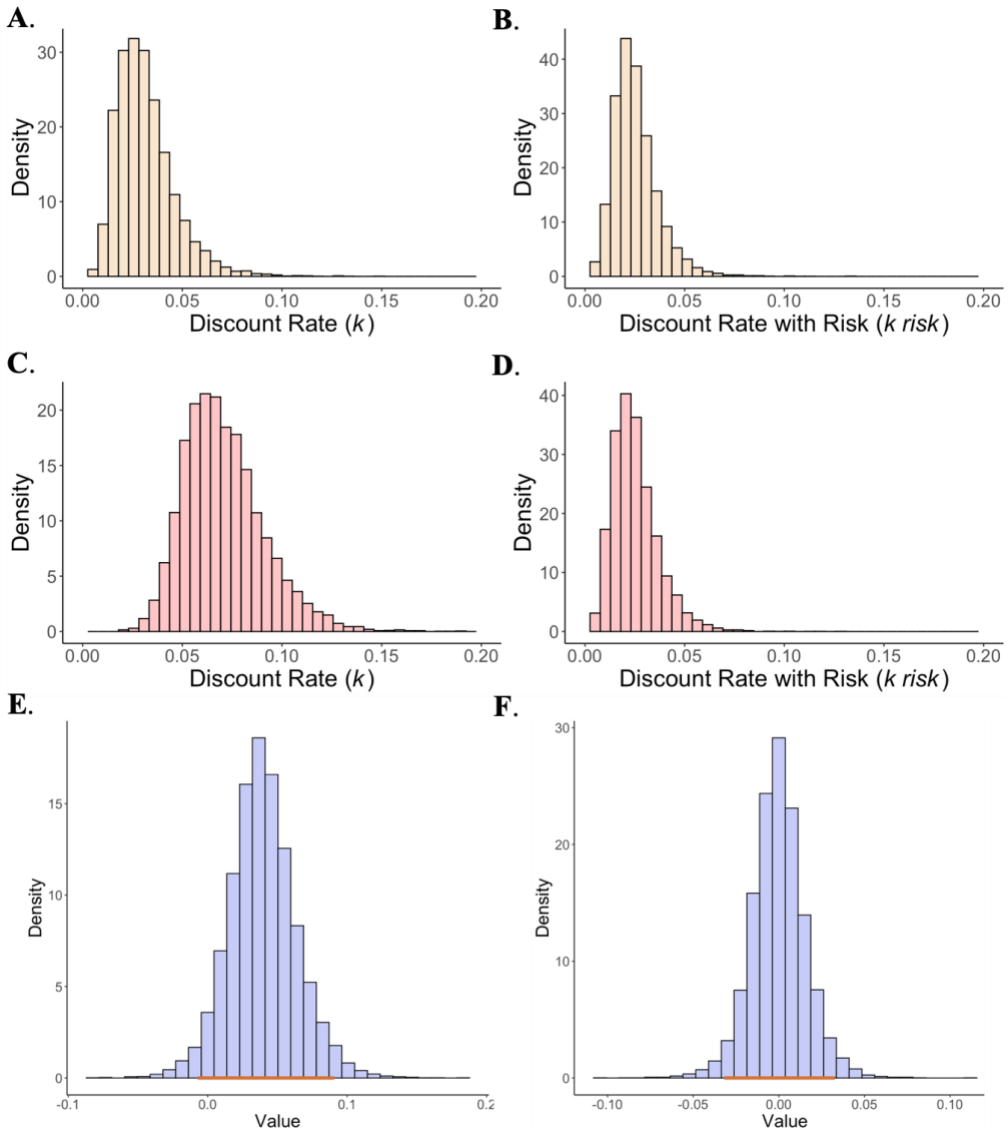

Figure 5.2. Posterior distributions of discount rates with linear utility (no risk tolerance) and with nonlinear utility (without risk tolerance). (**A-D**) Parameters were estimated using hierarchical Bayesian analysis separately for 13 HC (a, yellow) and 27 SUD (b, red) volunteers. One model assumed linear utility (*k*) and the other used a separate measure of utility curvature from the Choice under Risk and Ambiguity Task (*k risk*). The posterior distributions (i.e., group parameter estimates) of each parameter are plotted. Higher values indicate higher discount factors and more discounting of delayed rewards. (**E-F**) The posterior distribution of group mean differences was plotted with the 95% HDI indicated in red. Group differences are considered credible if the HDI does not contain zero. (**E**) When risk tolerance was not included in the model, 95.48% of posterior samples were above zero, suggesting higher discounting in the SUD vs. HC group (HDI: -0.0071-0.0906). (**F**) However, when risk tolerance was included in the model, the group difference was eliminated (HDI: -0.0317-0.0326). HDI = Highest Density Interval; SUD = Substance Use Disorder; HC = healthy control.

5.3.4 Association between ambiguity aversion and discount factor

Since discount rates were negatively skewed, a natural log transform was used for analysis. Variables that differed by group and/or were associated with behavioral parameters were included in the GLM (age, biological sex, years of education of the participant's mother, and smoking status). Ambiguity aversion (β) was positively correlated with the natural log of k [$\beta = 3.56, t(20) = 2.27, p = 0.034$] but not with the natural log of k *risk* [$\beta = -0.0884, t(20) = -0.322, p = 0.751$] (**Fig. 5.3**). The relationship between risk tolerance (α) and the natural log of k was trending [$\beta = -4.22, t(20) = -1.79, p = 0.089$].

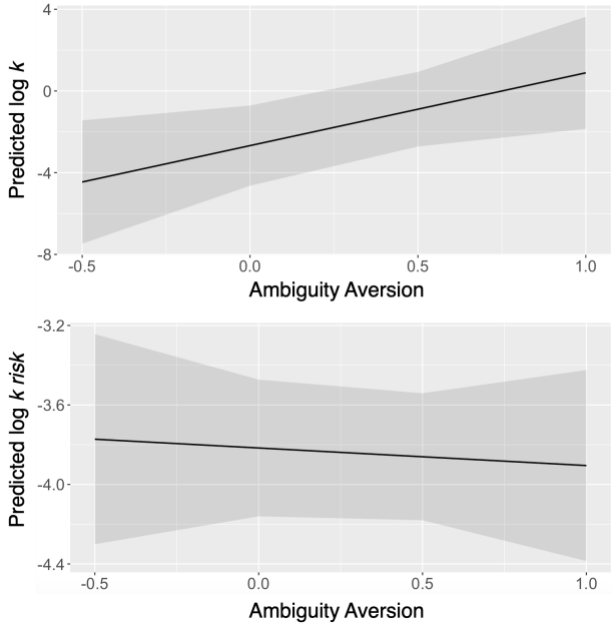

Figure 5.3. Estimated marginal effects of ambiguity aversion on discount factor. The posterior means of ambiguity aversion and discount factors were used in generalized linear models (GLMs) to account for covariates of age, biological sex, smoking status, and years of education of the participant's mother. The log transform of discount factors were used. Estimated marginal effects are plotted. Ambiguity aversion was correlated with the natural log of k (p = 0.034), but not with the natural log of k *risk* (p = 0.751). Thus, accounting for utility curvature eliminated the association.

5.3.5 Ambiguity aversion and drug use

A GLM with age in the model revealed that the average days per week that participants used their drug of choice (methamphetamine or cocaine) was positively correlated with ambiguity aversion [$\beta = 0.0080, t(28) = 3.27, p = 0.00284$], but not with risk tolerance (**Fig 5.4**). No

associations were found between *k* or *k risk* and measures of drug use. Results were unchanged when the log transform of parameters were used.

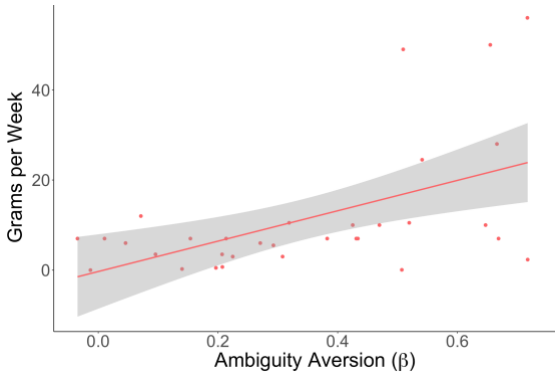

Fig. 5.4 Ambiguity aversion and grams of stimulants used per week. The posterior mean of ambiguity aversion was used in a generalized linear model (GLM) with the covariate of age to test for association with grams of stimulant (methamphetamine or cocaine) used per week. There was a significantly positive correlation between grams of stimulant use per week and ambiguity aversion (p = 0.0028), but not risk aversion.

5.3.6 Corticolimbic and frontostriatal connectivity and ambiguity aversion

Ambiguity aversion was correlated positively with RSFC of the right amygdala with the paracingulate/medial frontal cortex (peak MNI coordinates: x=0 y=54, z=-6) and the lateral occipital cortex (peak MNI coordinates: x=-38 y=-70, z=26) (**Fig. 5.5A-B**); and the left amygdala with the insula (peak MNI coordinates: x=-40, y=-24, z=22), precuneus (peak MNI coordinates: x=4, y=-70, z=26), superior parietal cortex (peak MNI coordinates: x=32, y=-48, z=72), and postcentral gyrus (peak MNI coordinates: x=-64, y=-24, z=44) (**Fig. 5.5C-D**). Ambiguity aversion was correlated negatively with RSFC of the right nucleus accumbens with the super frontal gyrus/frontal pole (peak MNI coordinates: x=22, y=54, z=16) (**Fig. 5.5E**) and the left caudate with the medial frontal gyrus/frontal pole (peak MNI coordinates: x=-2, y=58, z=30) (**Fig. 5.5F**). No associations were found with the risk aversion parameter (α).

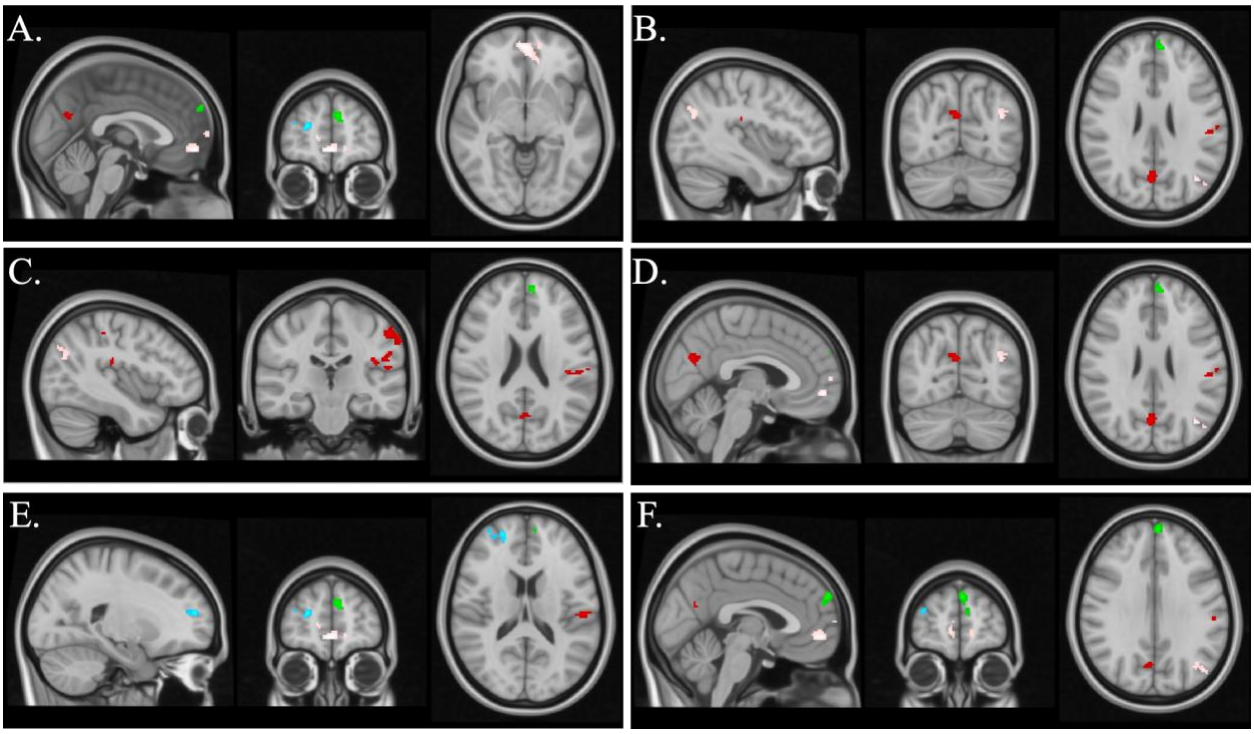

Fig. 5.5 Ambiguity aversion and cortico-amygdalar and frontostriatal resting-state functional connectivity. In 25 participants with Stimulant Use Disorder (SUD), ambiguity aversion was associated differentially with cortico-amygdala and frontostriatal resting-state functional connectivity (RSFC). (**A and B**) Ambiguity aversion was correlated positively with RSFC of the right amygdala (**pink**) with the (**A**) paracingulate/medial frontal cortex (x=0 y=54, z=-6) and (**B**) lateral occipital cortex (x=-38 y=-70, z=26). (**C and D**) Ambiguity aversion also was correlated positively with RSFC of the left amygdala (**red**) with the insula (**c**) (x=-40, y=-24, z=22) and precuneus (**D**) (x=4, y=-70, z=26). (**E and F**) Ambiguity aversion was correlated negatively with RSFC of the right nucleus accumbens (**E**, **blue**) with the superior frontal gyrus frontal pole (x=22, y=54, z=16) and left caudate (**F**, **green**) with the medial frontal gyrus/frontal pole (x=-2, y=58, z=30). Age and mean frame displacement were included as covariates and results were cluster-corrected using a voxel-height threshold of $p < 0.001$ ($Z > 3.1$) and cluster threshold of $p < 0.05$.

5.3.7 Dopamine D2-type binding potential and ambiguity aversion, risk tolerance, and discount factors

There was no association between dopamine D2-type BP_{ND} and risk tolerance, ambiguity aversion, or discount factors in striatal or amygdala regions.

5.4 Discussion

These findings demonstrated that ambiguity aversion was associated positively with cortico-amygdalar RSFC, but negatively with frontostriatal RSFC. Ambiguity aversion—but not risk tolerance or discount factor—was positively correlated with grams of stimulant (methamphetamine or cocaine) used per week. While initial findings indicate that ambiguity aversion may not be higher in individuals with SUD, the small sample size necessitates caution in the interpretation of results that may be driven by the extreme choices of SUD participants, who were shown by a chi squared analysis to have more extreme choices than HC participants. These results suggest that dynamic changes in ambiguity aversion may be an important factor in addiction that is modulated by frontostriatal and cortico-amygdalar RSFC.

Differences in delay discounting between HC and SUD volunteers, as well as the association between discount factors and ambiguity aversion, were eliminated when taking into account utility curvature, adding to the body of work demonstrating inflated measures of delay discounting when not accounting for risk tolerance (i.e., utility curvature) [135-139]. These findings suggest that group differences in delay discounting reflect more than "impulsivity" in the sense of preferring immediate gratification, as has been suggested [126], and instead are—in the very least partly—related to attitudes towards uncertainty.

In individuals with SUD, frontostriatal connectivity—specifically between the left caudate and the medial frontal cortex, and the right nucleus accumbens and a frontal area somewhat less medial—was correlated negatively with aversion to ambiguity. The role of frontostriatal circuitry is valuation is well-documented [2,24,111,577,578], and during choices that involve both risk and ambiguity, the striatum and areas of the PFC—most robustly the vmPFC/OFC—were implicated in the coding of subjective value [24,111]. While activity related to risk and ambiguity have not been

compared in SUD during fMRI, activity in the striatum and vmPFC of participants who use heroin encoded the value of ambiguous choices and correlated with striatum-vmPFC connectivity at rest [522].

While ambiguity aversion was correlated negatively with RSFC of frontostriatal regions, it was correlated positively with RSFC of the amygdala. Certain studies in HC volunteers demonstrated preferential activity in the amygdala for ambiguous versus risky choices [110,545], although others did not [4,111,579,580]. The amygdala has long been associated with emotional inputs into decision-making [6] and connectivity may be related to the negative emotions associated with ambiguity, which tends to be perceived as uncomfortable or aversive [71,547,549,581,582]. Such influences may be especially pertinent in SUD, as differences in amygdala connectivity have been found between HC and individuals with substance use disorders [583], who also have shown hyperfunction of the amygdala [47,584].

Specifically, RSFC of the left amygdala with the insula and precuneus, and the right amygdala with the paracingulate/medial frontal cortex, was stronger in individuals with higher ambiguity aversion. Connectivity of the amygdala with these regions may be involved in the visceral, emotional responses to ambiguity [110,545,582,585,586], thereby influencing frontostriatal value computation [460,587-589]. In HC volunteers, fronto-amygdalar and precuneus-amygdalar connectivity were related to self-reported impulsivity [590] and directing attentional awareness away from arousing and unpleasant stimuli [591]. In certain contexts in SUD, such functioning may be hyperactive and contribute to atypical decision-making [583,590,592,593]. For instance, self-reported impulsivity and connectivity of the amygdala with the insula and inferior frontal gyrus were elevated in heroin-dependent participants, who also showed differing network activity between the amygdala and precuneus compared to controls [590]. In participants with Cocaine Dependence,

reduced cortico-amygdala RSFC also was related to relapse within the first 30 days after treatment [592], suggesting a crucial role for such circuitry in drug-seeking behaviors.

While SUD participants did not have systematically higher ambiguity aversion than HC participants, we did demonstrate that those with SUD had more extreme levels of aversion on both ends of the spectrum. Since ambiguity aversion was correlated with grams of stimulant used per week, individual differences in ambiguity aversion—as opposed to global increases or decreases when compared to HC groups—may be a motivating factor in drug use. This may explain results of a recent longitudinal study that also found no significant difference between individuals with Opioid Use Disorder and HC volunteers, although they demonstrated that reductions in ambiguity aversion during the course of treatment preceded relapse [554]. Drug use at the time of testing may account for such differences, as short-term abstinence has been shown to increase ambiguity aversion [113], which may be decreased by recent drug use. Participants in the study were also in an outpatient treatment program, where drug use would be considered a negative outcome. For those not seeking treatment, drug use would presumably be a positive outcome. A recent study also found that opioid maintenance treatment was associated with better decision-making in an ambiguous context [594].

Since the positive correlation between ambiguity aversion and delay discounting disappeared when accounting for utility curvature, there may be overlap between risk and ambiguity aversion in terms of the delay. That group differences in delay discounting and its association with ambiguity aversion disappeared when risk tolerance was included in the model suggests that aversion to ambiguity may partly underlie the preference for sooner rewards demonstrated in addictions. Thus, exaggerated discounting considered characteristic of addiction [126] may be motivated at least in part by wanting to avoid a state of uncertainty [546], and not only the desire for

immediate gratification. Although speculative, it may be that the certainty of continuing to take a substance—whether positive or negative—is preferred to the relatively unfamiliar and less controllable option of abstaining, or searching for another source of reward. In this regard, ambiguity aversion has been associated with drug use aside from stimulants, including marijuana [113] and opiates [554].

In support of this theory, the related construct of intolerance for uncertainty was a motivating factor in alcohol misuse [542,543] and was higher in opiate-dependent participants than in control participants [541,544]. Although not the same as ambiguity aversion, which refers to the preference for known over unknown risk, intolerance for uncertainty involves the aversive feelings associated with uncertainty, but we can assume some overlap (although see Tanaka, Fujino, Ideno, Okubo, Takemura, Miyata, Kawada, Fujimoto, Kubota and Sasamoto (595)). Since uncertain situations are more likely to be perceived as threatening and aversive [547,549,581], and because stress and negative affect can provoke drug use and relapse [596,597], the stress of ambiguous situations may contribute to the vulnerability and maintenance of drug use. In opiate-dependent participants, intolerance for uncertainty was also positively related to conditioned place preference, which describes the preference for contexts that were previously paired with reward [544]. Thus, individuals with higher ambiguity aversion may be more susceptible to cues associated with the context of drug taking, which can cause drug use and relapse [598,599].

That we found no association between dopamine D2-type BP_{ND} and either ambiguity aversion, risk tolerance, or discount factors was somewhat surprising considering previous studies of delay discounting in stimulant-dependent groups [132] and decision-making under uncertainty [90,334,558]. Our lack of a correlation suggests that—at least at the level of dopamine D2-type receptors—dopamine signaling may be associated with behavior on tasks that more generally

assess decision-making under uncertainty and involve a variety of cognitive processes aside from ambiguity alone [69,90,334]. However, without a control sample, there is a possibility that the relationship between dopamine and ambiguity aversion is dysregulated in SUD and thus shows no association where one may exist in HC participants [545,558].

The main limitation of this study was the relatively small sample size and the lack of a comparison group for brain imaging. However, the robust correlation between ambiguity aversion and drug use, as well as the association of ambiguity aversion with cortico-amygdala and frontostriatal RSFC and to delay discounting behavior, present ambiguity aversion as a significant factor in SUD that merits further investigation. More accurate models for characterizing the behavior of individuals with substance use disorders can generate more precise results and provide a stronger foundation for therapeutic strategies that target decision-making in this population, including refining the measurement of delay discounting and its feasibility as a phenotype for addictions [600]. Understanding risk and delay is also understudied in neuroscience [601] and has never been assessed and related to markers of neural function in individuals with SUD.

CHAPTER SIX

Conclusions, Future Directions, and Implications

6.1 Overview

Individuals with addictive disorders engage in risky behaviors. Often taken as a reflection of "impulsivity," risky decision-making reflects various distinct and overlapping cognitive processes, most of which have evolutionary value and are not maladaptive per se. If one or many of these subprocesses takes on abnormal dominance, behavior can become disadvantageous or suboptimal. To design effective interventions for promoting recovery and relapse prevention, it is important to clarify which components of decision-making are dysregulated and thus would represent logical therapeutic targets.

The goals of this research were to investigate decision-making under uncertainty in individuals with Stimulant use Disorder (SUD). The behavior and neural function of SUD and healthy control (HC) participants were compared on four decision-making tasks paired with brain imaging. Participants performed the Balloon Analogue Risk Task (BART), a naturalistic decision-making task, and three economic choice tasks to isolate components of choice: the Loss Aversion Task (LAT), the Choice under Risk and Ambiguity (CRA) task to compare aversion to risk (known probabilities) and ambiguity (unknown probabilities), and a delay discounting task (DDT) to determine the contribution of risk and ambiguity to intertemporal choice. Different subsets of participants also received functional magnetic resonance imaging (fMRI) during the BART and at rest, as well as positron emission tomography (PET) for estimation of dopamine D2-type (D2 and D3) receptor binding potential (BP_{ND}).

Taken together, our findings suggest an impairment in value computation related to the estimation of uncertainty in SUD (**Fig. 6.1**). During the BART, reductions in behavioral updating and risk-taking, which were related to activations in the anterior insula and dorsolateral prefrontal cortex (DLPFC) and dysregulation in striatal, midbrain, and cortical dopamine D2-type receptors,

may reflect impairments in estimating ambiguous risk on the BART (**Chapter 3**). When isolating components of decision-making that influence subjective value, we found no disruption in sensitivity to loss (**Chapter 4**), but strong associations between ambiguity aversion and drug use (**Chapter 5**). The findings also pointed towards ambiguity aversion, associated with by cortico-amygdala and frontostriatal circuitry, underlying the exaggerated preference for immediacy found during delay discounting tasks (perhaps "impulsivity") (**Chapter 5**). Thus, value computation may be distorted in individuals with SUD due to a sensitivity to and difficulty in estimating ambiguous risk, perhaps in response to exaggerated arousal or affectual responses to the stress or negative affect provoked by uncertainty.

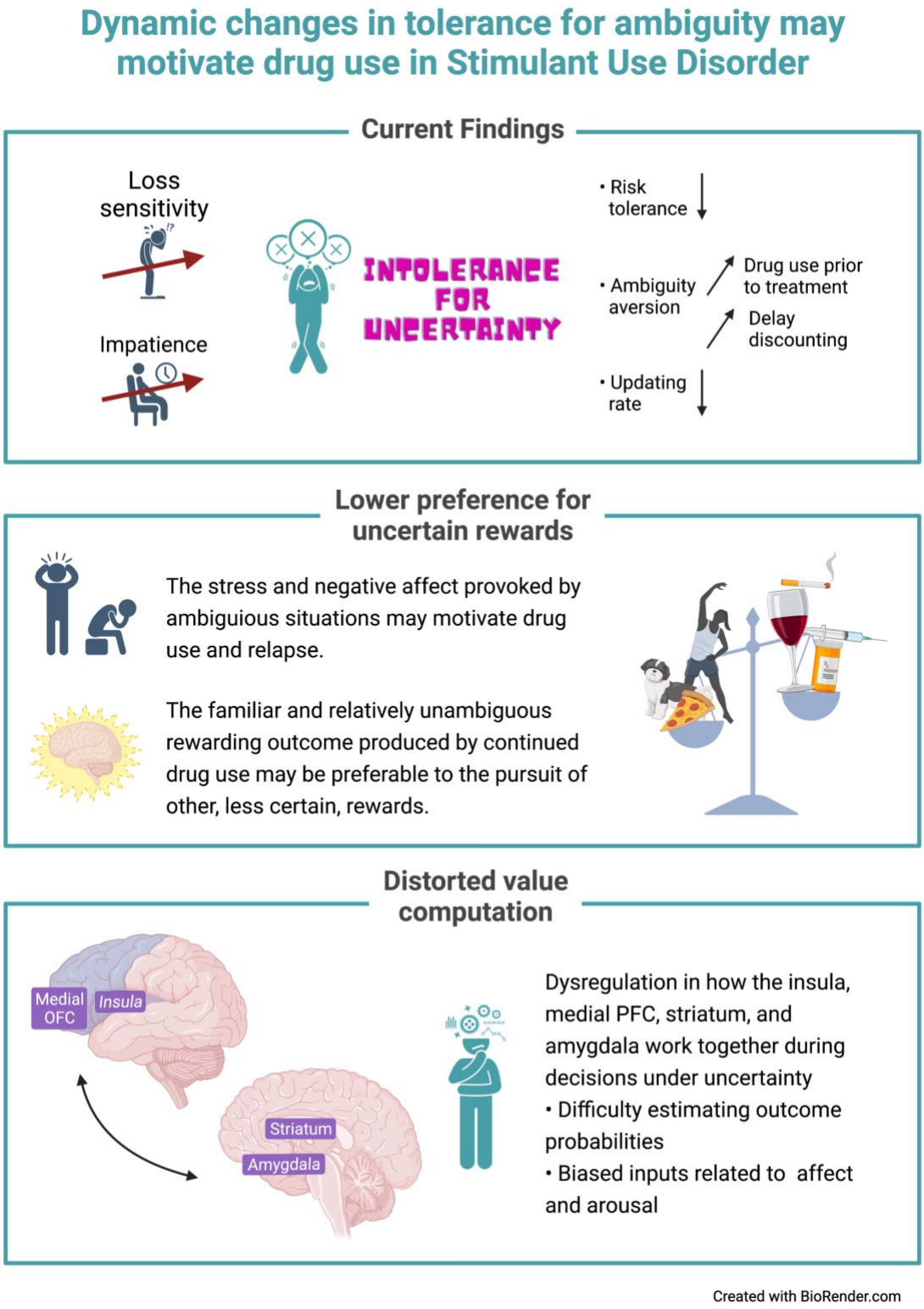

Fig. 6.1 Dynamic changes in tolerance for ambiguity may motivate drug use in Stimulant Use Disorder.

6.2 Risk-Taking and Dopamine D2-type Receptor Availability

One important finding was that individuals with SUD took less—not more—risk than HC participants on both an adaptive risk-taking task (the BART, **Fig. 3.2 and Fig. 3.3**) and an economic choice task (the CRA task, **Fig. 5.1**). Previous studies showed that individuals with Methamphetamine Dependence and those who heavily used marijuana, were problem drinkers, or smoked cigarettes took less risk under uncertain conditions [86,87,263,265]. These studies and the current findings demonstrate the importance of how risk is assessed and defined [69,231,521]. They also suggest that real-world maladaptive behaviors of individuals with substance use disorders may not stem from a blanket tolerance for risk.

While the CRA task does not assess adaptive risk, risk-taking on the BART is advantageous. In addition to lower risk-taking on the BART, SUD participants also showed marked impairments in behavioral updating. Their lower risk-taking may reflect an inability to update outcome contingencies and accurately assess ambiguous risk on the task. Optimal behavior on the BART requires learning, and—similar to the Iowa Gambling Task—the BART likely engages choice processes related to both risk and ambiguity [75]: ambiguity on early trials when little information about the probability of the balloon bursting has been presented, and risk as the participant learns through feedback. SUD participants may thus have not been as efficient in estimating outcome probabilities as were control participants [112].

Different subsets of participants who received PET scans performed the BART and LAT, which provided measures of risk-taking and economic risk tolerance (i.e., utility curvature), respectively. Risk parameters were negatively correlated with dopamine D2-type BP_{ND} in the striatum and midbrain of healthy control participants who performed the BART (**Fig. 3.5A-D**) and with striatal dopamine D2-type BP_{ND} in SUD participants who performed the LAT(**Fig. 4.6C**).

Thus, both naturalistic and economic risk tolerance were negatively related to dopamine D2-type receptor availability in the striatum and midbrain, following previous research [287-290,292-295]. However, associations were found only in healthy control participants on the BART, whereas they were found in SUD participants who performed the LAT (since control participants who performed the LAT did not receive PET scans, it remains unknown whether an association would exist). Paired with the findings of impairments in risk-taking and behavioral updating on the BART, that SUD participants did not show an association between risk-taking on the BART and D2-type BP_{ND} suggests that dysregulated signaling through D2-type receptors contributes to maladaptive decision-making under uncertainty in SUD.

6.3 Behavioral Updating, Cortical Activity, and D2-type Receptor Availability

A striking finding was the marked impairment in updating rate of SUD participants performing the BART (**Fig. 3.2 and Fig. 3.3**). That the model was able to quantify this decision-making deficit demonstrates the advantages of using computational models to parameterize behavior on complex tasks such as the BART. Since updating behavior requires learning and flexibility, diminished behavioral updating also connects maladaptive risk-taking on the BART to deficits exhibited by participants with SUD in other cognitive functions [45,270-273].

Updating rate was associated with parametric modulation of activation by risk in the anterior insula only in SUD participants (**Fig. 3.4**). Activity in the anterior insula is related to the integration of arousal and negative or aversive outcomes into decision-making [1,6,25,278,602], as well as to the estimation and prediction of risk [35,99,277-279]. Insula activation has also been related specifically to ambiguity [4] and tolerance for uncertainty [603]. Heightened or malfunctioning insular signaling related to arousal or the affective components of choice may compromise value computation and

thus adaptive risk-taking on the BART by biasing behavior away from pumping (and thus the risk of loss) and towards cashing out.

Further support for this theory comes from the finding that D2-type BP_{ND} in the insula was nonlinearly related to updating rate on in control participants (**Fig. 3.5E-F**), which may reflect dysregulations in how D2-type signaling influences behavioral updating. A similar U-shaped function was shown in a meta-analysis between a hypothesized fMRI signal in the insula and subjective value, where increases and decreases in insula activity are hypothesized to track subjective value [25].

In the present study, D2-type BP_{ND} in the medial orbitofrontal cortex (OFC)—an area also involved in integrating affect and arousal into choice [604]— was related to updating rate only in control participants (**Fig. 3.5E-F**). Resting-state functional connectivity (RSFC) of the amygdala with the insula and medial PFC, among other regions, was associated positively with ambiguity aversion (**Fig. 5.5A-B**), which is hypothesized to relate to the negative feelings and arousal provoked by uncertainty [71,547,549,581,582]. Thus, activity in the insula, medial PFC, and amygdala related to ambiguity may contribute to disadvantageous decision-making on the BART, and more generally to suboptimal choice selection under uncertainty. Our findings also extend prior work implicating the insula, medial OFC, and amygdala in integrating affect and arousal into the decision-making process.

The nonlinear relationships between updating rate and dopamine D2-type BP_{ND} in the insula and medial OFC support decades of research demonstrating quadratic relationships between dopamine function and behavior [93,289,297,301-305,358,373,507,605,606]. The present findings underscore the need to look beyond linear relationships [297], especially in a system as intricate and contradictory as the dopamine system—made more complex through neuroadaptations and homeostatic changes

produced by drug use [191,260,607]. Taking into account individual differences in preexisting factors [528-531], cognitive and personality traits [301,302,371,531], and environmental factors [235,608,609] can help refine the assessment of risk-taking in those with addictive disorders.

6.4 Loss Aversion and Dopamine D2-type Receptor Availability

While SUD participants exhibited higher sensitivity to risk and impaired behavioral updating in situations of uncertainty, they were either less sensitive to loss or showed no difference compared to healthy control participants (**Fig. 4.3-4.5**); the analysis indicated lower sensitivity to loss in SUD than control participants, but the group difference was eliminated when covariates were included in the model (**Fig. 4.3**). Future studies are needed to clarify differences in loss aversion in SUD, but that individuals with addictions persist in drug use despite negative consequences [23,195,500,501] suggests that loss may not be a motivating factor when considering mechanisms to encourage treatment and recovery.

However, whereas no association was found in SUD between striatal dopamine D2-type BP_{ND} and risk-taking on the BART, when loss was isolated on the LAT, the association between loss aversion and striatal D2-type BP_{ND} was trending in SUD but not HC participants (**Fig. 4.6**). These findings suggest that signaling through striatal D2-type receptors takes on a novel role in SUD. Feedback to modulate decision-making includes loss-related signals, and their distortion could account for the impaired responses to negative outcomes observed in individuals who use drugs [82,102,105,106,108,109,160]. It would be beneficial to extend investigations of the neural response to loss and how it affects value computation, including to investigate the mechanisms by which loss-related signaling is altered in SUD.

6.5 Ambiguity Aversion and Delay Discounting

The behavior of SUD participants on the BART demonstrated impairments in decision-making under uncertainty. When ambiguity aversion was isolated on the CRA task, the SUD group showed more extreme values of ambiguity aversion (both higher and lower) (**Table 5.2**), which was strongly associated with the amount of stimulant (cocaine or methamphetamine) used in the 30 days prior to testing (**Fig. 5.4**). Even more striking was that the group difference in delay discounting—often taken as a measure of "impulsivity"—disappeared when accounting for risk tolerance (**Fig. 5.2**). Participants with greater ambiguity aversion also discounted delayed rewards at a higher rate, but not when risk tolerance was taken into account (**Fig. 5.3**). Thus, tolerance for ambiguity, and not the desire for immediate gratification, may underlie exaggerated delay discounting in SUD. Preference for known over unknown risk and/or intolerance for uncertainty may thus be tractable therapeutic targets for improving decision-making in SUD.

These results suggest that dynamic changes in ambiguity aversion, as opposed to global increases or decreases when compared to control groups, may be a motivating factor in drug use. In support of this theory, a recent longitudinal study of participants in an outpatient treatment program found that changes in tolerance for ambiguity but not for risk were predictive of opioid relapse within one to four weeks [554]. Specifically, higher tolerance for ambiguity was predictive of drug use. These results may reflect a tendency to engage in riskier behaviors, such as venturing to locations with a closer proximity to drugs and alcohol, when tolerance for ambiguity was increased. If individuals with addictions have difficulty estimating ambiguous risk [112,260], then increases in tolerance for ambiguity paired with an underestimation of their chance of relapse when in risker situations may result in relapse.

However, while the value of drug use was presumably negative in the context of seeking treatment, drug use would likely be a positive outcome to individuals not in treatment. Thus, tolerance for ambiguity may motivate drug use by increasing the value of certain rewards (i.e., drug use) and decreasing the value of uncertain rewards (i.e., non-drug rewards). This mirrors findings of homeostatic alterations induced by chronic drug use in how the brain responds to drug and non-drug rewards: dopamine release in response to cues associated with drug use is increased, while non-drug rewards elicit less response [191,269]. It follows that the certainty of continued drug use may be preferably to the pursuit of relatively less certain alternatives.

In effect, drug use may render uncertain rewards (including non-drug rewards) less valuable, as was shown in an investigation of ambiguity aversion in individuals who reported heavy marijuana use (≥5 days per week, ≥twice per day, for ≥6 months) [113]. Participants who were deprived of marijuana for 3 days prior to testing were less likely to choose uncertain rewards than were non-deprived participants, and the magnitude of the effect of deprivation on preference for the certain reward was higher in those who reported higher levels of marijuana use. These findings suggest a greater preference for more certain rewards when in a drug-deprived state. While in the laboratory without the option of a drug reward, this preference for certainty manifested as a higher preference for the more probable reward. In the real world, a preference for certainty may motivate drug use and be reflected in the association found in the here between ambiguity aversion and drug use prior to entering treatment.

Day to day changes in the stress associated with ambiguous situations [546-549] also may influence drug use or relapse [550,610]. For instance, when participants viewed a series of visual threat cues, their stress response (measured by startle response) to unpredictable but not predictable cues was reduced in intoxicated compared to non-intoxicated participants [553,611]. The alcohol-induced

reduction in the stress response to uncertainty persisted during subsequent unpredictable cues and the magnitude of the reduction was moderated by negative affect and measures of alcohol use (e.g., binge drinking status and alcohol consumption) [553,611]. Alcohol and other drugs may thus act as a mechanism to manage exaggerated responses to uncertainty, a theory supported by findings of increased responses to uncertainty during abstinence in those with alcohol use disorder [612] and marijuana dependence [113,613] and in those who smoke cigarettes [614]. Since neuroadaptations that occur with chronic drug use include enhanced anxiety and negative affect in response to stressors [527,551], and uncertain stressors are especially poignant [615,616], attitudes towards uncertainty may be particularly meaningful with regard to drug use and relapse and thus represent a tangible target for intervention.

6.6 Treatment and Policy Implications

With no FDA-approved medication for SUD and a sharp increase in overdose deaths linked to stimulant use [617,618], new treatments are critically needed. The studies presented in this dissertation demonstrated impairments in adaptive decision-making under uncertainty in SUD, as well as an association between ambiguity aversion and grams of stimulant (cocaine or methamphetamine) used per week. Since individuals with substance abuse disorder make maladaptive decisions in response to uncertainty, and ambiguity aversion may motivate drug use itself, increasing tolerance for uncertainty may help in curbing drug use and maintaining recovery, or perhaps even help to prevent initiation.

On the other hand, that our results showed equal (or perhaps lower) levels of loss aversion in SUD compared to control participants suggests a lower sensitivity to negative consequences. Treatments or policies that emphasize negative consequences or aversive outcomes may thus be

ineffective in curbing substance abuse. In fact, punishing policies tend to exacerbate the very problems they are designed to treat; incarceration or engagement with the criminal justice system has little to no effect on curbing drug offenses and in many cases causes increases instead of deceases in recidivism [619-621].

Compared to costs associated with traditional public safety (e.g., criminal behavior, incarceration) and public health (e.g., mental health treatment, emergency visits), most treatments are highly cost-effective, especially when paired with programs such as Alcoholics and Narcotics Anonymous that pose virtually no cost [622-625]. Since treatment, including programs such as drug courts that pair supervision with mandatory treatment [626], has shown better outcomes [627,628], refining the objectives of treatments can continue to improve retention and recovery rates, which is especially important for those transitioning out of institutions [629]. Improving tolerance for ambiguity is simple, changeable, portable, and cost-effective. Supplementing existing treatment programs with a focus on tolerance for ambiguity thus may be an efficient and effective way to improve the choices of individuals with substance abuse disorders.

Psychological interventions designed to reduce ambiguity aversion have already been used effectively for individuals with Generalized Anxiety Disorder [630-632], multiple sclerosis [633], and autism [634]. A computerized Cognitive Bias Intervention [635] and transcranial direct current stimulation [636] also showed promise in reducing ambiguity aversion. Since mindfulness techniques have shown success in the treatment of addiction [637,638] as well as in dealing with uncertainty [639,640], they may be effective in increasing tolerance for ambiguity in those with addictions.

In fact, certain studies that examined the influence of mindfulness interventions on psychiatric disorders found associations with tolerance for uncertainty. For instance, mindfulness and intolerance for uncertainty predicted anxiety and depression in female college students, and

mindfulness partially mediated the relationship between intolerance for uncertainty and anxiety and depression [641]. In a different group of students, intolerance for uncertainty mediated the relationship between anxiety and mindfulness [642]. Mindfulness techniques may improve the ability to cope with aversive feelings or negative affect that provoke cravings and drug use [637,643], such as those elicited by uncertainty. Conditions such as depression and anxiety are highly comorbid with addiction [644,645] and can act as impediments to recovery [646,647], as can stress [610,648]. That addressing tolerance for uncertainty may help alleviate symptoms of anxiety and depression suggest that it also may improve substance abuse treatment retention and recovery rates.

More generally, treating addiction not as a physical or moral failing that needs to be punished, but as a brain disorder [649] shaped by neurobiological, psychosocial, and socioeconomic factors can not only improve the lives of those suffering from addictions and the people around them, but can also save the state costs associated with public safety and health. Supplementing existing treatments with a focus on improving tolerance for uncertainty may help improve decision-making by those with addictions, as well as helping to deal with factors like stress and anxiety that can trigger relapse in the long-term.

6.7 Limitations

Limitations of the studies presented in this dissertation include the relatively small sizes of certain analyses, the inability to isolate loss in the main loss aversion sample, and the lack of a comparison group when investigating associations between ambiguity aversion and resting-state connectivity. The use of our radiotracer for the PET analyses also precluded the separation of dopamine D2 and D3 receptors, which show differential functionality [350] as well as different distribution in healthy control participants and those who use stimulants [349]. It also remains unclear

whether decision-making deficits precede or result from drug use, as both preexisting individual differences [102,153,528-531] and neuroadaptations related to drug use [191,527] affect choices. Finally, the studies presented here are correlational and do not demonstrate a causal relationship between drug use and any of the choice processes discussed herein. Future interventions could determine such relationships.

6.8 Concluding Remarks

The studies presented here do not support the efficacy of treatments or policies that focus on negative consequences or aversive outcomes, but instead supplant existing research positing addiction as a disorder with neurobiological substrates and psychosocial motivations [649]. Improving our understanding of the cognitive and neural mechanisms of substance abuse can not only aid in the development of medication-assisted or behavioral treatments, but also adds to the understanding of addiction as a flawed neurocomputational process [260] in which the calculation of value is distorted, whereby the values of certain rewards vastly outweigh the alternatives. The extent to which choice selection by people with addictions reflects dysfunction in common neural mechanisms that are exaggerated or skewed, or rather a difference in the nature of what is valued, is an open question. Nonetheless, viewing value as central to the decision-making process in addictions provides a powerful framework by which addiction can help us understand the neural mechanisms of decision-making, and vice versa.

The field of neuroeconomics thus offers particularly relevant tools towards such aims [10,650]. The combination of neuroscientific methods with experimental economic tasks and models can help determine how valuation is affected by the complex components involved in making a decision. Our understanding of addiction can be refined by continuing to move towards

conceptualizing decision-making as the integration of different subsystems into a final, unified process that departs from the Cartesian divide [2,6,124,615]—viewing substance abuse not as a battle between "habits" and "goals" [651,652], but rather as a consequence of distorted value. Further examining the neurobiological basis of prospect theory [653] could provide insights into "irrationalities" of behavior and their implications for addictions. The significance of ambiguity aversion provides one such example of clarifying the fundamental processes that contribute to addiction vulnerability and maintenance

Value computation, however, is central to all decision-making, and understanding the cognitive and neural mechanisms of systematic deviations characteristic of human behavior can help gain insight into everyday choices. Indeed, aversion to ambiguity has tangible effects—including on vaccine hesitancy [654], legal decisions [655], medical decisions [656], and stock market prices and volatility [657]. Taking advantage of the biases inherent to human decision-making can thus help design policies to improve people's choices and bring about behavioral and social change.

CHAPTER SEVEN

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