

SEX DIFFERENCES IN RISKY DECISION-MAKING NEURAL PROCESSING AND
ITS LINK TO PROBLEMATIC SUBSTANCE USE IN ADOLESCENTS AT RISK
FOR SUBSTANCE USE DISORDERS

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DEDICATION

This dissertation is dedicated to my family, whose unwavering love, support, intelligence, humor, resilience, and creativity has not only shaped me into the woman and scientist I am today, but also has laid the foundation for my entire journey to becoming a physician-scientist.

This work is also dedicated to all the women in science and medicine who have paved the way for my ability to write this dissertation and pursue a career in these fields. Your contributions, determination, and trailblazing spirit continue to inspire me every day. I am deeply grateful for the paths you have forged, and I hope to honor your legacy by contributing to the progress that you started. To all the women in science coming after me, may you be empowered by the knowledge that you are capable of greatness—just as those before you have proven.

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Background: Risky decision-making deficits are associated with substance use risk. However, sex differences in risky decision-making neural processing among adolescents with externalizing disorders (EXT), like ADHD and conduct disorder, have been understudied though EXT youth are at high risk for developing substance use disorders (SUDs), partially due to impaired decision-making. While males with EXT tend to engage in more risky behavior, the neural mechanisms underlying these patterns may differ for EXT females. This dissertation presents two studies exploring 1) sex differences in brain activation during risky decision-making, and 2) how these differences relate to problematic substance use in EXT youth.

Method: The first study included 168 adolescents (81 EXT males, 39 EXT females, 33 control males, 15 control females), who completed the Balloon Analogue Risk Task (BART) during a magnetic resonance imaging (MRI) session. The second study utilized 115 drug-naive EXT adolescents (78 males, 37 females) who also completed the BART during an MRI session and were assessed for problematic substance use during longitudinal follow-up. Statistical analyses compared sex and EXT differences in brain activation during risky decision-making and the associated risk of substance use using Cox proportional hazards models, respectively.

Results: EXT males showed greater activation in the cingulo-opercular network during risky versus safe choice as that choice became riskier (modulated) compared to EXT females and controls. Greater modulated activation in the right nucleus accumbens (NAc) during risky versus safe choice was associated with less problematic substance use in EXT females, but not in EXT males. Greater unmodulated choice phase activation in the NAc in males and in the subgenual anterior cingulate cortex in females were associated with less problematic substance use.

Conclusions: This dissertation highlights significant sex differences in both the neural processing of risky decision-making and its connection to substance use in EXT youth. These findings suggest that proper risk processing in the cingulo-opercular and reward networks may protect against substance use, with distinct patterns in males and females. These results underscore the importance of sex-specific approaches for prevention and intervention in youth at risk for substance misuse.

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LIST OF ABBREVIATIONS

ACC	anterior cingulate cortex
ADHD	attention-deficit/hyperactivity disorder
AIC	Akaike Information Criterion
AUD	alcohol use disorder
BART	Balloon Analogue Risk Task
CBT	cognitive behavioral therapy
CD	conduct disorder
CI	confidence interval
dACC	dorsal anterior cingulate cortex
dIPFC	dorsolateral prefrontal cortex
dmPFC	dorsal medial prefrontal cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DUSI-R	Drug Use Screening Inventory-Revised
EPI	echo-planar imaging
EXT	externalizing disorders
fMRI	functional magnetic resonance imaging
FSL	fMRIB Software Library
GLM	general linear regression model
HR	hazard ratio
ICA	independent components analysis
IDRT-Y	Impulsive Decision Reduction Training for Youth
IFG	inferior frontal gyrus
IQ	intelligence quotient
KSADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version
MID	Monetary Incentive Delay
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
Nac	nucleus accumbens
ODD	oppositional defiant disorder
OFC	orbitofrontal cortex
POLR	proportional odds logistic regression
PSU	problematic substance use
ROI	region of interest [brain]
SAVE	Screen for Violence Exposure
SES	socioeconomic status
sgACC	subgenual anterior cingulate cortex
SGM	sexual and gender minorities
SUD	substance use disorder
TR	repetition time
VS	ventral striatum
WASI	Wechsler Abbreviated Scale of Intelligence

Chapter One: Introduction

1. Magnitude of Substance Use Disorder Problem

Substance use disorders (SUDs) are extremely deleterious with far-reaching consequences, affecting not only individuals but also families, communities, and society at large. SUDs impose a significant economic burden in the United States, with costs approaching a trillion dollars annually—a figure driven by the high expenses associated with opioid use disorder (2-4) and alcohol use disorder (5), two of the more extensively studied SUDs in terms of economic impact. The repercussions of SUDs extend far beyond monetary costs, of course, leading to family disruption including family disintegration, child abuse, violence, and an increased risk of mental illness in offspring (6, 7). Further, SUDs pose increased burden for the individual and society related to academic (8-10) and workplace failure (11, 12), and are usually accompanied by severe health complications (13). The Substance Abuse and Mental Health Services Administration (SAMHSA)'s 2023 National Survey on Drug Use and Health (14) reported that in 2023, approximately 48.5 million individuals aged 12 and older had a past-year SUD, including 28.9 million with alcohol use disorder, 27.2 million with drug use disorder, and 7.5 million with both. SUD rates were highest among young adults (18–25) at 27.1%, followed by those 26 and older at 16.6%, and then adolescents (12–17) at 8.5%. Given this widespread prevalence of disordered use and the associated harmful consequences, it is crucial to study SUDs more thoroughly, including factors such as sex differences, which play a significant role in the development and impact of SUDs. My dissertation aims to explore these important aspects to better inform prevention and intervention strategies.

2. Sex Differences in Substance Use Disorders

Sex differences in SUDs are evident in their progression, severity, and treatment. Women show lower rates of substance use than men, though this gap is narrowing (15, 16). And as a negative feature despite these lower rates, women tend to initiate substance use later than men but progress to dependence and severe clinical profiles more rapidly, a phenomenon known as “telescoping” (17-19). This telescoping effect for women in addiction has been shown across many drugs of abuse including alcohol (16, 20-22), cannabis (20, 21, 23), tobacco (20, 21), opiates (20, 24), stimulants (20, 23), and for multi-substance use (15, 25-29). Additionally, women tend to be more vulnerable to negative physiological consequences of nicotine and alcohol use disorders and report shorter abstinence periods and more severe drug use at intake for cocaine than men (15, 20, 21, 24, 25). Despite facing more stigma, women who adhere to specialized treatment often achieve better results than men (15, 25). With so many differences in SUD progression, severity, and outcomes, further exploration of sex differences in risk profiles are needed to unpack these sex-based differences in adult SUDs.

Regarding risk profiles for SUD, while not a focus of this dissertation, another commonly discussed sex difference in SUD risk is internalizing pathology for females. The internalizing pathway to SUDs is defined by mood disturbances such as negative affect, depression, and anxiety (30). Sex differences in this pathway become pronounced during puberty, with females exhibiting significantly higher rates of depression than males (31). Stress vulnerability further differentiates the sexes, playing a key role in this pathway: for example, adolescent girls who misuse alcohol are more likely than their male counterparts to have experienced high levels of stress or traumatic life events (32,

33), and some girls report that these stressors lead them to initiate alcohol or drug use as a coping mechanism (34). These mental health disparities culminate in the fact that women and girls tend to show a greater prevalence of comorbid conditions like depression or anxiety within addiction with the mood disorders often emerging before the onset of the SUD (15, 24, 25, 35-38). In summary, the internalizing pathway, which involves vulnerabilities like depression, anxiety, and stress, is a possible pathway for substance use in females. While this dissertation focuses on the *externalizing* pathway of substance use, it is important to acknowledge the relevance of the internalizing pathway, which may warrant further consideration as our investigation and findings continue to evolve.

3. Adolescence as a Crucial Time for SUD Development

Given well-established sex differences in addiction, it becomes crucial to trace their roots by examining disparities in risk factors, with adolescence offering a key window for investigation, as this developmental stage marks the onset of SUD vulnerability. Adolescence is a critical period for initiating substance use due to heightened risk-taking tendencies, a still-developing prefrontal cortex that impairs decision-making and behavior control, dopaminergic mechanisms that enhance the reward of drug use, misperceptions of social norms around substance availability, and strong peer influence that fosters engagement in substance use (34, 39, 40). Research consistently demonstrates that early substance use during adolescence significantly heightens the risk of developing SUD. This risk may be different for various substances with one study finding cannabis leads to the fastest transition from use to dependence, while nicotine has the highest probability of addiction overall (36%) (41). For alcohol, adolescent onset of alcohol use disorder (AUD) has been shown to lead to severe

psychosocial deficits with behavioral disinhibition predicting persistent AUD, and earlier onset of alcohol use has been shown contribute to more severe AUD later in life (32, 33). Importantly, prevention efforts should focus on high-risk adolescents, as 15% of all lifetime AUD cases develop before age 18 (42-44), and an earlier age at first alcohol use is strongly associated with an elevated risk of developing AUD, particularly through behaviors like binge drinking (45, 46). With this strong evidence that SUD has a strong developmental basis in adolescence, identifying indicators of progression to SUD is crucial, yet this transition of at-risk adolescents to those with SUDs has predominantly been studied in males (47, 48), particularly as it relates to deficits in decision-making (49). To enhance risk assessment, treatment, and prevention of SUD, it is crucial to evaluate sex differences in risk components.

4. Externalizing Psychopathology as SUD Risk Phenotype

Youth with externalizing disorders (EXT) represent an ideal population for examining adolescent risky decision-making and progression to SUD, as impulsivity and disinhibited decision-making are characteristic of both EXT pathology and SUDs. EXT disorders encompass a range of behavioral issues, including attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD). These disorders are characterized by behaviors that are directed outward, often manifesting as impulsivity, disinhibition, aggression, defiance, and emotion dysregulation (50-53), which in turn are associated with the tendency toward immediate gratification (i.e. delay discounting—the preference for immediate over delayed rewards), increased risk-taking behavior, and impaired decision-making processing (54-64). Consequently, EXT pathology is consistently associated with an increased risk for the

development of SUDs (47, 65-76). This connection between adolescent EXT disorders and future SUDs is understandably explained by the interplay between shared genetic and neurobiological factors related, in part, to behavioral disinhibition, which influences cognitive control, impulsivity, and reward sensitivity, and the co-occurring environmental and neurobiological risks during adolescence discussed above, all of which heighten the likelihood of addiction among those with EXT disorders (49).

Given the inherent vulnerabilities associated with EXT disorders, understanding the underlying mechanisms that link impulsivity, disinhibition, and risky decision-making to the onset of SUDs is crucial for developing targeted interventions and prevention strategies aimed at this high-risk population. However, sex differences in the relationship between disinhibited risky decision-making and SUD risk among EXT youth remains underexplored, preventing us from truly characterizing risk profiles and interventions for high-risk males and females. The longitudinal studies, which found increased SUD and substance use problems for youth with EXT traits/symptoms, either utilized males only or did not explore sex differences in EXT pathology and its relation to future substance misuse (47, 49, 67, 68, 70, 71, 73, 74, 76). Studies which have explored impulsivity traits and sex differences have found trends suggesting EXT traits/symptoms confer SUD risk in both males and females (65, 66, 69, 75), though none of these studies explored clinically diagnosed EXT disorders (just EXT traits) and none focused on substance naive, at-risk male and female adolescents with diagnosed ADHD and other EXT disorders.

5. Risky Decision-Making Deficits and SUD Risk

Building on the link between EXT pathology and SUD risk, it is crucial to explore how risky decision-making deficits, seen in both SUD and EXT disorders (77), contribute to higher substance misuse risk in EXT youth and how this relationship varies by sex, as decision-making deficits can be targetable for sex-specific SUD prevention. Decision-making deficits are prevalent in EXT psychopathology and SUDs, often resulting from an imbalance between an impulsive, amygdala-driven reward system and the reflective, prefrontal cortex-focused system responsible for considering future outcomes (78-81). Individuals with SUD, particularly those with antisocial traits, demonstrate a marked preference for immediate over delayed rewards (high delay discounting) and are prone to impulsive, high-risk decisions despite adverse long-term consequences (82-84). These tendencies are further complicated by working memory deficits, which heighten vulnerability to addiction through impaired self-regulation and cognitive control (85-87). The propensity to make risky, disadvantageous decisions is key to the SUD risk phenotype, yet several researchers have found sex differences in this aspect of the risk profile with males consistently exhibiting a greater tendency towards risky decision-making compared to females, particularly in populations with EXT pathology and substance use issues (88-92). While this suggests that sex differences in risk-taking behavior may play a critical role in shaping the overall risk profile for EXT youth, with males showing a stronger propensity for impulsive, disadvantageous choices, sex differences in the risk profile have not been explored in youth with clinically diagnosed ADHD and disruptive behavior disorders (ODD and CD) nor in substance-naive, at-risk adolescents with EXT psychopathology. This leaves a critical gap in understanding how sex-specific patterns of decision-making behavior may shape the progression to SUD,

particularly among high-risk, substance-naive youth, calling for further investigation into the unique, sex-specific vulnerabilities of this population.

6. Risky Decision-Making Circuitry

It is well-understood that risky decision-making engages a large network including cortical and subcortical regions in prefrontal, parietal, limbic, and subcortical structures (93-95). Risky decision-making can be conceptualized in two primary phases: the choice phase and the outcome phase. Although the choice, deliberative phase is arguably more complex, it is closely linked to the outcomes and learning that occur in the subsequent phase. This process involves both cognitive and emotional brain circuits, with factors such as predicted outcomes (including valence and probability), prior experience, and contextual influences shaping decision-making (93). Several neural circuits have been shown to be involved with risky decision-making, including the cognitive control network, which can be further subdivided into the frontoparietal network and the cingulo-opercular/salience network, along with the reward network and the limbic system (see Figure 1 and Figure 2 below adapted from Haber and Knutson 2010 (1) for graphical depictions of these network connections in the context of reward) (1, 96-98). The **cognitive control network** includes brain regions such as the dorsolateral prefrontal cortex, anterior cingulate cortex (ACC), and posterior parietal cortex, all of which are

involved in executive functioning (96). Subsections of this network, which also play roles in attention processing, are the **frontoparietal network** (which includes the frontal eye field and supplementary motor area) (99, 100) and the **cingulo-opercular/saliency network** (which includes the anterior insula) (97, 98).

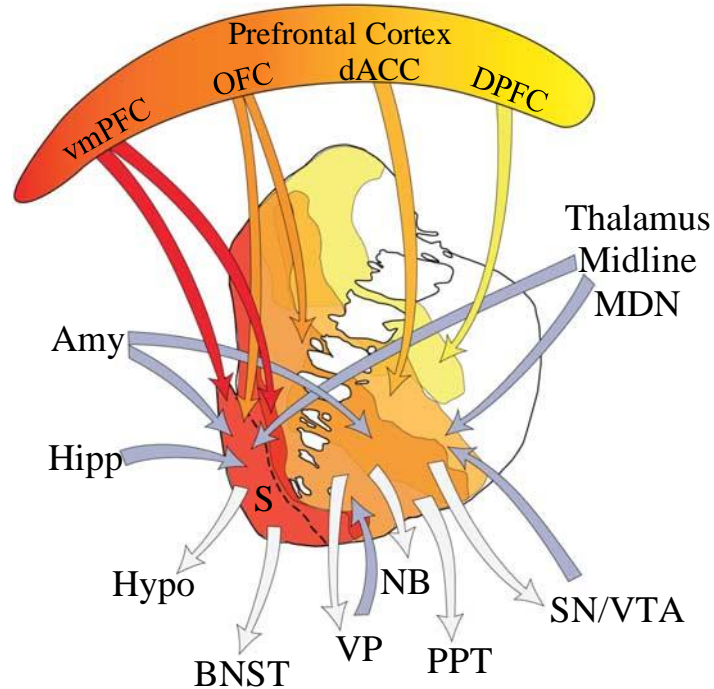


Figure 1. “Schematic illustrating the connections of the VS. Blue arrows=inputs; gray arrows=outputs; Amy=amygdala; BNST=bed nucleus stria terminalis; dACC=dorsal anterior cingulate cortex; DPFC=dorsal prefrontal cortex; Hipp=hippocampus; Hypo=hypothalamus; NB=nucleus basalis; MD=medio-dorsal nucleus of the thalamus; OFC=orbital frontal cortex; PPT=pedunculo-pontine nucleus; S=shell; SN=substantia nigra, pars compacta; STN= subthalamic nucleus; VP=ventral pallidum; VS=ventral striatum; VTA=ventral tegmental area; vmPFC=ventral medial prefrontal cortex.” *Adapted from Haber and Knutson 2010 (1).*

Within these **cognitive control networks**, for instance, the parietal cortex is involved in assessing probability (101, 102), while the dorsal ACC (dACC) is associated with uncertainty and loss avoidance (103-106). Another important player in risky decision-making within this network, involved in voluntary and involuntary risk-taking (107), is the right dorsolateral prefrontal cortex, which has been shown to be involved with making decisions in ambiguous contexts, while risky decisions engage the orbitofrontal cortex and subgenual ACC (95). The **limbic network** (amygdala and

insula), and the **reward/motivation network** (orbitofrontal cortex and dopamine-rich mesolimbic regions including the midbrain, striatum/NAc, and their reciprocally connected frontal cortex) are key networks involved in generating, evaluating, and assigning emotional aspects to choices during the risky decision-making process (108-112). During risky decision-making, emotional intensity (or valence) of an option boosts activity in the ventral striatum, particularly the nucleus accumbens, which influences the decision by making emotionally charged options more attractive (109, 110, 113). Further, related to all of these networks' functions in the decision-making process, the ventral area of the ACC, which includes the sgACC, is also involved through its connection to the OFC, amygdala, NAc, and limbic system, and, therefore, functions to ascribe emotional and motivational significance to the reward evaluation process in order to avoid decisions that lead to reward loss (114, 115). The sgACC—well-known in relation to negative affect and depression—relatedly functions in processing aversive stimuli and negative emotions in the context of risk and reward and has been linked to uncertainty and under confidence when making decisions (116-120). In summary, the choice phase of decision-making involves a network of brain regions, including the **cognitive control network** for uncertainty, loss avoidance, and ambiguous decision-making, and the **limbic and reward networks** for emotional evaluation and assigning salience and emotional intensity of choices.

Following making a choice and acting on it in risky decision-making is experiencing the outcome of that chosen action. Emotions like regret, disappointment, and surprise play a key role in shaping future decision-making (121). Processing regret and disappointment during decision-making have been shown to activate regions in the

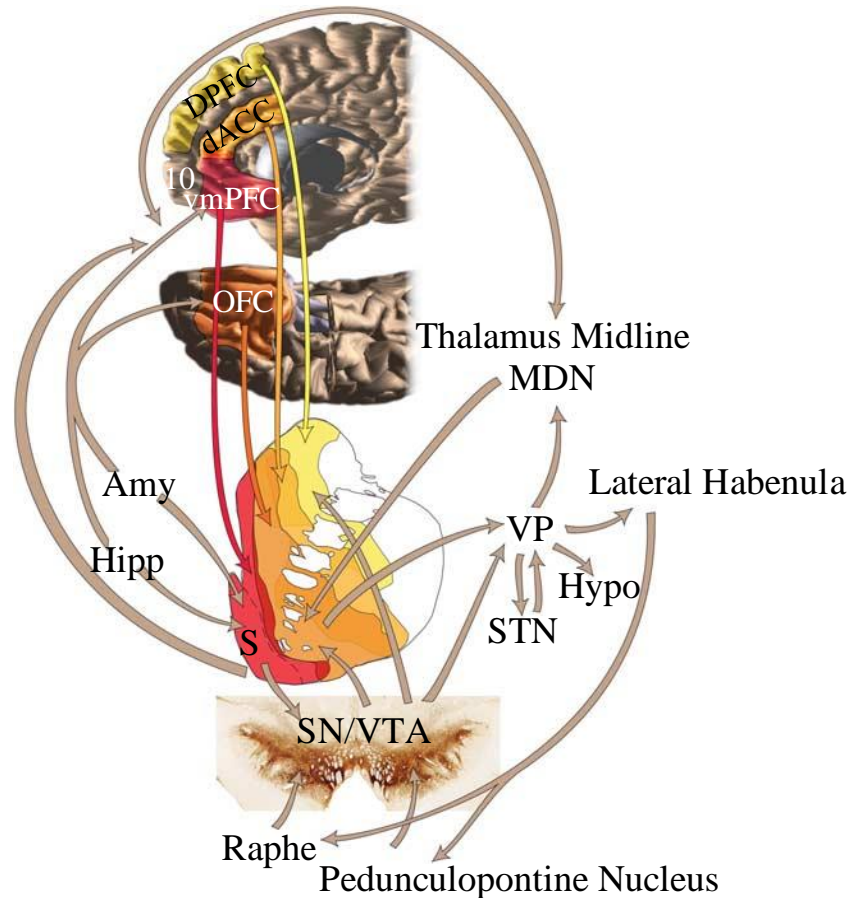


Figure 2. “Schematic illustrating key structures and pathways of the reward circuit. Red arrow=input from the vmPFC; dark orange arrow=input from the OFC; light orange arrow=input from the dACC; yellow arrow=input from the DPFC; brown arrows other main connections of the reward circuit. Amy=amygdala; dACC=dorsal anterior cingulate cortex; DPFC=dorsal prefrontal cortex; Hipp=hippocampus; Hypo=hypothalamus; MD=medio-dorsal nucleus; OFC=orbital frontal cortex; S=shell, SN=substantia nigra, pars compacta; STN=subthalamic nucleus; VP=ventral pallidum; VTA=ventral tegmental area; vmPFC=ventral medial prefrontal cortex.”
Adapted from Haber and Knutson 2010 (1).

cingulo-opercular and reward network including the anterior insula/dACC, dorsomedial prefrontal cortex, and medial and lateral orbitofrontal cortex (122, 123), while functional neuroimaging studies have indicated that the step following the interpretation of surprise, when expectations differ from the actual outcome, also involves **reward network** regions of orbitofrontal cortex (124, 125) and the ventral striatum (124, 126). Emotion processing/**limbic network** is present throughout decision-

making, so in addition to the aforementioned regions involved in this (amygdala, nucleus accumbens, orbitofrontal cortex, insula), the medial prefrontal cortex, especially Brodmann area 10, is crucial for integrating emotions in the feedback processes (127). Finally, the ventromedial prefrontal cortex, which has been identified as a key player in the **reward network**, integrates sensory information and communicates with brainstem structures, including the hypothalamus, to guide decision-making (128), assess rewards (129), and track rewarding outcomes (127). In summary, key neural networks of **cingulo-opercular** and **reward** are crucial in processing emotions like regret, disappointment, and surprise, which shape future decisions by integrating emotional feedback and assessing outcomes in the outcome-processing phase of risky decision-making.

7. Risky Decision-Making Circuitry Alterations in EXT Psychopathology

As discussed earlier, EXT disorders are characterized by impulsivity, disinhibition, and emotion dysregulation, which lead to impaired decision-making (54-64). Research into the neural basis of disrupted decision-making in EXT disorders seems to center around two key brain networks: cognitive control and reward networks. Issues with impulsivity, sensation-seeking, and emotion regulation understandably affect decision-making through alterations in brain processes that influence how choices are evaluated and acted upon. EXT psychopathology is associated with impaired cognitive control, making it difficult to suppress impulsive behaviors and assess choices based on long-term goals. Reward network abnormalities also lead to prioritizing immediate rewards over long-term consequences, likely due to an imbalance in cognitive processes that guide goal-directed decision-making through regulation of reward centers (130).

With EXT disorders' characteristic inattention, impulsivity, and hyperactivity, it is not surprising that neuroimaging research in individuals with EXT has revealed both structural and functional impairments in brain regions responsible for regulating attention, impulse control, and executive functions—processes occurring in decision-making networks including the cognitive control network. Notably, the inferior frontal gyrus (IFG) and dorsolateral prefrontal cortex (dlPFC) are involved in attention regulation and inhibitory control, and are crucial for inhibiting processing of irrelevant stimuli, maintaining attention, and coordinating divided attention (131). In ADHD, these regions show lower activity during tasks requiring sustained attention allocation, attentional shifting, and reward processing (132-135). This aligns with theories suggesting a disruption in cognitive control/attention networks underlying ADHD.

When it comes to the disruptive behavior disorders like CD and ODD, which are primarily characterized by emotion dysregulation and rule-breaking behaviors and of course share overlapping symptoms with ADHD, neuroimaging findings show some notable differences in the brain areas related to motivation and emotional regulation compared to ADHD. Studies suggest that CD/ODD involve abnormalities in the paralimbic system, which includes the orbitofrontal cortex (OFC), dACC, superior temporal cortices, and underlying limbic regions. These areas are involved in the reward (OFC and limbic regions) and cognitive control (dACC) networks and disruptions in these networks are therefore linked to difficulties in emotion regulation and reward processing in individuals with CD, including those with more severe manifestations, such as psychopathy, who tend to experience poorer adult outcomes (132-137). Further, in an area connected to many of these previously discussed regions, the sgACC has displayed

greater activation during reward loss in youth with ADHD and a disruptive behavior disorder possibly indicating a dysfunction with the emotional processing of loss related to the area's known function in loss avoidance (138).

Considering ADHD and disruptive behavior disorders often co-occur, as they do in the sample analyzed within this dissertation, it is difficult to extract the unique neural processing changes associated with each type of pathology. Due to the frequent co-occurrence of these disorders, an independent analysis is also of limited utility, particularly when the population of interest exhibits both types of disorders, as in the present studies. If ADHD is largely associated with impairments in cognitive control, particularly in inhibitory control and CD/ODD is more closely tied to dysfunction in emotional regulation and reward processing (but also disruption in cognitive control activity), the overall network disruption for an individual with both types of psychopathology is a dual disruption of cognitive control and reward processing neural networks.

Therefore, the neurobiological decision-making disturbances broadly observed in those with EXT psychopathology reveal a complex relationship between cognitive control, emotion regulation, and reward processing. From the ADHD-side, deficits have been identified as being associated with delayed maturation of regions responsible for executive functions, particularly the prefrontal cortex and basal ganglia, leading to the characteristic difficulties with attention, inhibition, and working memory—skills relevant in all phases of risky decision-making (139-145). For those with CD/ODD-pathology, the described disruptions in emotion and reward-processing systems within the paralimbic region lead to impairments in motivation, emotion regulation, and reward responsiveness

which are all invaluable in risky decision-making processes (59). EXT disorders share neurobiological foundations in dysregulated networks responsible for executive function and reward processing, particularly involving prefrontal and striatal circuits, which may help explain the high rate of comorbidity between ADHD and disruptive behavior disorders.

Further on this point, research suggests that the risk for EXT psychopathologies arises from both impaired top-down executive function and hypersensitivity in bottom-up reward processing areas (49, 146). Previous studies have linked EXT symptoms to deficits in frontal lobe recruitment during cognitive control tasks (147, 148) and reward processing tasks (149, 150). While this theory of dysregulated networks governing cognitive control and reward processing existing at the core of EXT psychopathology is compelling, it has not been fully explored in the context of sex differences. This dissertation aims to address this gap, and further contribute insight, by investigating how sex might affect the relationship between neural activation patterns, risky decision-making, and future substance use behaviors in a sample of youth with EXT disorders and healthy controls. By exploring these factors, we hope to better understand the underlying mechanisms of EXT psychopathology and assess whether the existing models of neural processing dysfunction hold true across sexes, as well as how these imbalances may contribute to the development of risky and problematic behaviors for males and females with these disorders.

8. Risky Decision-Making Circuitry Alterations in SUD

As discussed above, a feature connecting individuals with EXT pathology and SUDs in risky decision-making is a tendency toward immediate gratification, increased

risk-taking, and impaired decision-making (54-64), which, in addition to the behavioral deficits, has been reflected in differences in risky decision-making circuitry for individuals with SUD psychopathology as well. The specific cognitive mechanisms contributing to these disordered decision-making patterns have been shown to involve greater activation in the medial and lateral prefrontal cortex of substance-dependent individuals in response to craving cues, which could indicate a heightened valuation of drug-related stimuli that alters the decision-making process (151-154), potentially also reflecting disrupted formation of preferences in the choice phase of decision-making. Dysfunctions in the ventromedial, ventrolateral, and dorsolateral prefrontal cortex in stimulant-dependent individuals during risky decision-making (155-157) suggest difficulties in associating positive outcomes with advantageous actions and therefore difficulty in identifying trends in choices and their respective advantageous or disadvantageous outcomes (157, 158). Additionally, dysfunction of the anterior insula, associated with harm avoidance, may contribute to substance abuse as lower activation in this area in substance-dependent individuals has been linked to their risk-taking behavior (116, 159, 160).

Research like that presented in this dissertation, which examines risky decision-making in substance-naive individuals at high risk for substance use due to EXT pathology prior to substance initiation, helps address a critical question in this area of whether decision-making deficits in substance use disorders precede substance misuse and contribute to the initiation of drug use (as suggested by our lab's and collaborators' findings (138, 161-164)), or whether these deficits are a consequence of drug use itself (165, 166). This dissertation provides additional insight into this debate via investigating

sex differences in how risky decision-making deficits among SUD at risk youth *before* they start using drugs may relate to real-world substance use outcomes.

9. Sex Differences in Risky Decision-Making Circuitry

Regarding sex differences in risky decision-making circuitry, a gap in the research exists in comparing substance-naïve, EXT youth to neurotypical youth, which this dissertation—particularly Chapter Two—aims to address. That said, neuroimaging studies in other risk populations do exist and help inform our hypothesis on sex differences in risky decision-making circuitry. Regarding the choice or decision phase in a risky decision-making task, in a mixed sample of adolescents with conduct and substance use problems and controls, before cautious/safe choices, males showed greater activation in the prefrontal cortex, striatum, insula, and thalamus while females showed greater activation in the right medial frontal gyrus (88). Before risky decisions in this same sample, males had greater activation in the left anterior cingulate cortex and medial frontal gyrus while females had greater activation in the right anterior cingulate cortex and medial frontal gyrus. In a prior study of a subset of our EXT sample (no control comparisons), Dir et al. found boys showed greater activation in bilateral middle frontal gyrus when making a safe decision over a risky one (167). And in a large sample of healthy adolescents who performed a risky decision task, when making a safe choice, girls had greater activation than boys in the caudate, middle/inferior temporal gyri, and posterior cingulate (90). Therefore, in the choice phase, sex differences seem to arise in the reward and salience networks, with males showing greater activation in the reward network during both risky and safe choices, while females show greater activation in this

network during safe choices only, and males activating left-sided salience network and females activating right-sided salience network before risky decisions (88, 90, 167).

Regarding the outcome phase, when learning the result of their choice in a decision-making task, healthy adult females showed more activation in the dorsolateral prefrontal cortex during losses than males (168). Girls had greater activation than boys in several regions when viewing a negative outcome of their risky decision including inferior parietal, insula, inferior temporal, lateral orbitofrontal, rostral and caudal middle frontal, and superior parietal regions. Boys only had greater activation than girls when experiencing a positive outcome of a risky decision and that was in the right caudal anterior cingulate/superior frontal region. In summary, for the outcome phase females activate frontoparietal and salience networks more when processing negative outcomes, where males activate frontoparietal cognitive control networks when processing positive outcomes (168). In summary, sex differences in risky decision-making, identified in primarily healthy adolescents and adults, show that males generally have greater activation in frontostriatal and salience networks during both risky and safe choices, while females show greater activation in these networks only during safe choices. During the outcome phase, females engage frontoparietal and salience networks more when processing negative outcomes, while males activate cognitive control networks more when processing positive outcomes, suggesting different brain mechanisms for reward processing based on sex. While these findings come from EXT-only or healthy samples, further investigation is needed in substance-naïve adolescents to determine whether sex differences in risky decision-making override EXT psychopathology (Chapter Two) and,

subsequently, whether these differences may relate to sex-specific outcomes in substance use (Chapter Three).

10. Balloon Analogue Risk Task (BART)

One established risky decision-making task which has been made fMRI-compatible is the Balloon Analogue Risk Task (BART). This dissertation utilizes the BART to examine differences in risky decision-making behavior and brain activity between boys and girls with and without EXT disorders, as BART performance has been associated with impulsivity (169), adolescent risk-taking (170, 171) and SUDs (172, 173), discussed further later in this section. The BART (Figure 4), which involves choosing whether to continue to inflate a virtual balloon to win more money for a bigger final balloon at the risk of popping it and losing all money, pairs the prospects of winning and losing money to model real-world drug choices with varying probabilities of reward and negative outcomes. During the BART, participants decide whether to risk cash rewards that increase with each balloon inflation or bank the amount and start inflating a new balloon. A jitter function is applied to the timing of the stimulus presentations between decision and outcome phases of each trial to differentiate decision-making and feedback-related processes (174). Participants are repeatedly presented a virtual balloon and have to press one of two buttons to either inflate the balloon (Choose Inflate), risking cash rewards that increase with the balloon's size, or to stop inflating and bank the accumulated money for that balloon (Choose Win) before starting a new balloon. If they choose to inflate, the balloon either expands, increasing the reward amount for that balloon (Outcome Inflate), or it bursts, resulting in the loss of the accumulated money for that balloon (Outcome Explode). After an explosion, a new balloon is presented. When

participants opt to win (Choose Win), the accumulated rewards are banked, and a new balloon appears.

Specific behavioral measures of the task that have been shown to correlate with key indicators of SUD risk—such as the adjusted number of balloon pumps on the BART (i.e., the average number of inflations made on each balloon, excluding those that exploded)—have demonstrated a significant positive association with impulsivity and sensation-seeking. In other words, higher scores on these EXT traits are linked to a greater number of balloon inflations (169). Further, the task developers (Lejuez et al.) found adolescents who took more risks on the BART also engaged in higher levels of risky behaviors, including activities like drug use, engaging in a physical fight, not using seatbelts, stealing, gambling, risky sex, or carrying weapons, in their everyday lives. The BART effectively predicted real-world risk behaviors, and when the variables of age, gender, impulsivity, and sensation seeking were entered into a regression model, they accounted for 27.6% of the variance in risk behaviors. Adding the BART scores as a predictor in the second step of the regression analysis increased the variance explained by an additional 4.5%, indicating that adolescents who were more willing to take risks on the task also tended to engage in more risk behaviors outside of the laboratory setting (170). Interesting enough, this study also found a significant effect of sex with female sex being associated with higher risk-taking behaviors in the regression model, although no direct relationship was found between sex and the number of pumps, indicating that sex's influence on risk-taking may depend on other factors like sensation seeking or impulsivity which were included in the regression models. In the second chapter, we have

the opportunity to further explore whether the BART measures are better predictive of risky behaviors in females vs males.

Lastly, studies of those with SUD frequently find measures of risk taking in the BART, like higher average adjusted pumps, are positively correlated with drug use (172) and differentiate those who do and do not use substances (173). When it comes to BART neural activation differences in SUDs, individuals with AUD have shown differential activation in all phases of the task compared to controls (175): during BART outcome processing, compared to healthy controls, participants with AUD displayed lower activation in regions of the mesocortical-limbic circuit, such as the orbital prefrontal cortex, dorsal striatum, insula, hippocampus, cerebellum, cuneus cortex, and superior temporal gyrus, while showing heightened activation in the inferior temporal gyrus and paracentral lobule (extending into the middle cingulate cortex and precuneus). When making the risky choice in BART (Choose Inflate), participants with AUD exhibited lower activity in the prefrontal and cingulate cortices, including the posterior cingulate cortex (extending to the middle cingulate cortex), middle frontal gyrus, medial prefrontal cortex, dorsolateral prefrontal cortex, orbitofrontal cortex, and ACC.

Sex differences in BART neural activation were highlighted in the previous section on neural circuits of risky decision-making. In summary, the BART is an ideal tool for examining risky decision-making in youth with EXT psychopathology, as it mimics real-world drug choices by balancing reward and risk. Behavioral measures and neural activation in this task have been linked to impulsivity, adolescent risk-taking, and substance use disorders, making it the perfect task to investigate the interaction between sex, EXT pathology, brain activation, and substance use outcomes. Both Chapter Two

and Chapter Three of this dissertation utilizes the BART with the second chapter focusing on sex differences in neural activation during the task among adolescents with and without EXT psychopathology and the third chapter analyzing how sex affects the association between brain activation during BART and real-world problematic substance use outcomes in EXT youth.

11. Chapter Two Manuscript Introduction

The second chapter of this dissertation tests the hypothesis that the interaction between sex and EXT pathology will lead to EXT females exhibiting activation patterns more similar to those of EXT males, characterized by greater frontoparietal/frontotemporal activation before risky choices and less activation before negative outcomes compared to control females. This chapter describes our study design, including an fMRI investigation with 168 adolescents performing the BART to assess decision-making and associated brain activity, comparing neurobiological patterns across four groups: EXT males, EXT females, control males, and control females.

Given these prior studies showing greater activation in fronto-striatal-thalamic regions during safe choices, we expect lower activation during risky choices relative to safe choices in these regions for females. And as males tend to show greater activation in the frontoparietal network during both risky and safe decisions, the contrast of risky versus safe choices may show stronger activation in these reward-related areas when males make risky decisions, versus females. Regarding the outcome phase, because females are expected to show greater activation in frontoparietal and salience network regions during negative outcomes and males to activate frontoparietal cognitive control networks when processing positive outcomes, the contrast of negative versus positive

outcomes is expected to reveal less activation in these reward-related regions for males. Thus, we hypothesize that when contrasting risky choice with safe choice, males are expected to show greater activation in frontoparietal and salience regions like the dorsolateral prefrontal cortex and anterior cingulate compared to females. Additionally, for the negative outcome versus positive outcome contrast, males are expected to have lower activation in frontoparietal regions relative to females. Regarding how EXT psychopathology may interact with these sex differences findings, Crowley et al. found three areas, two in the middle frontal gyrus and cerebellum before risky choice and one in the pre/postcentral gyrus before cautious choice, which showed a sex by group interaction (88). In all these regions, control males showed greater activation than males with EXT traits, but for females, those with EXT traits had more activation than controls. This literature helps form the hypothesis that female EXT in our sample are expected to have different activation than our female controls and that this different activation will be closer to male activation (greater frontoparietal and salience network activation before risky decision-making).

In sum, the second chapter, incorporating neuroimaging and behavioral assessments, aims to explore sex-specific mechanisms that underlie risky decision-making in male and female adolescents in a sample of 11–12-year-olds with and without EXT disorders. We hypothesize that nuances of the interaction between sex and EXT pathology will result in EXT females having activation closer to EXT males, which will be greater frontoparietal/frontotemporal activation before risky choices and less activation before negative outcomes than control females. These sex-specific findings

could guide new interventions and prevention strategies specifically aimed at defaults in risky decision-making processes among the highest-risk youth.

12. Chapter Three Manuscript Introduction

The third chapter of this dissertation focuses on the relationship between sex differences in risky decision-making neurobiological activation among adolescents with EXT disorders and their actual future substance use outcomes. This chapter does not explicitly analyze sex differences in brain activation but rather focuses on how sex influences the relationship between brain activation and substance use outcomes. Based on prior literature, we expect sex differences in EXT brain activation will differently affect the relationship between brain activation and substance use outcomes for EXT males and females. Chapter Three describes our study design, including evaluating the effect of sex on the relationship between risky decision-making brain activation during the BART, assessed with a baseline functional MRI, and future problematic substance use, assessed with longitudinal follow-up behavioral measures, in 115 male and female EXT youth.

To focus on the most relevant brain areas for examining sex differences in brain activity during risky decision-making and their relationship to problematic substance use in adolescents with EXT disorders, we pre-selected specific brain regions of interest (ROIs) where prior research has shown differential activation in individuals with ADHD (176, 177) or a family history of SUD (178, 179), as both are associated with heightened risk for SUD, as well as regions whose activation has been linked to future substance use. Additionally, in these ROIs, sex differences relating to SUD risk and brain activation in EXT youth have yet to be explored. The ROIs chosen, discussed, and analyzed further in

Chapter Three include the nucleus accumbens (NAc) and the subgenual anterior cingulate cortex (sgACC).

Due to prior research showing correlations between NAc activation and EXT behaviors in individuals with SUD family history (180-183), the relationship between lower frontal-NAc connectivity and earlier drinking behavior (184), and the finding that increased NAc activation during reward anticipation predicts more and earlier substance use (185, 186), we hypothesize that for EXT boys relative to girls, greater NAc activation when making risky choices will be associated with a higher hazard of problematic substance use. Considering these brain regions have been identified as members of the reward network (187-189), the summary hypothesis for Chapter Three is that greater activation in reward network areas during risky decision-making is associated with higher hazard of problematic substance use in EXT boys compared to EXT girls.

Sex differences in the SUD risk model of EXT pathology, particularly in how EXT deficits in risky decision-making contribute to future substance use, remain underexplored. This preliminary study aims to address this gap by investigating neuropsychological factors in at-risk 11–12-year-olds with EXT pathology. By leveraging our innovative sample and study design, which includes longitudinal data for empirical validation of substance use progression, we hope to uncover novel mechanistic insights. These findings provide crucial insights for developing sex-specific substance use prevention strategies to address the precise deficits in risky decision-making that put adolescents with EXT pathology at highest risk for SUD.

13. Conclusion

In conclusion, as SUDs are so highly detrimental, it is essential to examine factors like sex differences in their development and impact for better prevention and intervention strategies. Sex differences in SUDs are evident in their progression, severity, and treatment, with women generally initiating substance use later but developing dependence more quickly (telescoping), being more vulnerable to certain disorders, and facing unique risk factors such as internalizing pathology, stress, and trauma, highlighting the need for further exploration of these differences in substance use risk profiles. Given these well-established sex differences in addiction, adolescence represents a critical developmental window for investigating disparities in risk factors, as early substance use significantly heightens the risk of developing SUDs, with sex differences in the progression and onset of these disorders emphasizing the need for targeted prevention and treatment strategies. More specifically, youth with EXT disorders, characterized by impulsivity, disinhibited decision-making, and increased risk-taking, are at heightened risk for developing SUDs, yet sex differences in how these traits relate to SUD risk remain underexplored, highlighting the need for further research on the mechanisms linking EXT pathology and substance use in high-risk adolescents. Given the strong link between EXT pathology and SUD risk, it is crucial to examine how decision-making deficits, which are prevalent in both SUDs and EXT disorders, contribute to higher substance misuse risk in youth and how these deficits may differ by sex, as this could inform sex-specific prevention strategies. Risky decision-making engages a complex network of brain regions across the choice and outcome phases, with sex differences in neural activation patterns that suggest distinct mechanisms for reward processing in

males and females, highlighting the need for further investigation into how these differences may relate to substance use outcomes in substance-naïve adolescents.

This dissertation evaluates risky decision-making in youth with EXT disorders using the BART, as it models real-world drug choices by balancing reward and risk, with behavioral and neural activation measures linked to impulsivity, sensation seeking, and substance use behaviors. In the second chapter, the dissertation aims to explore sex-specific mechanisms underlying risky decision-making in 11–12-year-olds with and without EXT disorders, hypothesizing that EXT females will exhibit activation patterns closer to EXT males, with greater frontoparietal/frontotemporal activation before risky choices and less activation before negative outcomes than control females. The third chapter's preliminary study aims to address the gap in understanding sex differences in how EXT youth's deficits in risky decision-making contribute to future substance use. We hypothesize that deficits in risky decision-making will be more pronounced in males and will relate to their problematic substance use. Overall, this dissertation is poised to fill the gap in how sex differences in EXT youth's risky decision-making may relate to the sex differences observed in substance use disorder patterns and also may help guide sex-specific substance use prevention strategies aimed at addressing specific deficits in risky decision-making which puts these youth at high risk for problematic substance use.

Chapter Two: Sex Differences in Cingulo-Opercular Activation During Risky Decision-Making in Youth with Externalizing Disorders

14. Introduction

Deficits in adolescent risky decision-making have been linked to a variety of risky and dangerous behaviors later in life, such as substance abuse (78-80), motor vehicle accidents (190), and unsafe sexual practices which can lead to sexually transmitted infections and unplanned pregnancies (191). Youth with externalizing disorders, such as ADHD, oppositional defiant disorder, or conduct disorder, are characterized by impulsivity, aggression, hyperactivity, and rule-breaking (67, 68). These disorders represent an ideal population for examining adolescent risky decision-making and behaviors because deficits in risky decision-making are not only characteristic of these disorders, but are also often linked to their increased incidence of future risky behaviors compared to youth without externalizing pathology (47, 49, 66, 73-75, 81, 85, 87, 192). However, research on sex differences in risky decision-making among youth with externalizing disorders remains underexplored, limiting our understanding of how these differences may contribute to risk profiles and the development of targeted interventions for males and females at high-risk for unsafe behaviors. A well-studied mechanism of altered decision-making among youth and adults with externalizing psychopathology is an increased likelihood to make disadvantageous decisions and favor low-probability, high-reward choices (54, 55, 57-59, 61-64, 83, 86, 193, 194). The propensity to make risky, disadvantageous decisions is key to the risk phenotype, yet several researchers have found sex differences in this aspect of the risk profile with males consistently exhibiting a greater tendency towards risky decision-making compared to females (88,

90, 92). While this suggests that sex differences in risk-taking behavior may play a critical role in shaping overall risk, with males showing a stronger propensity for impulsive, disadvantageous choices, sex differences in the risk profile have been underexplored in youth with externalizing disorders. This leaves a critical gap in understanding how sex-specific patterns of decision-making may shape risk-taking behaviors, particularly among high-risk, externalizing youth, necessitating further investigation into the unique, sex-specific vulnerabilities of this population. Specifically, it remains unclear whether females with externalizing pathology exhibit the same deficits in risky decision-making as males with externalizing pathology, which have been associated with an increased risk of unsafe and dangerous behaviors.

Beyond behavioral measures, neuroimaging studies provide valuable insights into the cognitive and emotional mechanisms underlying risk. Insights from brain imaging studies are particularly important when studying risky decision-making behaviors as these are difficult to assess through laboratory and self-report measures. The neuroimaging studies which do evaluate sex in the context of risky decision-making have indeed found sex-specific mechanisms. These risky decision-making tasks typically involve choices between options with varying levels of risk, followed by feedback on the outcomes of those decisions. Regarding the decision phase, sex differences seem to arise in the frontostriatal and salience networks, with males showing greater activation in the frontostriatal network during both risky and safe choices, while females show greater activation in this network during safe choices only, and males activating left-sided salience network and females activating right-sided salience network before risky decisions (88, 90, 167). Regarding the outcome phase, females activate frontoparietal and

saliency networks more when processing negative outcomes, where males activate frontoparietal cognitive control networks when processing positive outcomes (168). Therefore, we hypothesize lower activation in fronto-striatal-thalamic regions during risky choices compared to safe choices for females. Males, however, may show stronger activation in frontoparietal and reward-related areas during risky decisions. For the outcome phase, we hypothesize females will show greater activation in frontoparietal and saliency regions during negative outcomes, while males may engage frontoparietal networks for positive outcomes, leading to less activation in these regions for males in negative-versus-positive outcome contrasts. Externalizing psychopathology may further influence these sex differences, with female externalizing showing different patterns of activation compared to controls, closer to male activation patterns (88).

In sum, the current study, incorporating neuroimaging and behavioral assessments, aims to explore sex-specific mechanisms that underlie risky decision-making in male and female adolescents in a sample of 11–12-year-olds with and without externalizing disorders (e.g., ADHD). We hypothesize that nuances of the interaction between sex and externalizing pathology will result in externalizing females having activation closer to externalizing males, which will be greater frontoparietal/frontotemporal activation before risky choices and less activation before negative outcomes than control females. These sex-specific findings could guide new interventions and prevention strategies specifically aimed at defaults in risky decision-making processes among the highest-risk youth.

15. Methods

15.1. Sample

223 English-speaking, right-handed, 11-12-year-old participants and their guardians completed psychiatric and behavioral assessments and an MRI session as part of an ongoing longitudinal study (138, 161, 163, 164, 167). For the externalizing (EXT) group, individuals met criteria for DSM-5-TR diagnoses of ADHD and a disruptive behavior disorder: oppositional defiant disorder, conduct disorder, or unspecified disruptive behavior disorder. The percentages of EXT pathology diagnoses and other comorbid DSM-5 diagnoses given for each group are presented in Table 1. Exclusion criteria at baseline were: (1) lifetime history of bipolar disorder, psychotic symptoms, autism spectrum disorders or SUDs, (2) DSM-5-defined current major depressive disorder, (3) history of neurological problems (e.g., epilepsy, traumatic brain injury, brain tumors), (4) estimated Full Scale IQ <80 (to ensure participants understood the self-report forms and tasks) (5) active or debilitating medical conditions, (6) maternal substance use disorder during pregnancy, (7) MRI-related contradictions, (8) reporting recreational drug use (other than caffeine), (9) left-handedness, (10) individuals with siblings already enrolled in the study. Patients taking psychostimulant medications were instructed to hold medication on study visit days and a urine drug screen was administered on study days to help confirm substance-naïve status. All procedures were conducted according to the Indiana University Institutional Review Board.

15.1.1. Psychiatric Disorders

Externalizing diagnoses were determined by a semi-structured clinical interview, the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (KSADS-PL). The KSADS-PL, modified from DSM-5, determines current and

lifetime psychiatric diagnoses (195) and was conducted with each participant and guardian(s) to assess psychiatric and SUD status at baseline.

15.1.2. Sex

Each child participant's sex was force choice reported as male or female by the adult guardian at baseline. Youth were asked at baseline "Which of the following best describes you?" with response options of "boy" or "girl." Parent-reported sex was used to determine group membership. To account for potential gender diversity not fully captured by these questions, we created a dichotomous variable reflecting discordant gender identity. This variable was defined by participants whose self-reported gender identity (boy or girl) did not align with their guardian-reported sex (male or female).

The four groups were defined by presence or absence of externalizing disorders and sex (male or female) as reported at baseline. Reasons for subject exclusions are identified in Figure 3. The final sample consisted of 168 subjects divided into four groups of externalizing males (n=81), externalizing females (n=39), control males (n=33), and control females (n=15).

15.2. Measures

15.2.1. Balloon analogue risk task (BART)

In the MRI scanner, participants completed an fMRI-compatible BART (107, 174) to explore brain activation during risky decision-making. The BART models real-world risky choices by balancing reward and negative outcome probabilities. BART performance correlates with impulsivity, adolescent risk-taking, and SUDs (170-173, 196), making it a valuable tool for examining sex influences on risky decision-making in externalizing youth. During the BART, participants decide whether to risk cash rewards

that increase with each balloon inflation or bank the amount and start inflating a new balloon (Figure 4). Participants are instructed to “inflate the balloon as much as you can without popping it” to earn money for each unexploded balloon. Participants are told that they will win more money (paid in real cash immediately after scanning) for larger balloons and they will attempt this task three times in the MRI scanner. The BART incorporates parametric increases in explosion probability over successive responses (174). The parametric modulation employed the following probabilities of balloon explosions at each pump: 0% for \$0.0; 2.1% for \$0.05; 4.2% for \$0.15; 6.3% for \$0.25; 14.6% for \$0.55; 23.9% for \$0.95; 31.3% for \$1.45; 43.8% for \$2.05; 56.3% for \$2.75; 68.8% for \$3.45; 79.2% for \$4.25; 89.6% for \$5.15. A jitter function is applied to the timing of the stimulus presentations between decision and outcome phases of each trial to differentiate decision-making and feedback-related processes (174). Participants were repeatedly presented a virtual balloon and had to press one of two buttons to either inflate the balloon (Choose Inflate), risking cash rewards that increased with the balloon's size, or to stop inflating and bank the accumulated money for that balloon (Choose Win). If they choose to inflate, the balloon either expands, increasing the reward amount for that balloon (Outcome Inflate), or it bursts, resulting in the loss of the accumulated money for that balloon (Outcome Explode). Except for the initial inflation, explosions could occur at any size, with the risk increasing as the balloon grows larger. When participants opt to win (Choose Win), the accumulated rewards are banked, and a new balloon appears. During the three 8-minute sessions, participants could complete as many balloons as possible, with a maximum of 12 inflations per balloon. Before performing the BART in the MRI scanner, participants practiced the task on a desktop computer. For measures of

BART performance, we included variables indicative of risk-taking or tempo within the task. Risk-taking variables included average adjusted pumps (the average number of inflations on unexploded balloons), average money bet (the mean amount of money at stake when participants risked an inflation), number of choose inflate choices, choose win choices, outcome explosions, and total balloons completed. The tempo-related variable was reaction time (average time to press the response button for all choices, inflate or win, in milliseconds). Performance behavioral variables were averaged over a participant's three runs.

15.2.2. MRI Data Acquisition

Participants completed brain scanning in <90-minute sessions on a research-dedicated 3.0-Tesla Siemens Prisma MRI scanner with a 32-channel head coil. A high-resolution 3D magnetization prepared rapid gradient echo (MPRAGE) scan consisting of 160 sagittal slices and $1.05 \times 1.05 \times 1.2 \text{ mm}^3$ voxels was completed. For BART runs, a T2*-weighted gradient echo-planar imaging (EPI) sequence was used (54 axial slices; voxel size $2.5 \times 2.5 \times 2.5 \text{ mm}^3$; TR/TE 1200/29 ms; flip angle 65° ; field-of-view $220 \times 220 \text{ mm}^2$; matrix 88×88), using a multiband sequence with a multiband factor of 3. In the same order for each participant, and as the BART was the overall study priority, three 8-minute BART sessions were administered consecutively as the first task following an anatomical and resting-state scan and proceeding a delay-discounting task and white matter-focused diffusion scan.

15.3. Covariates

15.3.1. IQ

IQ screening using the Wechsler Abbreviated Scale of Intelligence (WASI) (197) was used to ensure that all participants met a minimum threshold of general intelligence for understanding task instructions and as a possible covariate because prior work has found IQ to correlate with several aspects of risk calculation and decision-making (198-204). Due to COVID-19 restrictions and the necessity of conducting study visits online, only Verbal IQ scores from the WASI are reported, as virtual visits did not permit completion of Performance IQ tasks. Two (n=2) individuals were unable to complete the WASI and two study clinicians estimated their IQ was highly likely to be >80 based on the overall clinical interview.

15.3.2. Pubertal development

Pubertal development was reported via parental identification of Tanner scale pictures, which range from 1 (prepubertal) to 5 (complete pubertal development) (205). Three (n=3) participants had unknown pubertal stages. Tanner staging was used as a covariate to account for distinct levels of physical development between our groups, knowing our group has shown effects of pubertal staging on BART before (167).

Data missingness for IQ and pubertal development was handled with multiple imputations utilizing the MICE package in R (206). Mean imputation per group (i.e., control females, control males, externalizing females, externalizing males) was used to account for IQ missing values. Proportional odds logistic regression (POLR) model (accounting for age and sex) was used to impute pubertal development.

15.4. BART Behavior Analysis

We first assessed whether the behavioral variables met the assumptions required for an ANCOVA, specifically testing for the normality of residuals and homogeneity of

variance. Using diagnostic plots and statistical tests (e.g., Shapiro-Wilk test for normality and Levene's test for homogeneity of variance), several variables were identified that deviated from these assumptions, which could compromise the validity of parametric analysis (Appendix A.1). To address these violations, the Box-Cox transformation method was implemented in R (207) to identify an optimal transformation for each variable (e.g., square, square root, inverse square root, and logarithmic transformations). This approach systematically evaluates a range of power transformations (λ) to achieve a more normal distribution of residuals (207, 208), displayed for the transformed variables in Appendix A.2. Behavioral variables that showed significant deviations from normality or homoscedasticity were transformed accordingly, improving the fit to the assumptions of ANCOVA. Appendix A.3 includes histograms illustrating the variables' distributions before and after transformation, demonstrating the effectiveness of the Box-Cox transformations. Those variables which were not normally distributed or homoscedastic were Choose Inflate Count, which exhibited a negatively skewed distribution, and Choose Win Count, Balloons Completed, and Reaction Time, which all were positively skewed, before transformation. The applied Box-Cox transformations to better normalize those four variables were: squared, square root, inverse square root, and logarithmic, respectively. After applying the appropriate transformation, we analyzed the differences in behavioral performance across groups with ANCOVAs. Group membership was the primary independent variable of interest with two covariates: IQ and Tanner staging. Post-hoc analyses used estimated marginal means pairwise comparisons to explore specific group differences. These were conducted using the emmeans() package in R (209) to compute adjusted means for each group, accounting for the effects of the

covariates. To control the inflated risk of type I error associated with multiple comparisons, we applied Bonferroni correction during the pairwise tests.

15.5. MRI Data Preprocessing

Initially, EPI scans underwent spin-echo unwarping to correct distortions using fMRIB Software Library (FSL)'s "topup" tool. Anatomical scans were registered to Montreal Neurological Institute-152 (MNI152) standard MRI template brain volume space using nonlinear transformation to account for regional differences between individual subject brains and the MNI template. EPI data were aligned with each participant's anatomical scan using `afni_proc.py` (210, 211), a comprehensive processing pipeline in AFNI (Analysis of Functional NeuroImages). Also, using `afni_proc.py`, functional images were motion-corrected and spatially smoothed with a 6mm Gaussian kernel to account for anatomical variability and improve the signal to noise ratio, and time-series normalization to a T1-weighted image was conducted, followed by an adjustment to a 100-scale per voxel. Lastly, unsupervised independent components analysis (ICA)-based denoising with ICA-AROMA (212, 213) from FSL's MELODIC tool was used for robust data cleaning by identifying and removing noise-related components.

In the first step of imaging quality assessment, subjects with motion artifacts during the anatomical scan, which led to failure in the volume registration step, were excluded from the analysis ($n = 11$ subjects). Then, further visual inspection of brain activity was conducted to ensure the presence of expected activation patterns corresponding to the task. This step involved examining the spatial distribution of activation maps to confirm typical task-related regions were engaged (e.g., visual cortex).

Where expected activation in areas like the visual cortex were missing, those subjects were excluded (n = 5), and where there was widespread negative activation, which also could indicate global signal regression artifacts, those subjects were excluded (n = 7). Finally, if activation distribution within these maps were excessively dispersed, non-localized, or lacked a discernible pattern, this was attributed to motion artifacts and subjects exhibiting confirmed high motion were excluded (n = 13). Therefore, a total of 36 participants were excluded based on unsatisfactory functional imaging. Of note, these excluded participants did not differ significantly from the final sample (n = 168) in terms of age, race, ethnicity, parental education, Tanner stage, verbal IQ, or in proportions of ADHD subtypes, disruptive behavior disorders, mood, or anxiety disorders.

15.6. Neuroimaging Data Analysis: Subject Level Analysis

After preprocessing and noise reduction, runs were concatenated, and a general linear regression model (GLM) with random effects was used to estimate event-related responses in AFNI. *Choice events*, aligned to the repetition time (TR) that included the button press response, were modeled as Choose Inflate (choosing to continue inflating the balloon) or Choose Win (choosing to discontinue inflating and bank money) regressors. *Outcome events* were modeled as the TR that included balloon explosion (Outcome Explode), successful balloon inflation (Outcome Inflate), or the outcome of discontinuing inflations (Outcome Win). Balloon explosion probabilities were included as parametric modulators for each event-type regressor (e.g., Choose Inflate * P(explode), Outcome Inflate * P(explode)), except for Outcome Win, which has no uncertainty). Parametric modulators were incorporated to examine neural activation patterns that specifically track the escalating risk of both reward and loss as balloon size increases, providing insight

into how brain regions dynamically respond to varying levels of decision-making uncertainty. To compare activation differences between conditions, individual subject activation maps were subjected to a voxel-wise subtraction using the 3dcalc tool in AFNI to compute the difference in activation between conditions, adjusting for individual differences in baseline activation. There were four contrast subtraction maps: Choose Inflate – Choose Win (modulated and unmodulated) and Outcome Explode – Outcome Inflate (modulated and unmodulated).

15.7. Neuroimaging Data Analysis: Group Level Analyses

After unpacking the contrast subtraction maps for subject-level average activation to check for normality of imaging data to meet the requirements of ANCOVA analyses, we found that our imaging data activation violated the assumptions of normally distributed residuals across each subpopulation and homogeneity of variance. Therefore, we turned to a nonparametric analysis for our group analyses. For analyzing BART functional imaging, we conducted a whole-brain analysis using AFNI's 3dKruskalWallis to identify brain regions that differed across groups. The statistical models tested whether there were significant differences between the rank of each subjects' activation by sex/externalizing group across the brain and did not allow for inclusion of covariates. Multiple comparisons of this whole-brain voxel-wise analysis were addressed using cluster-wise thresholds (family-wise error rate of $p < 0.05$). Individual voxels were significant at $p < 0.001$, and a Monte Carlo simulation (AFNI's 3dclustSim) determined the cluster size needed to correct for group-level significance, $k=31$ ($p < 0.05$). Significant clusters' coordinate locations were mapped onto region names using standard Montreal Neurological Institute (MNI) brain atlases. Post-hoc analyses on extracted

parameter estimates were conducted in R to further investigate the differences in brain activation identified by the Kruskal-Wallis test across the four sex/externalizing groups. The Kruskal-Wallis test was utilized over ANOVA with our imaging data due to its ability to account for unequal variances and sample sizes across groups (214), providing a more robust analysis given the unbalanced nature of our data. As we could not include covariates in the Kruskal-Wallis whole brain analysis in AFNI, we controlled for covariates in the post-hoc analyses to determine whether the observed group differences in brain activation remained significant when adjusting for these factors. We performed ranked-based estimation regression with the `rfit.default()` function in R (215). The reference group variable was relevelled (first as female controls, second as male controls, and third as externalizing females), to 1) perform pairwise comparisons across all six group combinations; and 2) control for the pertained covariates (verbal IQ and Tanner stage due to reasoning described in section 2.3 above).

15.8. Gender Identity Sensitivity Analysis

To investigate whether gender identity might interact with the observed sex differences in brain activation patterns, we conducted a sensitivity analysis. In this analysis, we excluded imaging data from participants whose self-reported gender identity (boy or girl) did not match the guardian-reported sex (male or female; defined in our dichotomous variable as having a discordant gender identity). The whole-brain group level analyses described above were run without these participants to determine whether gender identity alignment with assigned sex influences the observed differences in brain activation patterns. The same parameters specified in the primary analysis were applied to this sensitivity analysis.

16. Results

16.1. Demographics and Clinical Characteristics

This cross-sectional analysis included 168 substance-naïve 11-12-year-olds who met criteria for usable imaging data, grouped as externalizing males (MEXT=81) and females (FEXT=39) and healthy control males (MC=33) and females (FC=15). Groups were similar on demographic, clinical and socioeconomic measures (Table 2) other than verbal IQ [$F(3, 164) = 3.05, p = 0.03$] and Tanner pubertal stage ($\chi^2 = 50.34, p < .01$). Controls had higher IQ than externalizers, though all groups had above average IQ, and, as anticipated, males had significantly lower Tanner stages than the females. Due to significant differences in verbal IQ and Tanner pubertal stage, and reasoning described above, these variables were included as covariates in the behavioral analyses and imaging post-hoc analyses.

16.2. BART Performance

In our ANCOVA analyses, there were sex/externalizing group differences on squared Choose Inflate Count and log transformed Reaction Time (Table 2). Male controls ($\beta = 1,737.70, p < 0.01$) and externalizing males ($\beta = 1,649.50, p < 0.01$) had greater average squared Choose Inflate Counts than control females. Male controls ($\beta = -0.41, p < 0.01$) and externalizing males ($\beta = -0.43, p < 0.01$) had significantly faster reaction times (log transformed) than control females. Full results are presented in Table 3.

16.3. BART Imaging Results

Two clusters were identified with significantly different activity between groups using AFNI's 3dKruskalWallis analyses. The two clusters demonstrated significant

differences between the four sex/externalizing groups for Choose Inflate – Choose Win modulated activity and were located in the left inferior temporal gyrus (Figure 5) and the right dorsal medial prefrontal cortex (dmPFC)/dorsal anterior cingulate cortex (dACC) (Figure 6). Table 5 contains information on cluster size and coordinates.

Regarding the unadjusted post-hoc analyses, in the left inferior temporal gyrus cluster, all groups had significantly greater modulated activation compared to control females; however, due to the small sample size of the reference group, this result should be interpreted with caution. In the right dmPFC/dACC, externalizing males had greater activation than the other groups. See Table 4 for reporting of all unadjusted and adjusted post-hoc results. Adjusting for covariates (“Adjusted” in Table 4) did not alter the direction nor significance.

16.4. BART Imaging Results- Gender Sensitivity Analysis

Eleven subjects were excluded for the gender sensitivity analysis due to the youth’s self-reported gender (boy or girl) not matching the guardian-reported sex (male or female). A whole brain analysis without the eleven subjects found that both clusters in the left inferior temporal gyrus and right dmPFC/dACC were again significant at $p < 0.001$ and exceeded the voxel size threshold of 31 voxels, as was observed when those participants were included.

17. Discussion

The goal of the current study was to examine sex differences in behavior and neural activation during risky decision-making among adolescents with and without externalizing disorders. In terms of behavioral performance on the BART, significant sex and externalizing group differences were found in both Choose Inflate Count and log-

Reaction Time (both transformed). Specifically, male controls and externalizing males exhibited greater squared Choose Inflate Counts compared to control females, indicating more frequent risky choices for males. Additionally, these same groups had faster reaction times (log-transformed) than control females. Interestingly, although these behavioral findings align with established sex differences in risky decision-making—where males typically engage in riskier and more impulsive behavior (54, 55, 57-59, 61-64, 83, 86, 88, 90, 92, 193, 194)—the results suggest that externalizing females did *not* display the same risky/impulsive patterns as their male counterparts. Instead, male controls exhibited more risky and impulsive behavior, suggesting that these differences may reflect broader sex-based tendencies in risk-taking behavior rather than being indicative of externalizing pathology or specific risk for unsafe behaviors, at least in the preadolescent period. This implies that sex differences in decision-making behavioral metrics on this task may not directly correlate with risky behaviors, particularly for externalizing females, but further study is needed to confirm.

Regarding brain imaging findings, the left inferior temporal gyrus and the dmPFC/dACC, nodes within ventral visual processing stream and cingulo-opercular circuits, respectively, were identified as differing between groups in our whole-brain analysis. The group differences were observed when contrasting a risky choice (Choose Inflate) with a safe choice (Choose Win), but only as those decisions became riskier (modulated) and not during any of the outcome phase contrasts. Findings in the left inferior temporal gyrus cluster revealed that all groups had significantly greater modulated activation compared to control females when making a risky choice (Choose Inflate) over a safe choice (Choose Win), as those choices became riskier (modulated).

The left inferior temporal gyrus is frequently identified in risky decision-making studies likely because of its role in the ventral stream of visual processing (216)—playing a critical role in higher-order visual processing (217, 218), visual working memory (218-220), and shows sustained activation during maintained visual representations of preferred objects (a particularly salient function in the current task where risk is represented visually as increasing balloon size) (221-225). Therefore, our findings may be a preliminary indication that deficits in visual memory during risky decision-making could impair an individual's ability to accurately evaluate risk by limiting their capacity to recall and integrate visual information about previous outcomes, leading to misjudgments in assessing potential rewards or consequences as the situation becomes riskier. However, because the observed group difference involves all groups compared to the smallest group, female controls, which has only fifteen participants and may be heavily influenced by outliers in this group, we view this finding as preliminary, warranting further investigation.

The second cluster that differed between groups was located in the dmPFC and dACC. In the dmPFC/dACC, male externalizers displayed greater activation in the Choose Inflate – Choose Win contrast as the probability of explosion increased. These regions are part of the cingulo-opercular (or salience) network, which supports cognitive control, task-set maintenance, sustained attention, and salience detection—functions often implicated in decision-making, externalizing behaviors, and addiction (97, 98). The dmPFC and dACC are essential for cognitive control and behavioral flexibility, particularly in maintaining internal goals, conflict monitoring, and adjusting cognitive processes across sensory, memory, and motor systems (105, 226-228). The dmPFC also

plays a significant role in set-shifting and response inhibition, aiding in modifying learned motor behaviors and inhibiting impulses (229-233). Regarding sex differences in normal function of the dmPFC, multiple studies have found that the PFC develops around two years earlier and matures more extensively in females than males, while males have larger PFC volume throughout development (234-241).

Given this cingulo-opercular network's function in cognitive control, the dmPFC/dACC arises as a crucial area for risky decision-making. Studies consistently demonstrate that dmPFC activity is associated with more conservative, risk-averse behavior (106, 242-246), and similarly, the dACC has been implicated in monitoring ongoing decisions, with activation increasing as individuals engage in risky or ambiguous choices (95, 247). With these prior findings, if choosing to win is the risk-averse choice, and risk-aversion increases activation in this region normally, then risky choice activation versus risk-averse choice activation would be smaller, which it was in every group besides our highest risk male externalizers. Heightened dmPFC/dACC activation during *risky* choices (inflating), whereas typical patterns show greater activation during *safer* choices (winning) may reflect dysregulation in cognitive control, conflict monitoring, and impulse inhibition during decision-making among the high-risk males. Prior findings of sex differences in dmPFC/dACC activation during risky decision-making, align with prior work and our findings: Crowley et al. found that males exhibited heightened activity in the left medial and dorsolateral PFC regions prior to making cautious choices while females demonstrated greater engagement in the corresponding right-sided areas (88). Therefore, aberrant activation in the cingulo-opercular network, in cognitive control,

when evaluating a risky vs safe decision is likely a large part of the risk profile for unsafe behaviors carried by our male externalizers.

Our study has several limitations. First, the small female control group limits the generalizability of the findings, particularly the finding in the inferior temporal gyrus, and the unequal group sizes may affect the statistical power and overall interpretation of the BART behavioral results as they were analyzed with an ANCOVA. Next, while we aimed for our gender sensitivity analysis to account for possible gender nonconformity in our sample, we were ultimately underpowered to be able to detect differences between gender conforming and gender non-conforming youth. However, the results of our gender sensitivity analysis suggest that using sex assigned at birth was a reasonable approach given the small sample size of gender non-conforming youth. In future studies, we would aim to collect more comprehensive data on both gender and sex to better capture these variables' effects. Second, we were unable to include covariates in our whole-brain analysis, limiting our ability to determine whether controlling for covariates would have altered the observed group differences in brain activation. While we adjusted for covariates after extracting imaging activation, and the results remained consistent, this represents only a partial check of the covariates' potential influence. Finally, as this study employed a cross-sectional design, its findings may have limited generalizability to other populations or contexts.

In summary, this work provides new insights into the neural mechanisms underlying risky decision-making which are affected by sex and externalizing pathology. We found that decision-making during the choice phase relies on cingulo-opercular circuits, with specific sex and externalizing differences emerging in modulated brain

activity as decisions become riskier. This suggests that risk-processing mechanisms in the cingulo-opercular circuits, specifically intact cognitive control, conflict monitoring, and impulse inhibition during decision-making, during the *decision* phase, may be critical in understanding sex differences in risky behaviors, warranting further investigation. Based on the findings of dysregulated cognitive control and heightened dmPFC/dACC activation during risky decision-making in male externalizers, a targeted behavioral therapy focusing on impulse control, conflict monitoring, and risk evaluation may be beneficial, particularly in males. This therapy could emphasize strategies to enhance self-regulation and improve choice-phase decision-making under risky conditions, helping these individuals better distinguish between risky and safe choices, which is critical in managing their heightened risk for unsafe behaviors. Future directions of this work are to continue evaluating whether females with externalizing disorders have distinct risk profiles for unsafe behaviors and further, to establish whether sex differences in externalizing decision-making relates to any differences in real-world risky behaviors. In summary, these findings emphasize that specific cingulo-opercular network brain regions, the dmPFC and dACC, during the choice phase of risky decision-making may contribute to heightened risk-taking behaviors observed in males with externalizing disorders. This work highlights an area to target with sex-specific interventions during the pre-adolescent/adolescent period.

Table 1. Demographics

	FC (n=15)	MC (n=33)	FEXT (n=39)	MEXT (n=81)	p-values
Age / M (SD)	11.93 (0.62)	12.01 (0.56)	12.02 (0.54)	11.83 (0.54)	0.24
<u>Race / N (%)</u>					0.90
White	9 (60.00)	22 (66.67)	22 (56.41)	52 (64.20)	
Black	5 (33.33)	8 (24.24)	13 (33.33)	19 (23.46)	
Multiracial	1 (6.67)	3 (9.09)	4 (10.26)	10 (12.35)	
Hispanic Ethnicity / N (%)	4 (26.67)	3 (9.09)	3 (7.69)	7 (8.64)	0.17
<u>Parental Education Max / N (%)</u>					0.36
High School	1 (6.67)	0 (0.00)	5 (12.50)	9 (10.71)	
Some college or college	7 (46.67)	18 (54.55)	23 (60.00)	42 (50.00)	
Some graduate or graduate school	7 (46.67)	15 (45.45)	11 (27.50)	27 (33.33)	
Unknown	0 (0.00)	0 (0.00)	0 (0.00)	3 (5.95)	
<u>Tanner Stage / N (%)</u>					<0.01
1	2 (13.33)	14 (42.42)	8 (20.51)	33 (40.74)	
2	4 (26.67)	10 (30.30)	5 (12.82)	34 (41.98)	
3	5 (33.33)	4 (12.12)	6 (15.38)	10 (12.35)	
4	4 (26.67)	3 (9.09)	12 (30.77)	3 (3.70)	
5	0 (0.00)	2 (6.06)	8 (20.51)	1 (1.23)	
Verbal IQ / M (SD)	114.33 (16.07)	114.79 (11.57)	106.82 (13.52)	107.94 (14.35)	0.03
<u>ADHD Subtype / N (%)</u>					<0.01*
Hyperactive/Impulsive			4 (10.26)	8 (9.88)	
Inattentive			28 (71.79)	27 (33.33)	
Combined			7 (17.95)	46 (56.79)	
Oppositional Defiant Disorder / N (%)			29 (74.36)	63 (77.78)	0.85*
Conduct Disorder / N (%)			3 (7.69)	6 (7.41)	1.00*
Unspecified DBD / N (%)			9 (23.08)	14 (17.28)	0.61*
Any Mood Disorder / N (%)	0.00 (0.00)	0.00 (0.00)	5 (12.82)	5 (6.17)	0.09
Any Anxiety Disorder / N (%)	0.00 (0.00)	0.00 (0.00)	11 (28.21)	12 (14.81)	<0.01

FC = female controls, MC = male controls, FEXT= externalizing females, and MEXT = externalizing males; DBD = disruptive behavior disorder; Any Mood Disorders included dysthymia and disruptive mood dysregulation disorder; Any Anxiety Disorder included separation anxiety, social anxiety, selective mutism, and generalized anxiety disorder; *p-values for ADHD subtypes and disruptive behavior disorders are solely comparing externalizing males and females

Table 2. BART Behavior Performance Variables Mean (SD) by Group

Behavior Outcome	FC	MC	FEXT	MEXT	p-value
Average Adjusted Pumps	4.46 (0.65)	4.83 (0.90)	4.73 (0.88)	4.87 (0.81)	0.32
Average Money Bet	0.23 (0.07)	0.26 (0.10)	0.27 (0.10)	0.27 (0.09)	0.41
Choose Inflate Count ¹	6772.30 (2017.71)	8587.70 (1601.27)	7835.67 (1496.84)	8377.30 (1558.40)	<0.01
Choose Win Count ²	3.53 (0.45)	3.53 (0.69)	3.54 (0.55)	3.51 (0.52)	0.99
Outcome Explode Count	5.42 (2.35)	6.58 (2.37)	6.09 (2.05)	6.35 (2.08)	0.34
Balloons Completed ³	0.24 (0.01)	0.23 (0.02)	0.23 (0.02)	0.23 (0.01)	0.41
Reaction Time (ms) ⁴	7.17 (0.47)	6.77 (0.40)	6.91 (0.35)	6.79 (0.40)	<0.01

Table 3. BART Behavioral Variables from all Group Pairwise Comparisons

Results are the pairwise comparisons from the ANCOVA of behavior variables between the sex and externalizing groups, adjusted for verbal IQ and Tanner stage. The beta estimates (β) represent the magnitude and direction of the differences in the behavioral outcome between groups and “Group X vs Group Y” should be read as the first group, Group X, versus the second group, Group Y, so the first cell is read FC was associated with 0.33 *less* average adjusted pumps than MC.

Behavioral Outcome	FC vs MC		FC vs FEXT		FC vs MEXT		MC vs FEXT		MC vs MEXT		FEXT vs MEXT	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
Average Adjusted Pumps	-0.33	1.00	-0.33	1.00	-0.39	0.70	0.00	1.00	-0.06	1.00	-0.06	1.00
Average Money Bet	-0.3	1.00	-0.05	0.64	-0.05	0.49	-0.01	1.00	-0.01	1.00	0.00	1.00
Choose Inflate Count ¹	-1737.7	<0.01	-967.6	0.35	-1649.5	<0.01	770.1	0.36	88.2	1.00	-681.9	0.35
Choose Win Count ²	-0.01	1.00	0.06	1.00	-0.01	1.00	0.08	1.00	0.00	1.00	-0.07	1.00
Outcome Explode Count	-1.11	0.68	-0.82	1.00	-0.90	0.97	0.28	1.00	0.20	1.00	-0.08	1.00
Balloons Completed ³	0.01	0.67	0.00	1.00	0.01	1.00	-0.01	0.92	0.00	1.00	0.00	1.00
Reaction Time ⁴	0.41	<0.01	0.22	0.46	0.43	<0.01	-0.19	0.36	0.02	1.00	0.21	0.09

¹Squared (e.g., Choose Inflate Count)²; ²Square Root (e.g., sqrt(Choose Win Count)); ³1/Square Root (e.g., 1/sqrt(Balloons Completed)); ⁴Log (e.g., log(Reaction Time)); FC = female controls, MC = male controls, FEXT= externalizing females, and MEXT = externalizing males

Table 4. Unadjusted and Adjusted BART Activation for Choose Inflate-Choose Win modulated clusters.

Results are the post-hoc pairwise comparisons of cluster activation between the groups. The table includes the beta estimates and p -values for each post-hoc comparison of robust regression with the `rfit.default()` function in R. The beta estimates (β) represent the magnitude and direction of the differences in activation between groups and “Group X vs Group Y” should be read as the first group as Group X is the comparison group, so the first cell is read MC was associated with 0.19 greater activation units than FC in the left inferior temporal gyrus. Adjusted results include covariates verbal IQ and Tanner stage in the robust regression. FC = female controls, MC = male controls, FEXT= externalizing females, and MEXT = externalizing males.

Cluster Location	FC vs MC		FC vs FEXT		FC vs MEXT		MC vs FEXT		MC vs MEXT		FEXT vs MEXT	
	β	p	β	p	β	p	β	p	β	p	β	p
Unadjusted												
Left Inferior Temporal Gyrus	0.19	<0.01	0.16	<0.01	0.16	<0.01	-0.02	0.31	-0.03	0.20	0.00	0.90
dmPFC/dACC	-0.02	0.50	-0.02	0.40	0.04	0.04	0.00	0.85	0.06	<0.01	0.06	<0.01
Adjusted												
Left Inferior Temporal Gyrus	0.19	<0.01	0.15	<0.01	0.16	<0.01	-0.04	0.10	-0.03	0.20	0.01	0.52
dmPFC/dACC	0.00	0.90	-0.02	0.52	0.06	<0.01	-0.01	0.52	0.06	<0.01	0.08	<0.01

Abbreviations: dmPFC = dorsomedial prefrontal cortex, dACC= dorsal anterior cingulate cortex

Table 5. Regions with significant group differences during the BART in the modulated Choose Inflate vs Choose Win contrast.

No clusters were significant in the outcome contrasts, nor unmodulated contrasts. Cluster size is defined by the number of voxels. Coordinates and Kruskal-Wallis statistics (K^*) are provided for the peak voxel in each cluster.

	BA	Peak K^* Value	Cluster Size	Talairach Coordinates		
				X	Y	Z
Left Inferior Temporal Gyrus	37	21.25	41	-59	-56	-10
Right dmPFC/dACC	9/32	26.77	34	2	42	14

Abbreviations: dmPFC = dorsomedial prefrontal cortex, dACC= dorsal anterior cingulate cortex, BA = Brodman Area

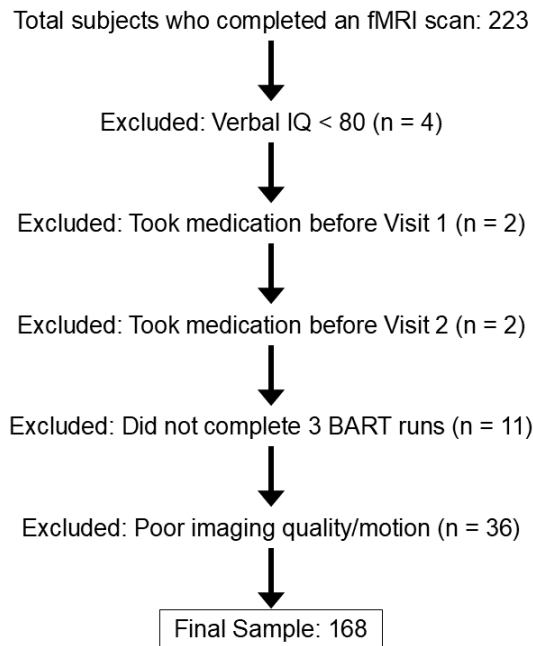


Figure 3. Flowchart of participant exclusion criteria.

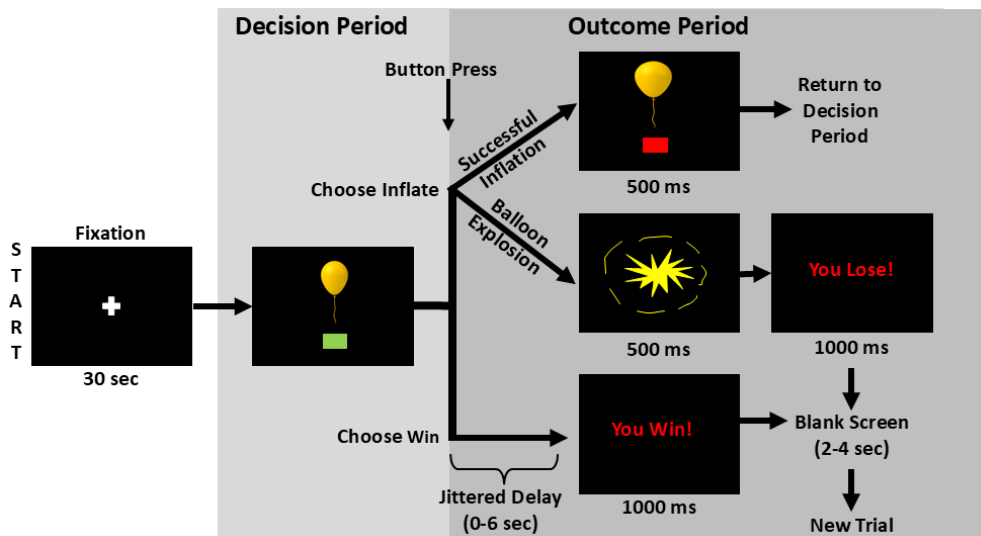


Figure 4. BART schematic.

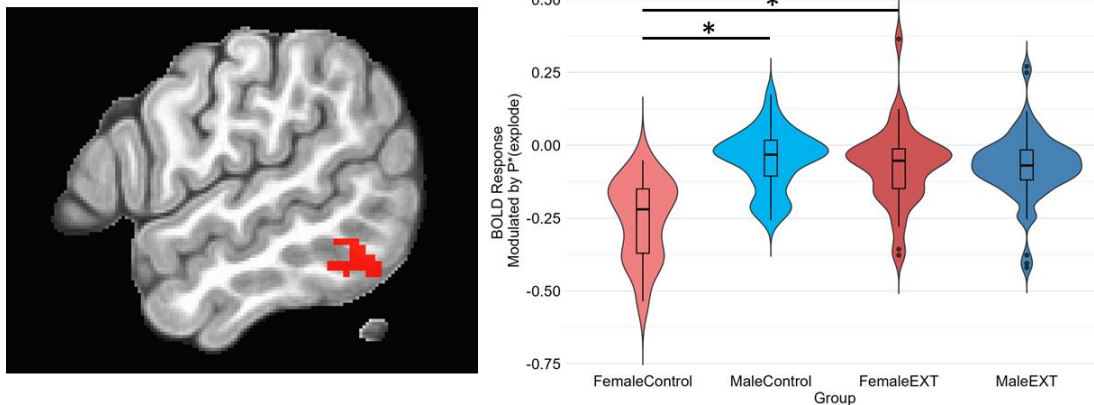


Figure 5. Left inferior temporal gyrus cluster.

Group differences on the parametrically modulated choice contrast in the left inferior temporal gyrus (Table 5). Group differences were driven by greater activation intensities as explosion probability increased in the male controls, male externalizing, and female externalizing groups compared to female controls. The violin plot displays the density of activation intensities during the modulated Choose Inflate—modulated Choose Win contrast (y-axis) for each group. *Indicates significant at $p < 0.05$.

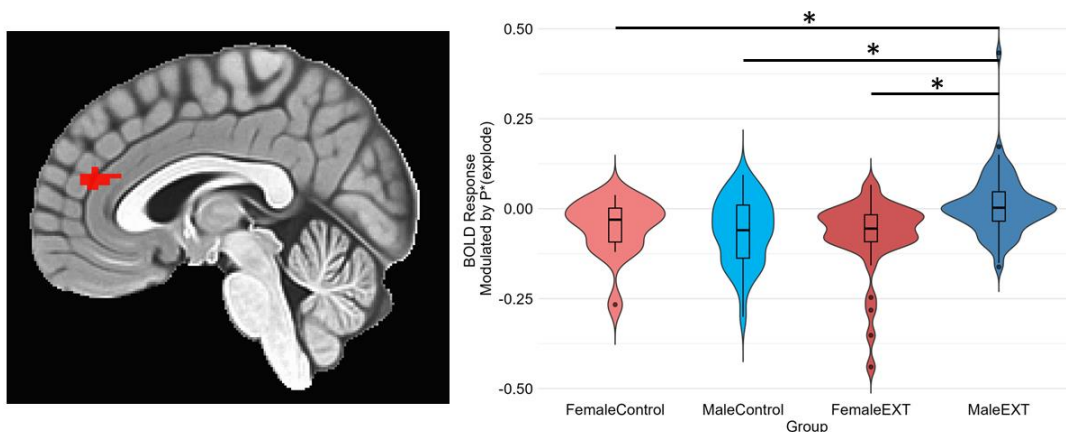


Figure 6. Right dorsomedial prefrontal/dorsal anterior cingulate cortex cluster.

Group differences on the parametrically modulated choice contrast in the right dorsomedial prefrontal/dorsal anterior cingulate cortex (dmPFC/dACC; Table 5). Group differences were driven by greater activation intensities as explosion probability increased in male externalizers. The violin plot displays the density of activation during the modulated Choose Inflate—modulated Choose Win contrast (y-axis) for each group. *Indicates significant at $p < 0.05$.

Chapter Three: Sex Differences in Reward Network Activation are Linked to Problematic
Substance Use Among High-Risk Adolescents

18. Introduction

Adolescents with externalizing disorders (EXT)—including attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, and conduct disorder—are an important group in which to investigate the development of substance use disorders (SUDs). Due to EXT disorders' characteristic impulsivity, hyperactivity, aggression, and rule-breaking, risky/disinhibited decision-making is a common feature of these disorders, which may increase risk for SUD (78-82, 87). Several longitudinal studies have shown increased SUD and substance problems for youth with EXT traits/symptoms, but these studies are limited to male samples or have not explored sex differences in how these psychopathologies relate to differences in SUD outcomes or risk (47, 49, 71, 73, 192), preventing us from truly characterizing risk profiles and interventions for EXT females.

Due to their propensity toward disadvantageous decisions and lower-probability, high-reward choices (57, 63, 64, 86), EXT adolescents' brain activity during risky decision-making is a promising aspect to evaluate in relation to their SUD risk profile. Indeed, neuroimaging studies have found sex differences in EXT youth's risky decision-making brain activation—with EXT females showing more activation before risky choices in the middle frontal pole than EXT males, a region of the frontoparietal network, involved in executive function (88, 167). Given that some studies have demonstrated sex differences in EXT youth's brain activation during risky decision-making, and considering how deficits in risky decision-making could contribute to their increased risk

of SUD, it is imperative to investigate how sex differences in EXT brain activation during risky decision-making may relate to sex differences in subsequent substance use.

To address that gap, we examined brain activity during risky decision-making in EXT youth in regions where prior research has shown differential activation in individuals with ADHD (176, 177) or a family history of SUD (178, 179), as both are associated with heightened risk for SUD, as well as regions whose activation has been linked to future substance use. Further, in the *a priori* regions, sex differences in EXT youth's brain activation have yet to be explored in the context of SUD risk. The brain regions of interest in this analysis include the nucleus accumbens (NAc) and the subgenual anterior cingulate cortex (sgACC).

The NAc has been extensively implicated in adolescent risk-taking and is a critical brain region for reward processing: spontaneous NAc activity predicts activity in other reward circuit nodes (248), and risky decision-making is associated with increased NAc activation in both the outcome/reward-receiving phase (249) and during the decision phase where heightened sensitivity to reward correlates with stronger NAc responses (109). In both subjects with ADHD and those with family history of SUD, hypoconnectivity in the frontostriatal network, between the NAc and prefrontal cortex, has been found, representing the brain basis for dysregulated prefrontal control over subcortical reward-related regions (182, 250-252); and those with family history of SUD show blunted/lower NAc activation during risky decision-making, particularly during reward anticipation (180, 183). Moreover, further connecting these at-risk populations, many studies examining NAc activity in those with SUD family history have shown that NAc activation correlates with EXT behaviors (180-183). NAc activation has been shown

to predict future substance use with lower fronto-NAc connectivity relating to earlier drinking behavior (184) and increased NAc activation during reward anticipation predicting more and earlier substance use (185, 186). Although these findings may initially appear to contradict the previously discussed comparisons between at-risk groups and controls, they align when considering that increased EXT behavior is linked to heightened NAc activation. One study reported sex differences where NAc volume was indirectly linked to future drinking through sensation seeking in males, but not females, with a positive association between volume and sensation seeking in males (253). In our sample, we therefore hypothesize that for EXT boys compared to girls, greater NAc activation when making risky choices (anticipating reward) will be associated with a higher hazard of problematic substance use.

The ACC has been shown to have functions related to loss avoidance—assessing how likely an error is and how problematic the consequences could be if the event occurs, guiding decisions to avoid risky situations, highlighting this areas' function in conflict monitoring/cognitive control (103-106). The ventral area of the ACC, encompassing the rostral ACC, sgACC, and pregenual ACC, is more specifically involved in loss avoidance in decision-making through its role in emotional and motivational processes of reward evaluation due to its links with the OFC, amygdala, NAc, and the limbic system (114, 115). While the sgACC is best-known for its involvement in negative affect and depression (118, 254-257), it is precisely this role in processing aversive stimuli and negative emotions that also links it to risk-reward processing: activity in the sgACC has been linked to uncertainty and under confidence in the decision-making process (116-120). In primate studies, over-activation of sgACC has been found to impair anticipatory

arousal and reward-seeking behavior (258), and lesions in the sgACC impair the ability to sustain autonomic arousal in response to anticipated rewards (259). Further, increased sgACC activation is frequently seen during cue exposure and is associated with increased craving for substances (260, 261); and relatedly, when participants are able to effectively control their cravings, there is greater activity in areas of the brain linked to cognitive control (dmPFC/dlPFC/vlPFC) paired with decreased activity in the sgACC—highlighting its craving-associated function (262). A similar relationship was found in resting-state synchrony analyses which revealed that the connectivity between the inhibitory control network (dlPFC) and the sgACC and NAc increased as individuals progressed from short-term to long-term abstinence—indicating that in alcohol recovery, decision-making networks may helpfully become less synchronous with regions linked to appetitive drive and more synchronous with inhibitory control areas (263, 264). Further, our group has found that youth at high risk for SUD related to diagnosed EXT disorders and family history of SUD showed increased sgACC area activation during reward loss (negative outcome) compared to healthy control youth (138). Lastly, patients with alcohol use disorder compared to healthy controls showed greater activation in the sgACC during anticipation of monetary reward (265). In conclusion, the sgACC appears to play a critical role in the interaction between risky decision-making and substance use; and for our sample, where we expect EXT boys will display greater risk and substance-use aligned behavior, we hypothesize that for EXT boys, greater activation in the sgACC during reward anticipation and reward loss will be associated with increased problematic substance use.

Prior findings of sex differences in risky decision-making brain activity among EXT youth has yet to be evaluated in its relation to sex differences in substance use outcomes, despite this possibly helping explain sex differences in substance use patterns. We will investigate these associations via the brain activation in two regions of interest: the NAc and sgACC—crucial nodes in the reward-processing network (187-189). The overarching hypothesis for this study is that for EXT boys compared to EXT girls, greater activation in reward network areas when making risky choices, anticipating rewards, and reacting to loss will be associated with higher hazard of problematic substance use. In sum, within the context of EXT pathology-oriented SUD risk models, sex differences are under-investigated and how sex differences in risky decision-making relate to future risky substance use has yet to be explored. With this study, we are poised to address this gap in a sample of 11–12-year-olds at-risk for SUD by virtue of their EXT pathology via neuropsychological underpinnings of risky decision-making. This work may reveal novel mechanistic information essential to informing appropriate, sex-specific substance use prevention strategies.

19. Methods

19.1. Study Design

The data for this study were collected as part of an ongoing longitudinal study in which youth were recruited from urban, suburban, and rural areas in Indiana in order to investigate the brain and behavioral basis of the development of risky behaviors (138, 161, 163, 164, 167). For this manuscript, we are focusing on youth with EXT pathology to address a gap in the literature as most research has centered on healthy youth (184) or those with a family history of SUD (185, 186, 266), rather than exploring how neural

processing deficits in risky decision-making contribute to risk of developing problematic substance use in EXT youth, specifically. Each eligible participant completed an MRI session as well as behavioral and psychiatric assessments at a baseline assessment at age 11-12 years. The MRI session, which only occurred at the baseline visit, included anatomical and functional MRI (fMRI) scans to assess functional connectivity measures and brain responses during risky decision-making tasks. Following their baseline imaging, participants were followed up into later adolescence with behavioral questionnaires every six months assessing substance use outcomes as discussed below in the Measures section. Besides substance use measures and unless otherwise noted, measures are taken from baseline questionnaires.

19.2. Sample

A total of 223 right-handed, English-speaking drug-naive 11-12-year-old participants and their guardians completed behavioral and psychiatric assessments. Each child's biological sex was reported as male or female by the adult guardian at baseline. Exclusion criteria at baseline were: (1) lifetime history of any substance use or SUDs, psychotic symptoms, bipolar disorder, or autism spectrum disorders, (2) current DSM-5-defined major depressive disorder, (3) neurological disorder history (e.g., brain tumors, epilepsy, traumatic brain injury), (4) Full Scale IQ <80 (to ensure understanding of the tasks and self-report forms) (5) active debilitating medical conditions, (6) maternal SUD during pregnancy, (7) MRI-related contradictions, (8) left-handedness, (9) siblings already enrolled in the study. The consort diagram explaining reasons for subject exclusions and numbers eliminated for each reason are displayed in Figure 7. All

procedures were conducted with approval from the Indiana University Institutional Review Board.

Of those who completed imaging, 167 were classified as high-risk for SUD due to EXT pathology and were considered for this study (see Figure 7). EXT youth met criteria for DSM-5 defined diagnoses of ADHD and a DSM-5-defined disruptive behavior disorder: oppositional defiant disorder, conduct disorder, or unspecified disruptive behavior disorder. A semi-structured clinical interview, the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (KSADS-PL) (195, 267), administered to guardians and youth, determined psychiatric diagnoses, including externalizing diagnoses. Participants using psychostimulant medications were asked to refrain from taking their medication on study visit days, and a urine drug screen was conducted on each visit to verify their substance-naïve status. Numbers of participants being treated with psychostimulant medications at the time of baseline assessment are presented in Table 6. The final sample included in analyses consisted of 115 total externalizing (EXT) subjects—78 males and 37 females (Table 6, Figure 7).

19.3. Measures

19.3.1. Balloon analogue risk task (BART)

In the MRI scanner, at baseline, participants completed a high resolution structural (MPRAGE) and field mapping scans, followed by three 8-minute fMRI-compatible BART scans (107, 174) to explore brain activation during risky decision-making. The BART models real-world risky choices and correlates with impulsivity, adolescent risk-taking, and SUDs (169-173), making it a relevant tool for investigating sex influences on EXT youth's risky decision-making. During the BART, participants

decide whether to risk cash rewards that increase with each balloon inflation or bank the amount and start inflating a new balloon (Figure 8). Participants are instructed to “inflate the balloon as much as you can without popping it” to earn money for each unexploded balloon and that they win more money for larger balloons (paid in real cash after scanning). The BART incorporates parametric increases in explosion probability over successive responses (174). The parametric modulation employed the following probabilities of balloon explosions at each pump: 0% for \$0.0; 2.1% for \$0.05; 4.2% for \$0.15; 6.3% for \$0.25; 14.6% for \$0.55; 23.9% for \$0.95; 31.3% for \$1.45; 43.8% for \$2.05; 56.3% for \$2.75; 68.8% for \$3.45; 79.2% for \$4.25; 89.6% for \$5.15. A jitter function is applied to the stimulus presentation timings between decision and outcome phases of each trial to distinguish decision-making and feedback-related processes (174). Participants were repeatedly presented a virtual balloon and had to press one of two buttons to either inflate the balloon (Choose Inflate), risking cash rewards that increased with the balloon's size, or to stop inflating and bank the accumulated money for that balloon (Choose Win). If they choose to inflate, the balloon either expands, increasing the reward amount for that balloon (Outcome Inflate), or it bursts, resulting in the loss of the accumulated money for that balloon (Outcome Explode). Except for the initial inflation, explosions could occur at any size, with the risk increasing as the balloon grows larger. When participants opt to win (Choose Win), the accumulated rewards are banked, and a new balloon appears. During three 8-minute scan sessions, participants could complete as many balloons as possible, with a maximum of 12 inflations per balloon. Before performing the BART in the MRI scanner, participants practiced on a desktop computer.

19.3.2. Substance Use Measures

Both youth and guardians completed virtual follow-up assessments at 6-month intervals after the baseline measurements, whenever feasible. Time points from our longitudinal follow-up included in this analysis ranged from 6 months to 84 months after the baseline MRI session. Substance use was assessed with the revised Drug Use Screening Inventory's substance use domain (DUSI-R) (268) with additional categories covering more recent commonly used substances since the inventory's release. The DUSI-R administered here includes 25 substance classes and assesses the frequency of monthly substance use (0 times, 1-2 times, 3-9, 10-20, 21+) and endorsement (yes/no) of DSM-5-based, substance-specific problems (e.g., Have you accidentally hurt yourself or someone else after using *substance in question?*). Our primary outcome of interest was adolescent problematic substance use, defined here as two or more self or parent-reported DSM-5-based problems for any one substance. The outcome of interest, problematic substance use, was operationalized as the first time point at which the outcome was endorsed. Thus, the outcome was classified as either an event (child or guardian-reported problematic substance use) or as censored.

19.3.3. Covariates

19.3.3.a. Family History of SUD

A covariate of significant interest associated with substance use risk is familial history of SUD due to its aforementioned genetic liability (178, 179). Family History of SUD is defined here as the subject having a biological father *and* another first or second-degree family member with a past or present DSM-5-defined SUD (excluding isolated alcohol or tobacco use disorders).

19.3.3.b. Violence Exposure

Violence exposure was included as a possible covariate due to the established positive association between adolescent violence exposure and future substance use (269, 270), as well as the likelihood of greater substance availability in high violence areas (271-275). At baseline and in yearly follow-up surveys, adolescents completed portions of the Screen for Violence Exposure (SAVE) pertaining to subscales regarding the child's exposure to traumatic violence and indirect violence (276). Individual subscale scores were summed, with higher scores indicating greater violence exposure. Scores at baseline were used where available and then, if subjects were missing the baseline measure, their next completed measure at a yearly survey was utilized.

19.3.3.c. Parental Monitoring

At baseline, guardians described how frequently (i.e. Likert scale never to always) they monitor their children outside of school hours with 4 items adapted from the Silverberg Parental Monitoring Scale, on topics including knowing where their child is after school, calling/texting them to find out what they're doing, scheduling their child's time after school, and checking up on them when not in school. Their answers to these four items were averaged with higher final scores indicating more frequent parental monitoring. Parental monitoring was included as a potential covariate due to evidence that it causally affects adolescents' substance use patterns (277).

19.3.3.d. Gender Diverse Youth

Gender is a social construct, where the term 'cisgender' refers to gender which aligns with sex assigned at birth. In this report we use the term, 'gender diverse' to describe youth whose self-reported gender identity (boy or girl), two or more times throughout the study period, did not align with their guardian-reported sex assigned at

birth (reported at baseline) (n=11). While the relationship between gender identity and risky decision-making neural activation has not been studied, the increased risky decisions, more impulsive behaviors, and increased substance use among gender diverse individuals compared to cisgender individuals is well-established (278-282).

19.4. MRI Data Acquisition and Preprocessing

Participants completed brain imaging in <90-minute sessions on a research-dedicated 3.0-Tesla Siemens Prisma MRI scanner with a 32-channel head coil. A high-resolution 3D magnetization prepared rapid gradient echo structural (MPRAGE) scan consisting of 160 sagittal slices and 1.05 x 1.05 x 1.2 mm³ voxels was acquired first in 5 minutes and 12 seconds. For BART runs, a T2*-weighted gradient echo planar imaging (EPI) sequence was used (54 axial slices; voxel size 2.5 x 2.5 x 2.5 mm³; TR/TE 1200/29 ms; flip angle 65°; field-of-view 220 x 220 mm²; matrix 88 x 88), using a multiband sequence with a multiband factor of 3.

EPI scans were first distortion-corrected using fMRIB Software Library (FSL)'s "topup" tool, using distortion field estimates from the two opposite-phase spin echo field mapping. Anatomical scans were registered to Montreal Neurological Institute-152 (MNI152) standard MRI template brain volume space using nonlinear transformation to account for regional differences between individual subject brains and the MNI template. EPI data were aligned with each participant's anatomical scan using `afni_proc.py` (210, 211), a comprehensive processing pipeline in AFNI (Analysis of Functional NeuroImages). Also, using `afni_proc.py`, functional images were motion-corrected and spatially smoothed with a 6mm Gaussian kernel to account for anatomical variability and improve the signal to noise ratio, and time-series normalization to a T1-weighted image

was conducted, followed by an adjustment to a 100-scale per voxel. Lastly, unsupervised independent components analysis (ICA)-based denoising with ICA-AROMA (212, 213) from FSL's MELODIC tool was used for identifying and removing noise-related components. Visual inspection of brain activity ensured the presence of expected activation patterns corresponding to the task. This step involved examining the spatial distribution of activation maps to confirm typical task-related regions were engaged (e.g., visual cortex). Additionally, care was taken to avoid the occurrence of widespread negative activation, which could indicate global signal regression artifacts, head motion, or other preprocessing issues. Based on this evaluation, participants (n = 44) with unsatisfactory functional imaging were excluded from the analyses, with specific reasons for exclusions presented in the Supplementary Material.

19.5. Neuroimaging Data Analysis of the BART

After preprocessing and noise reduction, runs were concatenated, and a general linear regression model (GLM) with random effects was used to estimate event-related responses in AFNI. *Choice events*, aligned to the repetition time (TR) that included the button press response, were modeled as Choose Inflate (choosing to continue inflating the balloon) or Choose Win (choosing to discontinue inflating and bank money) regressors. *Outcome events* were modeled as the TR that included balloon explosion (Outcome Explode), successful balloon inflation (Outcome Inflate), or the outcome of discontinuing inflations (Outcome Win). Balloon explosion probabilities were included as parametric modulators for each event-type regressor (e.g., Choose Inflate * P(explode), Outcome Inflate * P(explode)), except for Outcome Win, which has no uncertainty). Parametric modulators were incorporated to examine neural activation patterns that specifically track

the escalating risk of both reward and loss as balloon size increases, providing insight into how brain regions dynamically respond to varying levels of decision-making uncertainty. To compare activation differences between conditions, individual subject activation maps were subjected to a voxel-wise subtraction using the 3dcalc tool in AFNI to compute the difference in activation between conditions, adjusting for individual differences in baseline activation. There were four contrast subtraction maps: Choose Inflate—Choose Win (modulated and unmodulated) and Outcome Explode—Outcome Inflate (modulated and unmodulated).

19.5.1 ROI Mask Creation and Analysis

Regions of interest (ROIs) of the NAc and sgACC were selected as discussed in the Introduction due to their relevance for risky decision-making and SUD risk, and their masks were generated in AFNI using the MNI Glasser HCP atlas (283) (sgACC) and the Brainnetome atlas (284) (NAc; Table 7). For each participant, we extracted the average activation within each region for each of the four contrasts. To account for the broad range of activation across the ROIs and facilitate comparison of activation between these ROIs, average brain activation was standardized by z-scoring for each ROI and contrast.

19.6. Statistical Analyses

To investigate sex differences in the association between brain activation and the hazard of problematic substance use in EXT youth, we selected the two ROIs discussed above, which are highly relevant in risky decision-making and SUD risk, and we applied a Cox proportional hazards model for each ROI and for each contrast (e.g. parametrically modulated Choose Inflate—Choose Win). Standardized brain activation (z-scored), sex, and their interaction were modeled with time to child problematic substance use events

(or censorship) in these models. Cox proportional hazards models were conducted using the survival package in R (285) and hazard ratios (HR) with 95% confidence intervals (CI) are reported. Correction for multiple comparisons involved adjusting p -values using the Hochberg procedure to control the family-wise error rate using the stats package in R. Significance threshold was set at $p < 0.05$.

Covariate selection was determined by a stepwise model selection procedure using the Akaike Information Criterion (AIC). The baseline model included average brain activation as the sole predictor of time to problematic substance use. A full model incorporated sex and the covariates described above which are related to adolescent development and substance use risk, including family history of substance use, traumatic violence subscale score from the SAVE questionnaire, and the average parental monitoring score. Using stepAIC from R's MASS package (207), models for each contrast's activation in each ROI were iteratively evaluated in both forward and backward directions to determine the most parsimonious model with the lowest AIC. Results from stepAIC model selection can be found in Appendix B.

Given the small number of gender diverse youth in our sample and to explore the possible effects of gender diversity on the association between sex, risky decision-making brain activation, and problematic substance use, we conducted a supplementary analysis using the same parameters described above, adding gender (cisgender = 0 and gender diverse = 1) to the previously described models.

20. Results

All hazard ratios and their corresponding confidence intervals for each ROI and contrast are presented in Table S1.

20.1. Choice Phase Results

Parametrically modulated BOLD signal: There was a significant main effect of modulated Choose Inflate—Choose Win brain activation and its association with problematic substance use in the right NAc. For every unit increase in standardized average brain activation the hazard of having problematic substance use decreased across all participants (HR = 0.68, 95% CI [0.49, 0.94], $p = 0.01$). In this same region on the same modulated choice contrast, average brain activation (i.e., activation which increased with increasing probability of balloon explosion) in females was also significantly associated with a lower hazard of problematic substance use (HR = 0.64, 95% CI [0.44, 0.92], $p = 0.01$). Average activation in males was not significantly associated with problematic substance use (HR = 0.78, 95% CI [0.43, 1.41], $p = 0.40$). Differences in hazard ratios were found between males and females ($p = 0.04$). However, none of these differences survived correction for multiple comparisons. Figure 9 shows a visualization of the right NAc region alongside a forest plot displaying the hazard ratios with 95% confidence intervals for the overall sample, females, and males corresponding to the relationship between average activation intensities during the modulated Choose Inflate—Choose Win contrast and problematic substance use. There were no significant findings with parametrically modulated BOLD signal in the left NAc, left sgACC, or right sgACC.

BOLD signal, without parametric modulation: In the right NAc during the Choose Inflate—Choose Win contrast, unmodulated, standardized brain activation in males was associated with a lower hazard of problematic substance use (HR = 0.60, 95% CI [0.37, 0.97], $p = 0.03$), although this finding did not survive correction for multiple

comparisons. Unmodulated brain activation in the right NAc region during the choice contrast was not significantly associated with problematic substance use for the overall sample or for females, and there was no difference between the hazard ratios for males and females for this contrast in this region. Figure 10 shows a visualization of the right NAc region alongside a forest plot displaying the hazard ratios with 95% confidence intervals for the overall, female, and male samples corresponding to the relationship between average activation intensities during the unmodulated Choose Inflate—Choose Win contrast and problematic substance use.

In the right sgACC during the Choose Inflate—Choose Win contrast, unmodulated, standardized brain activation in females was associated with a lower hazard of problematic substance use (HR = 0.49, 95% CI [0.24, 0.97], $p = 0.03$). No differences in hazard of problematic substance use were observed for the overall sample or for males in this region on the unmodulated choice contrast. A difference was found when comparing the hazard ratios for males and females in the right sgACC ($p = 0.02$). However, none of these differences survived correction for multiple comparisons. Figure 11 shows a visualization of the right sgACC region alongside a forest plot displaying the hazard ratios with 95% confidence intervals for the overall, female, and male samples corresponding to the relationship between average activation intensities during the unmodulated choice phase contrast and problematic substance use.

There were no findings with unmodulated BOLD signal in the left NAc or left sgACC.

20.2. Outcome Phase Results

There were no significant uncorrected or corrected findings for the outcome phase contrasts, modulated or unmodulated.

20.3. Gender Diverse Youth Supplementary Analysis Results

All HRs and their corresponding confidence intervals for each ROI and contrast adjusting for gender are presented in Table S2. With the adjustment of gender and before correction for multiple comparisons, most models retained direction and significance apart from the findings in the sgACC for EXT females where the strength of the association between greater unmodulated choice phase activation and problematic substance use (HR = 0.51, 95% CI [0.26, 1.00], $p = 0.05$) was slightly weaker. And for modulated choice phase activation in the right NAc, the comparison between females and males' HRs became non-significant ($p=0.05$). No finding retained significance after correction for multiple comparisons as in the main analysis.

21. Discussion

The goal of the current study was to investigate sex differences in associations between brain activation during risky decision-making and the emergence of problematic substance use during early adolescence in youth with externalizing disorders (EXT). Two brain regions were selected for analysis due to prior evidence linking activation in these regions to decision-making in adolescence. The included regions which have been shown to be activated during decision making, and abnormally so in youth with ADHD and other SUD risk factors were the bilateral nucleus accumbens (NAc) and bilateral subgenual anterior cingulate cortex (sgACC). Our findings before correction for multiple comparisons were all isolated to the choice phase of the decision-making process (i.e., Choose Inflate—Choose Win contrast), both parametrically modulated and unmodulated

analyses. Choice phase brain activation results can be interpreted as brain activation during the approximately two second interval when participants made risky choices (Choose Inflate) compared to safe ones (Choose Win), as those choices became riskier (parametrically modulated) or were averaged, ignoring risk of balloon explosion (unmodulated). We observed that among a sample of youth at particularly high risk for the development of substance use and SUDs, by virtue of their externalizing disorder diagnoses, there were sex differences in the association between both NAc and sgACC modulated and unmodulated activation during risky decision-making and problematic adolescent substance use: for females, greater activation in either of these regions was associated with a lower hazard of developing problematic substance use. For males, unmodulated activation in the NAc was associated with a lower hazard of developing problematic substance use.

Regarding the findings in the NAc, one possible explanation for these sex differences may lie in the well-studied sex differences in NAc anatomy are observed during adolescence with males exhibiting first an increase in ventral striatal volume before volume begins to decline, whereas females exhibit a steady decline throughout adolescence (239, 286). Lastly, some sex-specific differences in how the NAc relates to SUD, particularly in relation to impulsivity, have been identified: one study found that in males, larger NAc volume was associated with increased sensation seeking, which mediated their higher likelihood of alcohol use, while in females, NAc volume directly predicted alcohol use without mediation by sensation seeking (253). Therefore, levels of trait impulsivity likely play a larger role in the relationship between reward network processing during decision-making and real-world substance use outcomes in EXT

males. Interestingly, a sex difference existed in our NAc findings across brain activation during the choice phase where only modulated brain activation was associated with lower problematic substance use in females, but for males, it was unmodulated brain activation that was associated with lower problematic substance use. In other words, greater activation in the NAc with increasing chance of balloon explosion when making a risky versus safe choice was associated with a lower rate of problematic substance use in EXT females, but not in EXT males. And on average, greater activation when making a risky over safe choice, ignoring risk of explosion, was associated with a lower rate of problematic substance use in EXT males, but not in EXT females.

With the understanding that the NAc is typically engaged during risky choices as it plays a key role in shaping reward-driven behaviors through connecting reward experiences to emotional and motivational aspects (109, 110), these findings suggest that a possible explanation for sex differences in substance use outcomes is the different maturation of the NAc between girls and boys where females may derive greater benefit from appropriately ascribing emotional/motivational valence to risky decisions *as those decisions become increasingly risky*, which may be a marker of a biologically protective system. Essentially, the modulated sex difference finding indicates EXT females may be appropriately calculating increasing risk and chance of poor outcome via successful attribution of emotional or affective value to risky choices. For EXT males, it appears that engaging the emotional/motivational valence-ascribing NAc during choice, regardless of the level of that choice's riskiness, is associated with a lower rate of problematic substance use. Based on the female-specific findings in the NAc, a potential target for behavioral therapy targeting decision-making deficits (like that successfully

implemented by our group with the IDRT-Y (287)) could focus on appropriately assigning emotional and motivational valence, as risk increases, during decision-making to reduce the risk of future problematic substance use, particularly for females who do not show this skill. Further, given the male-specific findings of lower rates of problematic substance use associated with greater NAc activation with risky versus safe choice independent of balloon size, a potential targetable therapy for externalizing males could involve improving overall risk calculation and enhancing the ability to recognize signals of varying levels of risk associated with different choices during decision-making.

Our sgACC finding in the choice phase contrast showed that when females were making a risky choice over a safe choice (Choose Inflate—Choose Win), greater unmodulated activation in the right sgACC was associated with a lower hazard of developing problematic substance use. Other studies have found sex differences in this region during risky choice in a mixed sample of adolescents with and without EXT symptoms: females showed greater activation than males during risky choice in the right subgenual ACC (88)—indicating our findings *may* exist outside the context of EXT psychopathology and instead reflect a general sex difference. Atypical functional connectivity seen in ADHD may also be at play here: stronger positive connectivity between the striatum and both the vmPFC and the ACC has been found in children with ADHD compared to typically developing controls and was more pronounced in girls with ADHD (288). These prior findings on sex differences in the sgACC associated with EXT pathology and reward processing taken together with our finding suggest that sgACC activation during reward processing is a biomarker that differentiates males and females who are at-risk for SUD. Given sgACC's previously discussed role in avoiding loss

through a similar reward-related emotion and motivation processing (114, 115) and uncertainty/lack of confidence during decision-making (116-120), it follows that making a risky choice would appropriately correspond with increased sgACC activation due to a signal in this region that making a risky choice could result in a negative outcome which it typically functions to avoid (106). Therefore, this finding indicates that sex differences in substance use outcomes may be related to dysfunctional loss avoidance in EXT males when making risky choices. Specifically, their lack of risk-averse behavior during decision-making may be driving the effect. In contrast, when loss avoidance functions appropriately in females during decision-making, it may serve as a protective factor against problematic substance use.

While not a sex-specific finding, the whole group overall main effect finding in the right NAc is noteworthy. In the right NAc, increased average brain activation during risky choice is associated with a lower hazard of problematic substance use. This aligns well with the existing research of the NAc's role in risky decision-making discussed above. Additionally, individuals with family history of SUD often show blunted NAc activation during decision-making (180, 183), supporting the idea that the relationship between NAc activation and problematic substance use observed here may be more related to sensation seeking and EXT pathology rather than the genetic risk of family history of SUD (which was controlled for in this study) (181). Furthermore, research on ADHD, an EXT disorder, has demonstrated hypoconnectivity between the prefrontal cortex and NAc (250-252), which may be part of the explanation for blunted NAc activation during risky decision-making in EXT pathology.

Adjusting for gender marginally influenced the results, which emphasizes the need for further exploration of how gender diversity interacts with the relationships analyzed here. The observed changes may be partly due to an imbalanced sample—possibly resulting in statistical artifacts, which may be further evidenced by the small magnitude of statistical changes seen in the HRs and *p*-values in the adjusted models. Prior research has established that gender diverse individuals are more vulnerable to EXT behaviors and ADHD (279, 281, 282) as well as to SUDs and other risky behaviors (278-280), but there is a gap in the research examining how deficits in risky decision-making neural processing may underlie the increased impulsive and risky behaviors observed among gender diverse people.

This study has some limitations. The lack of findings after multiple comparisons correction is likely due to our sample size, although our uncorrected findings are consistent with prior literature. A further limitation of this study is that problematic substance use was derived from self and guardian-report data, as urine drug screens were not collected from all participants during the COVID-19 pandemic. This self-reporting of substance use carries potential biases like social desirability, memory and recall issues, underreporting for protection, and lack of objective verification (289-291), which could compromise the accuracy and reliability of the data, although the inclusion of both guardian and child reports may mitigate some of these biases and offer a more comprehensive and accurate representation. Another limitation relates to the fact that some members of our sample, with diagnosed externalizing disorders, have previously and throughout the study taken psychostimulant medications, which could potentially affect brain activation and substance use behaviors. Across our participants who have

taken medication, dosage and the oral method of administration differs greatly from those typically associated with stimulant abuse. With that, fewer than one-third of ADHD participants were taking medication at baseline, and stimulant medication was withheld for at least 24 hours before imaging and subjects were excluded who did not hold medication before baseline visits (see Figure 7). Although medication effects could influence these results, participants were not under the immediate effects of psychostimulant medication during their baseline behavioral assessments and brain imaging; and recruiting an externalizing sample entirely naive to psychotropic drugs would have been quite unrealistic and unrepresentative. Another limitation of this study related to the sample size is the unbalanced sex distribution, with fewer females than males. While this ratio reflects the overall population of individuals with EXT disorders (292-294), which guided our sampling approach, the uneven sex distribution may limit our ability to fully examine sex differences. To better explore sex differences in future research, a larger sample and oversampling females with EXT disorders would be beneficial. Although, a related strength of this sample, and a key aspect of its novelty, is that we investigated sex differences in substance use risk within a population where previous studies were not able: subjects with clinician-diagnosed ADHD and a disruptive behavior disorder.

In summary, we believe this study provides novel insights into sex differences in the relationships between neural activation during risky decision-making and problematic substance use among particularly high-risk youth. To summarize, greater activation in the right NAc when making a risky versus safe choice, as that choice became riskier, was associated with a lower hazard of problematic substance use in the overall sample and in

females. Our NAc findings suggest that intact motivational valence ascription during risky decision-making is a function which may be predictive of lower problematic substance use in EXT youth. Similarly, we found that greater unmodulated activation in the right sgACC during the choice phase was associated with a lower hazard of problematic substance use in females only. Our sgACC findings suggest that functions which are associated with lower rates of problematic substance use in EXT females (i.e., proper loss avoidance), may either not share the same association for EXT males or may be dysfunctional in males. Future directions for this work, in addition to replication with a larger sample size, include evaluating whether measures of sensation seeking and impulsivity influence the relationship between brain activation during risky decision-making and substance use outcomes, as well as exploring the role of sex in this relationship. In conclusion, these findings highlight specific cognitive, emotional, and behavioral targets when developing sex-specific interventions for SUD during adolescence.

Table 6. Demographics

	EXT Females (n=37)	EXT Males (n=78)	<i>p</i> -values
Age at Visit 1 / M (SD)	12.08 (0.53)	11.89 (0.56)	0.08
Gender Diverse Youth / N (%)	5 (13.51)	6 (7.69)	0.51
Family History of SUD (%)	21 (56.76)	36 (46.15)	0.38
<u>Race / N (%)</u>			0.48
White	20 (54.05)	49 (62.82)	
Black	13 (35.14)	19 (24.36)	
Multiracial	4 (10.81)	10 (12.82)	
Hispanic Ethnicity / N (%)	3 (8.11)	7 (8.97)	1.00
<u>Parental Education Max / N (%)</u>			0.63
High School	4 (10.81)	8 (10.26)	
Some College/College	23 (62.16)	42 (53.85)	
Some Graduate/Graduate	10 (27.03)	28 (35.90)	
SAVE TV / M (SD)	12.59 (1.07)	14.38 (5.42)	0.04
SAVE IV / M (SD)	24.76 (9.12)	30.64 (11.15)	< 0.01
Parental Monitoring / M (SD)	3.31 (0.69)	3.09 (0.73)	0.13

Stimulant Med Treatment at Baseline / N (%)	13 (35.14)	38 (48.72)	0.24
PSU (any substance) / N (%)	12 (32.43)	18 (23.08)	0.40
PSU for Alcohol / N (%)	4 (10.81)	3 (3.85)	0.29
PSU for E-Cigarettes / N (%)	4 (10.81)	7 (8.97)	1.00
PSU for Cannabis / N (%)	6 (16.22)	13 (16.67)	1.00
PSU for Tobacco (smoke/chew) / N (%)	0 (0.00)	2 (2.56)	0.82

EXT = externalizing, SAVE = Screen for Violence Exposure, TV = Traumatic Violence exposure subscale, IV = Indirect Violence exposure subscale, PSU = problematic substance use, defined by experiencing two or more consequences for one substance as reported by child or guardian

Table 7. Size, Brodmann Area (BA), and Center of Mass Coordinates for *a priori* Regions of Interest (ROIs)

ROI	BA	Cluster Size	Center of Mass MNI Coordinates (mm)		
			X	Y	Z
Left NAc		152	-17	4	-9
Right NAc		159	13	11	-9
Left sgACC	25/32	113	-5	21	-12
Right sgACC	25/32	118	3	20	-12

NAc = nucleus accumbens, sgACC = subgenual anterior cingulate cortex, MNI = Montreal Neurological Institute; cluster size is determined by the number of voxels

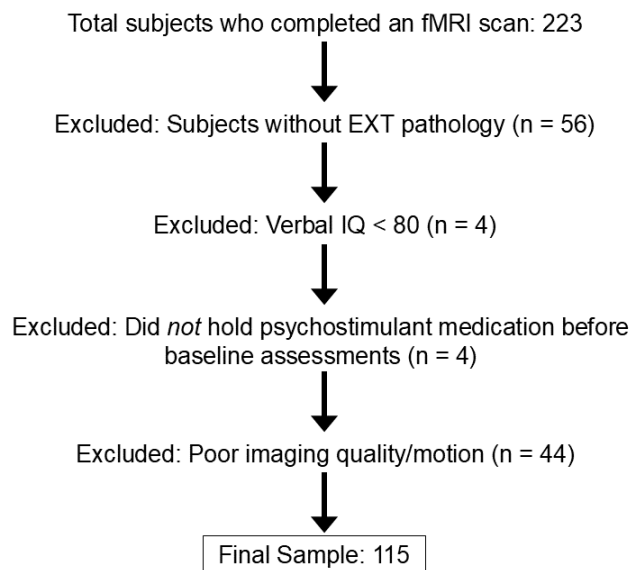


Figure 7. Flowchart of reasons for participant exclusion.

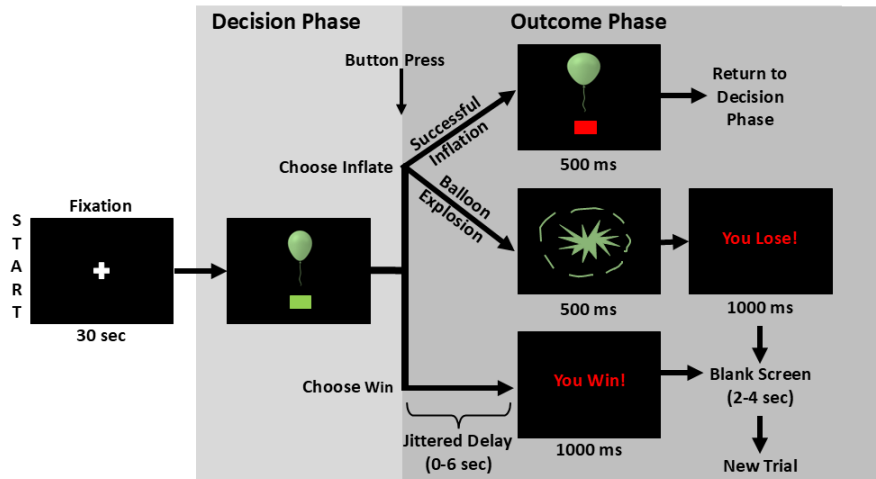


Figure 8. BART schematic.

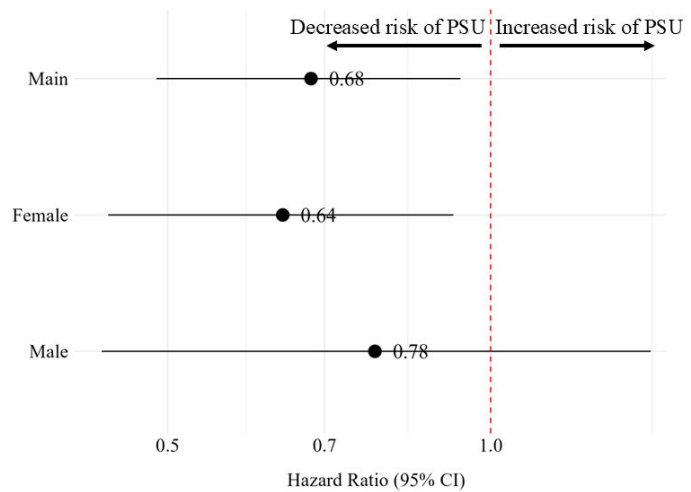
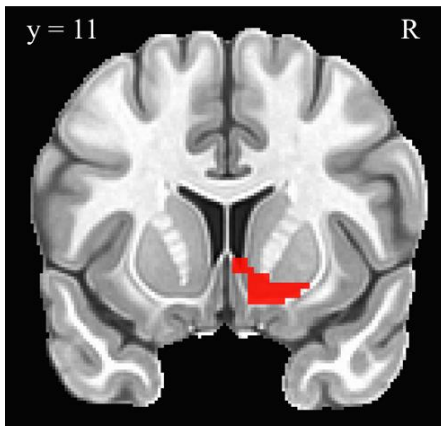


Figure 9. Hazard ratios for problematic substance use (PSU) risk based on modulated choice phase activation in the right nucleus accumbens. Models were adjusted for family history of substance use, parental monitoring, and traumatic violence exposure.

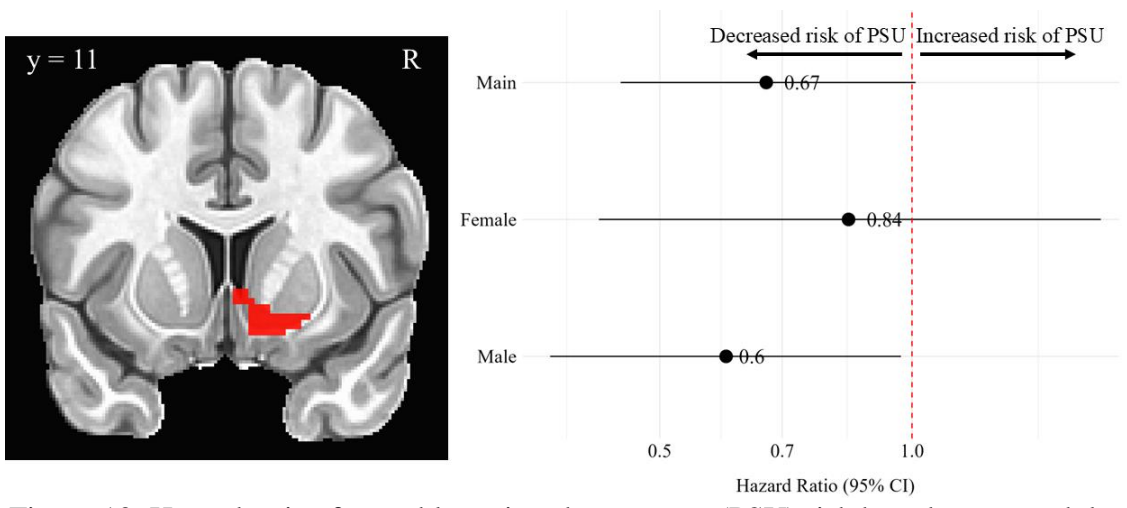


Figure 10. Hazard ratios for problematic substance use (PSU) risk based on unmodulated choice phase activation in the right nucleus accumbens. Models were adjusted for family history of substance use, parental monitoring, and traumatic violence exposure.

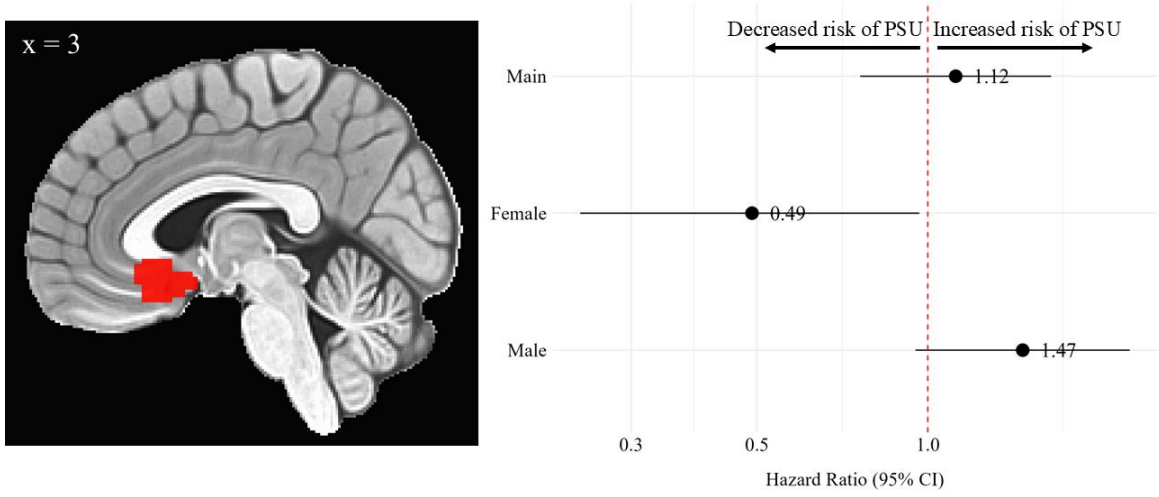


Figure 11. Hazard ratios for problematic substance use (PSU) risk based on unmodulated choice phase activation in the right subgenual anterior cingulate cortex. Models were adjusted for family history of substance use, parental monitoring, and traumatic violence exposure.

22. Supplementary Material

Potential Covariates not included in final model:

Socioeconomic Status (SES)

SES was approximated by parental education as a possible covariate as low parental education has been identified as a risk factor for drug abuse among adolescents (295). At baseline, guardians were asked the highest degree/level of school the child's mother and father completed. For this analysis, the SES variable was coded as the highest/max education reported by either parent in a factor variable of 1) less than high school, 2) high school, 3) some college or college, 4) some graduate or graduate school, or 5) unknown. Data missingness for SES was handled with multiple imputations utilizing the MICE (Multivariate Imputation by Chained Equations) package in R (206) which employed a proportional odds logistic regression (POLR) model to impute SES accounting for family history of substance use disorder (SUD) and sex.

Specific reasons for n=44 unsatisfactory functional imaging participant exclusions:

First, eight subjects were unable to complete the entire three runs of BART due to visibly excessive motion/restlessness, talking during the task, taking breaks in the MRI session for things like using the restroom, or in one case, a fire drill. The data from these subjects were not analyzed and were excluded (n=8). In the first phase of imaging quality evaluation of those who completed three BART runs, participants showing motion artifacts during the anatomical scan, which led to problems with volume registration, were excluded from the analysis (n = 11). Subsequently, a visual review of the brain activity was conducted to confirm the presence of anticipated activation patterns corresponding to the task. This involved inspecting the spatial distribution of activation

maps to ensure engagement of typical task-related regions, such as the visual cortex. Participants were excluded if expected activation in regions like the visual cortex was absent ($n = 5$), or if there was widespread negative activation, indicating possible artifacts from global signal regression ($n = 7$). Lastly, if the activation distribution in the maps appeared excessively diffuse, non-localized, or lacked a clear pattern, this was attributed to motion artifacts, and participants with confirmed high motion were excluded ($n = 13$). As a result, a total of 44 participants were excluded due to suboptimal functional imaging.

Table S1. Hazard ratios (HR) for activation (standardized) and problematic substance use

ROI	Main HR (95% CI)	p^a	Female HR (95% CI)	p^a	Male HR (95% CI)	p^a	Sex Diff. HR p
Choose Inflate—Choose Win modulated							
Left NAc	0.92 (0.61-1.41)	0.71	0.77 (0.44-1.34)	0.35	1.14 (0.64-2.03)	0.65	0.58
Right NAc	0.68 (0.49-0.94)	0.01	0.64 (0.44-0.92)	0.01	0.78 (0.43-1.41)	0.40	0.04
Left sgACC	0.94 (0.63-1.40)	0.75	1.18 (0.63-2.23)	0.59	0.81 (0.49-1.34)	0.40	0.61
Right sgACC	0.92 (0.65-1.30)	0.64	0.92 (0.58-1.46)	0.71	0.93 (0.56-1.54)	0.76	0.89
Choose Inflate—Choose Win unmodulated							
Left NAc	1.02 (0.69-1.50)	0.92	1.05 (0.47-2.35)	0.91	1.01 (0.64-1.60)	0.96	0.99
Right NAc	0.67 (0.45-1.01)	0.05	0.84 (0.42-1.68)	0.63	0.60 (0.37-0.97)	0.03	0.10
Left sgACC	1.16 (0.80-1.70)	0.43	0.90 (0.51-1.59)	0.72	1.37 (0.86-2.18)	0.18	0.37
Right sgACC	1.12 (0.76-1.65)	0.56	0.49 (0.24-0.97)	0.03	1.47 (0.95-2.27)	0.08	0.02
Outcome Explode—Outcome Inflate modulated							
Left NAc	1.29 (0.77-2.18)	0.33	2.00 (0.84-4.76)	0.11	0.98 (0.57-1.68)	0.94	0.29
Right NAc	1.26 (0.85-1.88)	0.25	1.55 (0.92-2.62)	0.10	0.88 (0.45-1.70)	0.69	0.24
Left sgACC	0.87 (0.60-1.26)	0.46	0.96 (0.56-1.65)	0.88	0.80 (0.48-1.34)	0.39	0.68
Right sgACC	0.88 (0.63-1.22)	0.44	1.11 (0.40-3.06)	0.84	0.86 (0.62-1.18)	0.34	0.62
Outcome Explode—Outcome Inflate unmodulated							
Left NAc	1.02 (0.67-1.54)	0.92	1.02 (0.51-2.06)	0.94	1.02 (0.61-1.70)	0.94	0.99
Right NAc	1.15 (0.82-1.62)	0.41	1.24 (0.74-2.05)	0.41	1.09 (0.68-1.72)	0.72	0.67
Left sgACC	1.04 (0.76-1.42)	0.80	1.00 (0.70-1.43)	0.99	1.20 (0.62-2.32)	0.58	0.86
Right sgACC	0.99 (0.75-1.32)	0.96	1.02 (0.75-1.38)	0.90	0.89 (0.46-1.71)	0.73	0.93

Models were adjusted for family history of substance use, parental monitoring, and traumatic violence exposure; NAc = nucleus accumbens, sgACC = subgenual anterior cingulate cortex; problematic substance use is defined by experiencing two or more consequences for at least one substance as reported by child or guardian; p^a = p -value uncorrected for multiple comparisons; sex diff HR p = the p -value indicating whether the hazard ratio (HR) differs significantly between males and females

Table S2. Supplementary analysis hazard ratios (HR) for activation (standardized) and problematic substance use adjusted for gender

ROI	Main HR (95% CI)	p^a	Female HR (95% CI)	p^a	Male HR (95% CI)	p^a	Sex Diff. HR p
Choose Inflate—Choose Win modulated							
Left NAc	0.96 (0.63-1.46)	0.83	0.83 (0.47-1.46)	0.51	1.12 (0.63-2.01)	0.69	0.75
Right NAc	0.66 (0.47-0.94)	0.02	0.62 (0.41-0.94)	0.02	0.75 (0.42-1.35)	0.34	0.05
Left sgACC	0.93 (0.62-1.39)	0.71	1.12 (0.59-2.11)	0.73	0.83 (0.5-1.37)	0.45	0.71
Right sgACC	0.93 (0.66-1.3)	0.65	0.93 (0.6-1.44)	0.73	0.92 (0.56-1.53)	0.75	0.90
Choose Inflate—Choose Win unmodulated							
Left NAc	1.02 (0.68-1.52)	0.92	1.13 (0.48-2.69)	0.78	0.99 (0.61-1.59)	0.95	0.96
Right NAc	0.68 (0.45-1.03)	0.06	0.94 (0.48-1.86)	0.85	0.57 (0.34-0.93)	0.02	0.08
Left sgACC	1.12 (0.75-1.67)	0.58	0.72 (0.38-1.36)	0.31	1.43 (0.88-2.31)	0.14	0.21
Right sgACC	1.13 (0.77-1.65)	0.53	0.51 (0.26-1)	0.05	1.48 (0.97-2.27)	0.07	0.02
Outcome Explode—Outcome Inflate modulated							
Left NAc	1.26 (0.73-2.17)	0.39	2.26 (0.89-5.75)	0.08	0.95 (0.58-1.58)	0.85	0.23
Right NAc	1.24 (0.81-1.9)	0.32	1.64 (0.92-2.92)	0.09	0.83 (0.44-1.57)	0.56	0.21
Left sgACC	0.92 (0.63-1.33)	0.65	1.15 (0.66-2)	0.62	0.77 (0.46-1.28)	0.31	0.54
Right sgACC	0.88 (0.64-1.23)	0.46	1.21 (0.44-3.32)	0.71	0.85 (0.63-1.16)	0.32	0.57
Outcome Explode—Outcome Inflate unmodulated							
Left NAc	1.02 (0.67-1.56)	0.92	0.97 (0.49-1.94)	0.93	1.05 (0.62-1.78)	0.85	0.98
Right NAc	1.11 (0.78-1.58)	0.56	1.11 (0.65-1.9)	0.71	1.11 (0.69-1.79)	0.66	0.84
Left sgACC	1.05 (0.78-1.42)	0.73	1.01 (0.72-1.41)	0.96	1.34 (0.65-2.74)	0.43	0.73
Right sgACC	0.99 (0.76-1.3)	0.95	0.99 (0.74-1.34)	0.97	0.98 (0.47-2.02)	0.95	0.99

Models were adjusted for gender (cisgender = 0, gender diverse = 1), family history of substance use, parental monitoring, and traumatic violence exposure; NAc = nucleus accumbens, sgACC = subgenual anterior cingulate cortex; problematic substance use is defined by experiencing two or more consequences for at least one substance as reported by child or guardian; p^a = p -value uncorrected for multiple comparisons; sex diff HR p = the p -value indicating whether the hazard ratio (HR) differs significantly between males and females

Chapter Four: Discussion and Conclusion

23. Restatement of Dissertation Objectives and Hypotheses

The overall objective of this dissertation was to address the critical need for understanding how sex influences neural processing during risky decision-making in adolescents with externalizing psychopathology (EXT), given their elevated risk for substance use disorders (SUDs). The overarching research question focuses on the role of sex differences in risky decision-making processes in high-risk adolescent populations, and how these differences may contribute to the development of SUDs. By examining youth with EXT, which are characterized by impulsivity, risk-taking, and disinhibited decision-making, this dissertation aims to fill a significant gap in the literature regarding how these traits interact with sex differences in substance use risk. In Chapter Two, the main research question addresses whether EXT females exhibit neural activation patterns similar to EXT males in a risky decision-making task, with the hypothesis that EXT females will show greater activation in frontoparietal/frontotemporal regions before making risky choices, and lower activation before negative outcomes, compared to control females (an activation pattern that is closer to male activation patterns shown in other literature on sex differences in healthy adolescent and adult decision-making). Chapter Three extends this investigation by exploring how deficits in risky decision-making in EXT youth contribute to future problematic substance use, with the hypothesis that deficits will be more pronounced in males and closely linked to their problematic substance use outcomes. This dissertation aims to deepen our understanding of sex-specific mechanisms in risky decision-making for at-risk youth and their implications for

substance use/SUD development, ultimately informing more targeted, sex-specific prevention strategies targeting decision-making deficits for adolescents at risk for SUDs.

24. Summary of Key Findings

In Chapter Two, we summarize the key results regarding activation patterns in EXT youth compared to controls, with particular attention to sex differences. Our analyses revealed significant behavioral performance differences during risk-taking between males and females in both the control and EXT groups. Specifically, male controls and EXT males exhibited greater Choose Inflation Counts and faster reaction times than control females, indicating greater engagement in riskier and more impulsive behavior than control females. EXT females were not significantly different from males, but also were not significantly different from control females on performance measures.

Regarding brain activation, we identified two clusters showing significant differences between groups during the Balloon Analogue Risk Task (BART). In the right dorsomedial prefrontal cortex/dorsal anterior cingulate cortex (dmPFC/dACC) region, EXT males showed greater activation than all other groups. In the left inferior temporal gyrus, all groups, including EXT females, demonstrated greater modulated activation compared to control females.

These findings partly support our hypothesis that EXT females would exhibit activation patterns similar to EXT males; however, the result that aligns with this hypothesis, namely the activation in the inferior temporal gyrus, should be interpreted with caution due to the small size of the comparison group, female controls. While EXT females did show heightened activation in the left inferior temporal gyrus, the significant differences in neural activation in the right dmPFC/dACC were more pronounced in EXT

males, challenging the idea that EXT females mirror EXT male patterns of brain activation. Furthermore, the performance results, which show that males—regardless of EXT psychopathology—exhibit significantly more risky and impulsive behavior than control females, suggest that sex may have a greater influence on actual performance in risky decision-making than EXT psychopathology.

In Chapter Three, we build on the findings from Chapter Two by examining whether sex differences in neural activation during risky decision-making are associated with sex differences in substance use outcomes among EXT youth. Our preliminary results found future problematic substance use was associated with choice phase activation in the nucleus accumbens (NAc) and subgenual anterior cingulate cortex (sgACC) in a sex-specific manner. In the right NAc, greater modulated brain activation during risky decision-making (Choose Inflate—Choose Win contrast) was associated with a decreased hazard of problematic substance use, particularly in females. For females, higher brain activation in this region, as balloon explosion probability increased (modulated), significantly reduced the likelihood of reporting problematic substance use, while this relationship was not significant in males. This difference in hazard ratios between males and females was statistically significant. Interestingly, for EXT males, it was unmodulated NAc brain activation during the choice phase, not modulated like it was for females, which was associated with less problematic substance use.

Further, in the right sgACC, females again showed a significant association between brain activation and a lower hazard of substance use. In contrast, the activation in this region was not significantly linked to problematic substance use in males. Again, there was a significant difference in the hazard ratios between males and females, and

while, not significant, the male hazard ratio indicated that greater activation in this region was actually associated with an increased hazard of problematic substance use. These findings suggest that sex differences play a critical role in the relationship between brain activation during risky decision-making and future substance use, with females experiencing lower rates of problematic substance use when their NAc and sgACC activation during risky choice aligns with expected activation in these reward network nodes during risky decision-making. Notably, EXT males did not exhibit the same strong links between brain activation and substance use risk, possibly showing the opposite direction of risk with activation association, further supporting the suggestion from this dissertation that neuropsychological risk profiles for EXT youth are influenced by sex.

25. Interpreting Results and Discrepancies with Prior Evidence

In the following sections, I outline how, taken together, the findings in this dissertation support the idea that not only are unbalanced reward and cognitive control network function during risky decision-making in EXT youth affected by sex, but also that the relationship between risky decision-making neural activation and future substance use in EXT youth is sex-specific as well. I first discuss what the findings may mean for addressing my original research aims, and then discuss some possible explanations for why our findings violated our *a priori* hypotheses.

25.1. Interpretation of Results

Our motivation for the studies presented in this dissertation was to investigate the role of sex differences in risky decision-making among youth with and without EXT disorders, particularly the mechanisms whereby these decision-making deficits contribute to increased substance use disorder risk, and how such deficits may vary by sex to inform

the development of sex-specific prevention strategies. We hypothesized, for the first manuscript, that EXT females would exhibit activation patterns more similar to EXT males than to control females with greater frontoparietal/frontotemporal activation before risky choices, and that for the second manuscript, partially due to the sex differences found in the first manuscript, that deficits in risky decision-making neural processing in the reward network would relate to greater problematic substance use in EXT males. Our findings indicate that male and EXT females show distinct neural processing during risky decision-making—with only EXT males showing deficits in cognitive control network activation and EXT females actually showing how intact cognitive control network activation is associated with less problematic substance use.

Specifically, in the first study we identified a potential deficit with EXT male decision-making neural processing compared to EXT females and control male and females where they appeared to inappropriately engage an area of the cingulo-opercular network, the dmPFC/dACC, which, as a cognitive control area, is normally activated during risk *averse* behavior (i.e. selecting the safer choice, for example) (106, 242-246), but EXT males engaged this area more than other groups during a risky over safe choice, as that choice became riskier. This may indicate an inappropriate calculation of the risk or an assumption of safety in an option or choice which is not safe. A direct counterpart to this finding, demonstrating the deleterious effects of dysfunctional risk-averse neural processing, is seen in our second study. Greater activation in the sgACC, which is involved in loss avoidance (114-120), during risky choice *would be expected* as the chance of balloon explosion (a negative outcome/loss) increased (106), as a signal of awareness a choice is being made that could lead to loss. And indeed, in our second

study, higher activation in the sgACC during the risky over safe choice was associated with less problematic substance use in EXT *females* only, which potentially aligns with the prior research that appropriately balanced cognitive control/reward network signaling allows one to shield oneself from losses/harms and potentially leads to less problematic substance use behaviors. Therefore, a key biological signature that distinguished EXT males from EXT females in terms of problematic substance use, and by extension overall increased SUD risk, could be male-EXT-specific deficits in the ACC during risky choice-making, presumably related to loss avoidance.

The findings from the second study in the NAc were that for EXT females, modulated activation during the choice phase was associated with less problematic substance use. In contrast, for males, it was unmodulated activation that drove this association with lower rates of problematic substance use. Based on the NAc's functions in risky decision-making, this sex difference in how NAc activation is related to future problematic substance use suggests that EXT females may more effectively respond to increasing risk by accurately assessing emotional value in those increasingly risky choices and that this is necessary to reduce problematic substance use behaviors. EXT males' engagement of the NAc in response to increasing risk level appears relatively deficient. Therefore, for a practical interpretation, enhancing overall risk calculation during decision-making, and specifically improving the ability to recognize signals of a choice carrying additional risk of a negative outcome, may help reduce EXT males' risk of problematic substance use.

25.2. Exploring Discrepancies between Hypotheses and Findings

25.2.1. Prior evidence of sex differences in EXT neural processing support Chapter Two findings

Our primary finding from the first study was that EXT males' activation in the dmPFC/dACC was significantly different from all other groups, including EXT females. This did go against a portion of our initial hypothesis that EXT females' activation would be more similar to EXT males' activation than it would be control females. First, there is a potential that these results are affected by the uneven sample sizes with fewer females than males, though the findings are significant after adjustment and with the Kruskal-Wallis method which is more robust in handling unbalanced samples. Second, sex differences in EXT youth's risky brain-activation have been identified before, and specifically in the same youth from our longitudinal sample, where Dir et al. found EXT boys had greater middle frontal gyrus during *safe* over *risky* choice (167), and Crowley et al. found that male and female adolescents with substance and conduct problems displayed different neural processing before risky responses in the medial and superior frontal gyrus (88). So, first, what these admittedly few studies on sex differences in risky decision-making in individuals with EXT disorders taken with our findings may indicate that despite similar clinical diagnoses, there likely exists distinct underlying risk-reward neural processing strategies between males and females which are potentially influenced by varying developmental trajectories, hormonal influences, or sex-specific environmental factors.

25.2.2. Sex, EXT psychopathology, and the balance of reward and cognitive control networks

While tracing the specific neural, developmental, hormonal, or environmental reasons for sex-specific neural processes of risk and reward in EXT youth is complex and outside the purview of this dissertation, the resulting sex differences in the interplay between cognitive control and reward networks' dominance in risky decision-making neural processing and this interplay's interaction with our results are worth considering. Prior research in this area indicates that what influences EXT females and males' different neural processing of risky decision-making are that 1) impulsivity may drive sex-specific changes in reward-related functional connectivity in EXT boys more so than in EXT girls and 2) EXT girls' functional connectivity may be more reflective of weaker attention regulation (rather than impulsivity regulation) and stronger cognitive control. In the following 3.2.2 sections, I examine existing evidence suggesting that inherent sex differences in the connectivity and balance between the reward and cognitive control networks in EXT psychopathology may contribute to associated deficits in risky decision-making neural processing, sex differences within these, and how the findings presented in this dissertation fit into this narrative.

25.2.2.a. Prior evidence of reward network dominance in EXT boys

Impulsivity in boys has been linked to stronger reward-related functional connectivity between regions like the ventral striatum and the ventromedial prefrontal cortex (296, 297), with some analyses showing a direct positive correlation between EXT problems in boys and positive connectivity between the dorsomedial and dorsolateral prefrontal cortex (dmPFC and dlPFC), regions involved in cognitive control and decision-making (297). These neural patterns suggest that EXT behaviors and impulsivity in boys may stem from overactive reward-processing networks, which require

engagement of the cognitive control regions of the dmPFC and dlPFC to regulate and manage impulsive behavior. However, these cognitive control regions appear to be insufficient in this process for boys, as they are overridden by reward-related circuits. This concept is further supported by sex differences observed in two tasks requiring sustained attention and inhibition of responses to non-target stimuli: (1) girls engaged regions such as the sgACC and dmPFC when this task demanded cognitive control and males engaged the reward-processing right medial orbitofrontal cortex (298); (2) in a task that required paying attention to a switching paradigm interspersed with a repeating paradigm (assessing attention and cognitive flexibility), females activated cognitive control areas of bilateral inferior prefrontal and anterior cingulate areas more than males (299).

25.2.2.b. Prior evidence of preserved cognitive control network in EXT girls

Further evidence that EXT girls' connectivity patterns reflect a bias toward inattention with preserved cognitive control (rather than disruptions in impulsivity and reward-motivated behavior), is that EXT girls relative to EXT boys show a tendency for stronger positive connectivity between medial prefrontal cortex and striatum and lateral prefrontal regions (288, 296). This suggests a lack of functional segregation between default mode (medial prefrontal cortex) and ventral attention networks which could lead to difficulties regulating attention. Additionally, EXT girls compared to EXT boys have been shown to exhibit weaker functional connectivity between the vmPFC and amygdala indicating a disconnect between top-down regulation of their emotions specifically motivated or driven by rewards (288). These findings suggest that sex differences in neural processing of risky decision-making, observed in our study and elsewhere, may

stem from overall sex differences in the strength and functional connectivity of, and thus the balance between, cognitive control and reward-motivated networks.

25.2.2.c. Our findings in the context of EXT reward/cognitive control network imbalance

Therefore, sex differences in neural processing of cognitive control and reward network regions observed in this dissertation may be driven by the dominance of reward-related circuits interacting with impulsivity in boys, contrasting with complex cognitive control mechanisms involving attention and flexibility in girls. Girls seem to engage a broader set of brain regions related to cognitive control (e.g., dmPFC, inferior prefrontal cortex) with some attentional network connectivity deficits which might indicate that their challenges lie more in maintaining attention within tasks rather than in reward-based impulsivity, which may be where boys' deficits lie. Thus, while both sexes show relationships between brain connectivity and EXT behaviors, the underlying neural mechanisms appear to be sex-specific, with boys' behaviors more driven by reward processing and girls' behaviors more affected by attention regulation and cognitive flexibility.

25.2.3. Trait impulsivity, task motivation, risky decision-making neural processing, and SUD risk

As discussed in Chapter Three with the NAc findings, impulsivity also likely affects the relationship between risky decision-making neural activation and substance use. For example, one study found that in males, larger NAc volume was associated with increased sensation seeking, which mediated higher likelihood of alcohol use, while in females, NAc volume directly predicted alcohol use *without* mediation by sensation seeking (253). Therefore, levels of trait impulsivity, which we did not examine here,

likely play a larger role in the relationship between reward network processing during decision-making and real-world substance use outcomes in EXT males. In our sample, the proportions of ADHD subtypes including hyperactive/impulsive, inattentive, or combined type, were significantly different between males and females with relatively more inattentive type females and more combined type males. Therefore, these sex-based differences in circuitry, influenced by impulsivity or attention biases, could be impacting our findings. Future analyses should adjust for ADHD subtypes and/or measures of impulsivity and attention.

Another possible explanation for the NAc sex difference in risky decision-making and substance use outcomes, and one that also possibly relates to the impulsivity and reward-network dominance in males, is the interaction of self-reported motivation on decision-making tasks and sex. One study in healthy youth found a sex difference in NAc activity during a risky decision-making task where boys' increased neural response was partially explained by the boys' self-reported higher motivation to earn money and therefore perform well on the task (300). This type of money-motivation driving a sex difference in neural processing could certainly be present in our sample of sensation-seeking, impulsive boys performing a task where they were told they would earn cash based on their task performance. It is possible that the omission of factors such as impulsivity, measures of attention, and task motivation in our models may explain why our results indicate a lower rate of substance use associated with these neural processes rather than an increased risk for substance use (for males in particular) and/or why some results which did follow our hypotheses did not meet significance. Future research should consider incorporating these critical metrics, as they could provide a more comprehensive

understanding of the underlying mechanisms and better inform interventions aimed at preventing substance use.

25.2.4. Investigating hypotheses based upon reward anticipation findings in prior research using the Monetary Incentive Delay task

In addition to the explanations above, another reason for the surprising findings in the second manuscript, specifically, could be that our hypotheses were developed in response to conflicting prior research regarding whether increased or blunted NAc activation during reward anticipation predicts future substance use. Reward anticipation refers to a phase of the Monetary Incentive Delay task (MID), a task developed by Knutson et al. with the purpose of disentangling motivational processes underlying reward and punishment (301-303). Reward anticipation in the MID task is measured during the interval between the presentation of a cue indicating the possibility of winning money and the participant's cue to press a button to claim it (303). The MID task and the BART both assess decision-making processes related to rewards, but they differ in their focus and structure. The MID task primarily examines reward anticipation and motivation, while the BART assesses risk-taking behavior and decisions. Thus, the MID task analyzes reward anticipation (cue) and feedback (reward notification), whereas the BART focuses on decision-making under risk and uncertainty. However, elements shared in both tasks include the assessment of reward processing, association with impulsivity (169, 304), choices motivated by possibility of reward, and phases of the task where rewards are being anticipated. Currently there is no study which examines the differences in neural processing of the MID task and BART. Therefore, the interpretation of how the task components of choosing to inflate or choosing to win in BART can be compared to

reward anticipation in the MID task are speculative based on prior findings with each task. This gap in the literature presents an interesting direction for future research on the relationship between MID task and BART activation patterns, future substance use, and how the activation patterns of each task interrelate.

Returning to conflicting prior evidence, normal activation in healthy adolescents and adults during reward anticipation appears to be greater activation in the NAc, and specifically the right NAc (301, 305). Therefore, it may be expected that what is abnormal (*lower/blunted* NAc activation during reward anticipation) would be associated with increased substance use; and indeed, this association has been found in several studies with healthy young adults (306). However, this relationship appears to be altered in those with family history of alcohol use disorder (AUD): despite showing blunted NAc activation during reward anticipation compared to controls (180, 183, 307), it is *increased* NAc activation during reward anticipation in these individuals that is associated with their greater current alcohol consumption (183), future alcohol problems (185), and initiation of substance use by age 16 (186). These studies also found that greater impulsivity was associated with less NAc activation (180, 183) and the best model predicting initiation of substance use by age 16 was one that controlled for EXT behaviors and family history of AUD (186). Therefore, the sensitivity of the NAc to rewards, and consequently the risk for substance use, appears to be significantly influenced by externalizing traits and a family history of SUD. Lastly, as previously discussed, another study using the MID task in adolescents also found a sex difference in the predictability of NAc activation during reward anticipation for substance use: higher activation in boys, but blunted activation in girls, predicted increased alcohol use (308).

The relationship between reward processing during the MID task in the NAc and substance use appears to be quite complex and likely affected by EXT traits, sex, and the genetics and/or environmental factors related to family history of AUD.

To better interpret these MID task findings alongside our results from the BART, we must consider which phase of the BART most closely resembles reward anticipation. 'Choose Win' seems the most analogous as it also involves the anticipation of a monetary reward contingent upon the participant's current action/choice. As our findings were derived from a contrast of Choose Inflation versus Choose Win (Choose Inflation versus Choose Win), a decrease in activation in our contrast may align more with the greater activation observed during reward anticipation in the MID studies. This comparison is tenuous given the different imaging tasks, making it difficult to draw clear comparisons, but given this as the best comparison with prior work, then our findings of increased Choose Inflation – Choose Win activation associated with decreased risk of problematic substance use would possibly align with prior findings: if prior work shows increased NAc reward anticipation activation associated with increased substance problems, then a greater value in our contrast means less reward anticipation (potentially less NAc Choose Win) and therefore, fewer substance problems, which is the appropriate opposite of prior findings. In conclusion, our findings may align with some of the relationships uncovered in past work with the MID task and substance use risk, while the discrepancies in prior research—stemming from complex relationships between reward anticipation and EXT traits, family history of SUD, and sex—may help explain some of the unexpected results in our manuscript.

Overall, our findings suggest that the relationship between NAc and sgACC activation during risky decision-making and future substance use may be highly sex dependent. Additionally, both EXT traits and genetic predispositions to substance use appear to influence these relationships, adding complexity to the interpretation of these neural mechanisms in the context of risk. It is worth noting that we controlled for family history of SUD in our sample, and this variable did not significantly differ between groups, which helps rule out family history as a confounding factor in our findings. These complexities emphasize the need for more nuanced research into the relationship between sex, brain activation, EXT traits, genetic risk, and substance use behavior.

26. Theoretical Implications

Overall, to summarize the preceding discussion, our findings suggest that sex differences in risky decision-making neural processing deficits associated with EXT psychopathology, substance use, and their interrelationship reflect a dysregulation and imbalance between the cognitive control and reward networks in EXT youth. And, most notably, this imbalance is influenced by sex and, likely, impulsivity traits. It is well established that both cognitive control and reward networks are dysregulated in EXT psychopathology, with research even suggesting it may be this very imbalance between executive function and reward processing which leads to EXT traits and psychopathology (49, 146). With this understanding, however, the nuances of how sex affects network disruption has yet to thoroughly be explored, particularly in the context of risky decision-making. In this space, our findings have significant theoretical implications for understanding the neural circuitry dysregulation underlying EXT disorders as our findings suggest that cognitive control and reward networks' balance in EXT youth likely

differs by sex and also may interact with individual traits levels of impulsivity and genetic/environmental risk factors like family history of SUD. Therefore, not only are our findings extremely interesting in how they indicate that EXT youth's neural processing of risk may predict their risk for problematic substance use in a sex-specific manner, but also our findings suggest that EXT youth's underlying neural deficits associated with their EXT psychopathology may be unique to sex, as well. Further, it warrants more investigation what, if any, *are* the risky decision-making neural deficits for EXT females as in our studies, they did *not* differ from control youth and were *not* shown to be at significantly increased risk for problematic substance use. Our EXT females' attention and emotion regulation circuits are likely still disordered or they would not meet sufficient criteria for DSM-5 defined EXT diagnoses, but it is interesting that their cognitive control and reward network neural processing in our analyses appears sufficiently "normal" as it relates to lower rates of problematic substance use and being more similar to control females function compared to their EXT male counterparts.

Overall, the intriguing and potentially surprising sex differences observed in our male and female participants with EXT psychopathology highlight a critical gap in the literature that has yet to deeply explore underlying neuropathology in EXT females. Our findings underscore the need for further investigation into how sex influences well-established models of risky behaviors, particularly models involving EXT traits and disorders and how they relate to the increased susceptibility for SUDs.

27. Practical Implications

Lastly, the practical implications of this dissertation fall within the field of behavioral therapy interventions which incorporate appropriate risky decision-making

skills into evidence-based cognitive behavioral therapy (CBT) interventions. Our findings could be applied to further improve these kinds of therapies, an approach with which our laboratory has extensive experience, expertise, and a proven record of success. The best example of this is how Dr. Leslie Hulvershorn and collaborators Drs. Zachary Adams and Peter Finn developed the Impulsive Decision Reduction Training for Youth (IDRT-Y) to address the need for effective interventions targeting impulsive decision-making in adolescents by adapting a similar program initially designed for adults (287). IDRT-Y is a structured, 8-session CBT model that aims to help youth identify and modify their harmful decision-making patterns, similar to those identified in this dissertation and other analyses with youth at risk for substance use in our group (138, 161, 163, 309, 310). The intervention therapy program focuses on enhancing adolescents' ability to consider long-term consequences when making choices and teaching more effective, adaptive strategies to stem impulsive and risky behaviors. In one case report of a 16-year-old boy with strong EXT traits and a history of making poor, unsafe decisions, who completed the IDRT-Y program, the youth showed significant reductions in impulsivity, substance use, and both internalizing and EXT symptoms. Additionally, there was a notable improvement in his ability to consider the potential future consequences of his decisions (287). Our clinical research group's success in this area of integrating targeted risky decision-making improvement provides a feasible model of translating the findings from this paper to therapeutic interventions for substance use prevention in high-risk youth.

The specific areas of decision-making which could be targeted by these types of therapies in a sex-specific manner to reduce substance use risk involve focusing on conflict monitoring and loss avoidance during the choice phase of decision-making. The

first study's male-specific findings in the choice phase as the choices became riskier (parametrically modulated) were in the dmPFC/dACC, which, as part of the cingulo-opercular/salience network, support cognitive control, task-set maintenance, sustained attention, and salience detection (97, 98) and are essential for behavioral flexibility, particularly in maintaining internal goals and conflict monitoring (105, 226-228). The dmPFC specifically plays a significant role in set-shifting and response inhibition (229-233). In the second study, EXT males relatedly did not see a significant association between increased subgenual ACC activation during risky versus safe choice and problematic substance use. The sgACC plays a critical role in loss avoidance (114-120). Therefore, the lack of increased sgACC activation in EXT males during risky choices suggests a dysfunction in the neural mechanisms that are typically involved in evaluating risk and avoiding loss and tendency to not properly identify safe vs risky choices, likely resulting in higher engagement in risky behaviors such as substance use. When combining the findings from both studies, it becomes clear that EXT males may struggle with monitoring the conflict of changing risk levels associated with choice and responding according to the potential for losses during risky decisions. Given this, targeted behavioral (or medication) therapy for EXT males should focus on improving impulse control, conflict monitoring, and risk evaluation. Specifically, interventions could address 1) reducing impulsive behavior in decision-making (i.e., stimulant treatment) and helping males pause and reflect before making high-risk decisions, 2) conflict monitoring through enhancing awareness of signals indicating the possibility of negative outcomes and improving the ability to recognize when it is appropriate to avoid risky choices, and 3) improving overall risk evaluation in weighing long-term

consequences versus immediate rewards of risky choices, helping better predict and avoid negative outcomes.

For EXT females, our findings may be hopeful in that they indicate EXT females might not carry the same increased risk for substance use as EXT males, and if at increased risk, not from the same risky decision-making deficits. Our second manuscript revealed significant overall and female-specific associations between NAc activation during risky versus safe choice and lower rates of problematic substance use. The NAc connects reward experiences to appropriate emotional and motivational aspects (109, 110). Based on the female-specific findings in the NAc, where increased modulated activity during risky versus safe choice was associated with less problematic substance use, a potential target for behavioral therapy could focus on appropriately assigning emotional and motivational value, as risk increases, particularly for females who lack this skill. Further, for males, whose decreased rates of problematic substance use were not significantly related to brain activation as risk increased but rather on average when making risky versus safe choices, a potential deficit in their decision-making (also supported by the previously discussed findings) may involve recognizing signals of increasing risk of a negative outcome (e.g., in the BART, the balloon expanding). Therefore, therapy for EXT males should aim to improve overall risk assessment through enhancing their ability to recognize varying risk levels carried by different choices in decision-making.

In conclusion, supporting the development of impulse control and conflict monitoring in EXT males, as well as improving their risk evaluation skills, may be effective in reducing their tendency to make risky choices and therefore reduce their risk

of problematic substance use and SUD. For EXT females, who may not exhibit the same deficits in risky decision-making as their male counterparts, focusing on enhancing emotional and motivational value assignment and proper loss avoidance during risk-related decisions could help prevent substance use problems. Lastly, these suggested risky decision-making skills could practically be integrated into CBT-type interventions in a manner which our clinical-research group has already had success designing and implementing for addressing impulsive decision-making in adolescents at risk for substance use. Potentially, the suggestions from this dissertation's findings could be incorporated into the existing IDRT-Y used by our group and investigated to further refine and enhance therapeutic strategies for high-risk youth in a more sex-specific fashion, ultimately improving outcomes in substance use prevention.

28. Limitations

The work presented in this dissertation has several limitations which should be acknowledged when interpreting the findings and when considering future directions. One significant limitation are the smaller sample sizes in both manuscripts, particularly with the female control group in the first manuscript which makes the result in the inferior temporal gyrus, where they are significantly different from every group, harder to interpret and less dependable. The smaller sample size of the female control group may have reduced the statistical power of the study, potentially affecting the reliability of the results. That being said, part of the motivation for utilizing the Kruskal-Wallis method in the first manuscript for the group level whole brain analysis was that this method, which is a non-parametric version of an ANOVA that relies on ranking values and then comparing groups on ranked values, was more robust to unbalanced/unequal variance

between our small and uneven groups. Additionally, the sample sizes likely contributed to the lack of significance after correction for multiple comparisons in the second manuscript. Although, as discussed above, our findings are consistent with prior literature, the smaller sample size limits our ability to generalize these results to larger, more diverse populations. However, as a primary motivation and driving factor for the work presented in this dissertation was the dearth of research in females with EXT psychopathology, these preliminary studies are exciting and important in that they addressed the questions others have ignored and indeed found sex differences in neural processing during risky decision-making and its association with future problematic substance use which warrant further investigation. Future studies with larger sample sizes are needed to validate and extend our findings. In addition to our sample size, one factor that may be affecting the significance of our findings in the second manuscript is the relatively small number of participants reporting problematic substance use. This aligns with a nationwide trend of youth engaging in substance use behaviors later and less frequently, particularly after the COVID-19 pandemic, a pattern also observed in the ABCD study (311, 312). This trend may limit the ability of even larger studies than ours to achieve the statistical power necessary for these analyses. Unfortunately, despite a general decline in substance use after the pandemic, drug overdose deaths have been rising among adolescents in recent years due to the increased lethality of fentanyl products present in a variety of drugs of abuse (313). Therefore, research into the sex-specific SUD risk profiles of substance-naïve youth is crucial for prevention efforts.

A strength of this dissertation lies in its evaluation of youth with clinician-diagnosed, DSM-5 based ADHD and disruptive behavior disorders, rather than relying

solely on EXT traits like impulsivity or sensation-seeking, which are commonly used in other studies investigating risk profiles for SUDs. By focusing on a specifically identifiable population—youth with diagnosed EXT disorders—our sample offers more targeted and clinically relevant insights into the risk profile for SUDs. This approach enhances the precision of our findings and their potential to inform interventions tailored to individuals with these diagnoses.

Furthermore, as we hoped to begin to address with the gender sensitivity (Chapter Two) and gender diverse (Chapter Three) analyses, our studies were underpowered to incorporate gender diversity (cisgender vs. transgender) into our analyses—though the results of the supplementary analysis in the second study support the need to consider gender in larger, more robust samples. While research on sex assigned at birth in the areas studied here is already limited, there is even less research exploring how gender identity interacts with the relationships between risky decision-making, EXT psychopathology, and substance use outcomes. This limitation highlights the need for future studies with larger, more diverse samples to better understand the role of gender in these associations. Future research incorporating diverse gender identities is crucial, as it can address the overlooked disparities in substance use and mental health outcomes within these populations. Previous research highlights the significance of this future work due to the well-understood fact that sexual and gender minorities (SGM) have been shown to engage in more problematic substance use and higher rates of drug and alcohol use disorders compared to their heterosexual and cisgender peers, often exacerbated by experiences of discrimination (278-280). Their heightened vulnerability to SUDs is potentially linked to EXT behaviors and ADHD, as individuals in these groups often

exhibit increased impulsivity and sensation-seeking tendencies—both of which are known contributors to SUD (279, 281, 282). Additionally, the increased prevalence of ADHD and other mental health challenges in these populations (282) further underscores the need for more targeted research, as this association between EXT-like behaviors in SGM individuals and SUD risk has not been explicitly studied. Only one study, by Hoenigl et al., has examined the interaction between risky decision-making, EXT traits, and substance use in a SGM population, but this study focused solely on men who have sex with men, limiting the opportunity to explore sex differences. Additionally, the study was cross-sectional and conducted with adults who were not substance-naive, and therefore could not address risk or prevention factors. That all being said, the authors found sensation-seeking and impulsivity behaviors were a key factor in risky decision-making deficits and substance use among men who have sex with men, and also found these EXT traits further associated with a real-world risk prevention outcome of HIV pre-exposure prophylaxis adherence (314). These findings underscore the likely interaction of EXT traits and environmental stressors in SGM populations and real-world risk taking, supporting the need for more research like that presented in this dissertation to incorporate SGM identities and populations. For our first manuscript, the fact that removing adolescents whose gender did not align with their guardian’s identification of their sex in our gender sensitivity analysis did not significantly alter our findings suggests that using guardian-identified sex from the baseline assessment was a reasonable approach given the small sample size. But the small alterations to the findings in our second manuscript when adjusting for gender suggests future studies must consider more comprehensive data on gender identity to better capture these variables' effects.

Further, in the first study's whole-brain analysis, the inability to include covariates like IQ and pubertal development stage—factors shown to influence risky decision-making (198-204) and interact with sex differences in our EXT sample's BART neural activation (167), respectively—complicates the interpretation of our results, as we cannot fully assess whether adjusting for these factors would have altered the observed group differences in brain activation. Another limitation regards the self-report data from guardians and youth to assess substance use in the second study, as urine drug screens were not feasible due to the COVID-19 virtual protocol. Self-reporting carries potential biases, such as social desirability, memory issues, and underreporting (289-291), which could affect data accuracy. However, our use of both guardian and child reports for problematic substance use outcome may have helped mitigate these biases and provide a more comprehensive representation. Another limitation affecting the entirety of the dissertation is the high-risk, EXT sample's use of psychotropic medications, which could influence brain activation and substance use behaviors. Medication dosage varied widely across our sample and fewer than one-third of our ADHD participants were medicated at baseline. Further, medications were withheld for at least 24 hours before the MRI session and baseline assessments, and participants who had not followed this protocol were excluded from each analysis. While medication effects could influence results, participants were not under the immediate effects of psychostimulants during assessments. Recruiting a sample entirely naive to psychotropic drugs would have been unrealistic as well. Additionally, for the second manuscript, while we focused on two brain regions known to show abnormal activation in individuals with EXT disorders and substance use, a whole-brain analysis would provide a more comprehensive view of the

neural processing of risk potentially associated with substance use risk, but it would require a larger sample size, as even our current *a priori* region-of-interest analysis did not survive correction for multiple comparisons. Finally, another limitation characterizing each study is an unbalanced sex distribution, with fewer females than males possibly resulting in some statistical artifacts. While this ratio reflects the broader EXT population, future studies should include a larger, more balanced sample to better explore sex differences. However, a strength of this dissertation is its novel examination of sex differences in substance use risk within a population of ADHD and disruptive behavior disorder subjects, a group not previously studied in this context.

Despite these limitations, our study provides preliminary, exciting mechanistic insights into sex differences in risky decision-making neural processing and substance use risk in EXT youth. Regarding sex-specific risky decision-making neural mechanisms in EXT youth which could be targeted for substance use prevention, interventions could focus on impulse control, conflict monitoring, and risk evaluation strategies for males, while encouraging proper loss avoidance and motivational valence ascription for females. This approach would focus on improving self-regulation and decision-making under risky conditions, with the goal of reducing substance use risk across sexes. Overall, we hope that the findings in this dissertation encourage further research into sex differences in adolescent risk profiles for SUD with larger, more diverse samples.

29. Future Directions

Building on the gaps and unanswered questions raised by this dissertation's work, future research should focus on several key areas to expand our understanding of how sex affects the relationship between neural activation, risky decision-making, and substance

use outcomes. First, replication with a larger, more diverse sample like the ABCD study and dataset is essential to validate these preliminary findings and improve the generalizability of the results. In addition to increasing sample size, future studies could examine how individual EXT traits such as sensation seeking and impulsivity influence the relationship between brain activation during risky decision-making and substance use outcomes. Understanding how these traits interact with neural activation patterns could provide a more nuanced view of the mechanisms underlying substance use risk, particularly in at-risk populations like those with EXT disorders.

Another promising direction for future research involves tracking deficits in risky decision-making neural processing as it precedes or follows substance use over time. This dissertation highlighted distinct patterns of brain activation in males and females during risky decision-making, particularly in brain regions of the cingulo-opercular and reward circuits *before* exposure to substances. These networks are implicated in cognitive control, conflict monitoring, and impulse inhibition and reward processing—all critical processes in regulating risky behavior. Future work could further investigate whether these neural differences between sexes change over time and with the initiation of substance use to further clarify the issue of risky decision-making neural activation deficits preceding problematic substance use, resulting from substance use, or both. Again, a study design like the ABCD, with a much larger sample and repeated neuroimaging tasks over time, will hopefully be able to address this—an increasingly promising possibility with other recent neuroimaging work being able to explore how neurodevelopmental variability in brain structure predicts substance use initiation and the

risk of later substance involvement and mental health disorders in the ABCD sample (315, 316).

Given the sex-specific patterns we observed in decision-making deficits and neural activation, future research could explore how tailored, sex-specific interventions could be developed. For example, based on the findings that males with EXT disorders exhibit dysregulated cognitive control and heightened activation in the dmPFC/dACC, interventions could focus on impulse control, conflict monitoring, and risk evaluation, particularly in males. And, with our preliminary finding that greater activation during risky choice, as that choice became riskier, in the reward network area of emotional/motivational valence ascription (NAc) was associated with less problematic substance use in the overall EXT sample and in females specifically, a future behavioral target could involve focusing on appropriately assessing and evaluating the meaning of increasing risk for decisions, particularly for females who may not show this skill. Behavioral therapies that enhance self-regulation and improve decision-making under risky conditions could be beneficial, helping individuals distinguish between safe and risky choices—a key factor in managing their heightened risk for substance use disorders.

The incorporation of therapies and interventions targeting risky decision-making deficits is not new and has proven efficacy as evidenced with our group's IDRT-Y, discussed above in section. This approach has been shown to produce promising outcomes such as decreased binge drinking and improved future orientation (287). Similar to how the IDRT-Y develops attention-regulation skills, future orientation, and the consideration of long-term consequences to help modify youth's maladaptive decision-making habits, future therapies could incorporate strategies targeting the deficits

identified in this dissertation around impulse control, conflict monitoring, loss avoidance, and understanding the emotional/motivational reasons for selecting an option given its level of risk. Theoretically, interventions aimed at improving realistic and appropriate risky choice processing could help reduce the risk of problematic substance use by addressing decision-making deficits.

Overall, the findings and conclusions from this dissertation call for future research to examine sex differences in decision-making and brain activation patterns and how these differences can distinguish sex-specific SUD risk profiles. Further, we hope that the preliminary insight presented in this dissertation may serve to guide the development of targeted, sex-specific interventions for SUDs for youth at the highest risk for problematic substance use. By investigating how sex and specific cognitive, emotional, and behavioral targets interact, and change over time, we can better understand the unique risk profiles of males and females with EXT disorders and design more effective prevention strategies for this population.

30. Concluding Remarks

This dissertation provides critical insights into sex differences in risky decision-making among youth with EXT disorders, particularly regarding their neural mechanisms of risky decision-making and implications for their SUD risk. The findings reveal that sex and EXT psychopathology influence brain activity during risky decision-making, particularly within the cingulo-opercular network, including the dmPFC and dACC, the reward circuit, including the NAc and the sgACC. In males with EXT disorders, dysregulated cognitive control, and heightened activation in these regions during risky choices, suggest the need for targeted behavioral therapies focusing on impulse control,

conflict monitoring, and risk evaluation. In contrast, females with EXT disorders exhibit significant associations between lower problematic substance use and appropriate responses in areas like the NAc and sgACC when making risky choices. Our preliminary findings of how risky decision-making neural mechanisms, and how they relate to real-world substance use outcomes, may function differently in males and females with EXT psychopathology highlight sex-specific targets for behavioral interventions.

The findings presented in this dissertation have the potential to contribute to both scientific knowledge and clinical approaches. In the scientific space, there has been a significant gap in investigating sex differences in EXT youth's SUD risk phenotype as that phenotype was primarily established and validated in EXT males. We hope the findings presented here that sex differences do exist in the relationship between risky decision-making neural activation and real-world substance use encourages further evaluation of how sex differences in EXT youth's risk profile may relate to the sex differences seen in SUD. The clinical and therapeutic implications involve targeting sex-specific brain activation patterns related to risky decision-making, which are associated with the risk of problematic substance use, through prevention and intervention strategies that address the unique decision-making strengths of EXT males and females. In conclusion, these insights aim to guide future research and therapeutic strategies by exploring how sex differences in neural processing of risky decision-making relate to real-world substance use behaviors, thereby laying the groundwork for personalized interventions that improve decision-making and reduce substance use risk during adolescence.

Finally, the work presented in this dissertation has facilitated significant skill development, personal and professional growth, and knowledge acquisition, while also laying the foundation for the author's future career as a clinician-scientist in addiction psychiatry. Through conducting the experiments and analyses outlined herein, I have gained firsthand experience in designing and executing imaging studies with human subjects, including running MRI protocols with resting-state, structural, task-based, and DTI scans. I learned MRI data preprocessing, as well as subject-level and group-level analyses of imaging data. I have applied new statistical techniques to analyze imaging data, explored behavioral tasks associated with substance use risk, and was exposed to longitudinal study methods and data management. Additionally, I have collaborated with teams of psychiatrists, statisticians, epidemiologists, psychologists, and social workers to brainstorm project ideas, develop hypotheses, and craft presentations aimed at communicating science effectively to a broad audience. Collaborating with this interdisciplinary team has enhanced my ability to critically identify gaps in our understanding of psychiatric disorders and addiction, and to formulate scientific questions, hypotheses, and methods to address these gaps. The practical skills, knowledge, and scientific thinking framework, or philosophy, I have gained throughout the completion of my doctoral work have greatly prepared me for integrating translational research into my future career as an addiction psychiatrist. I intend to complete my medical doctorate, pursue psychiatry residency and addiction fellowship, and seek early career awards to establish a neuroimaging laboratory or a neuroimaging data science lab as an early career addiction psychiatrist. I am deeply grateful for the support of those acknowledged in the Acknowledgments section, without whom this work and my

personal and professional development would not have been possible. I am excited for the next stage of my training and eager to apply the skills and insights developed through my Medical Neuroscience doctoral training to the next steps in my career.

APPENDICES

Appendix A: Box-Transformations

Appendix A.1. ANCOVA Assumptions Test Results for BART Behavior

Performance Variables

Table A1. Results of Levene's Test for Homogeneity of Variance and Shapiro-Wilk Test for Normality Across BART Behavior Performance Variables

Behavior Outcome	Levene's F	p	Shapiro Stat	p
Average Adjusted Pumps	0.67	0.57	0.99	0.13
Average Money Bet	0.63	0.59	0.99	0.20
Choose Inflate Count	1.97	0.12	0.98	0.04
Choose Win Count	1.03	0.38	0.97	< 0.01
Outcome Explode Count	0.47	0.70	0.99	0.14
Balloons Completed	0.66	0.57	0.95	< 0.01
Reaction Time (ms)	3.98	< 0.01	0.94	< 0.01

$p < 0.05$ indicates a violation of the respective assumption; violation of either test would qualify the variable for Box-Cox transformation

Appendix A.2. Lambda Box-Cox Plots for Behavior Variables Violating ANCOVA

Assumptions

Figure A1. Lambda Box-Cox Plot for Choose Inflate Count

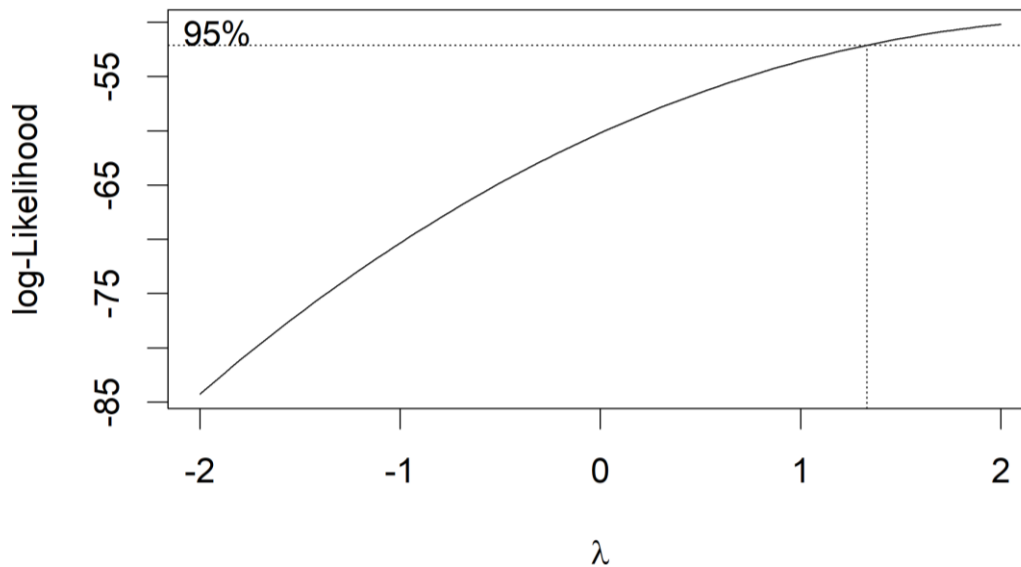


Figure A2. Lambda Box-Cox Plot for Choose Win Count

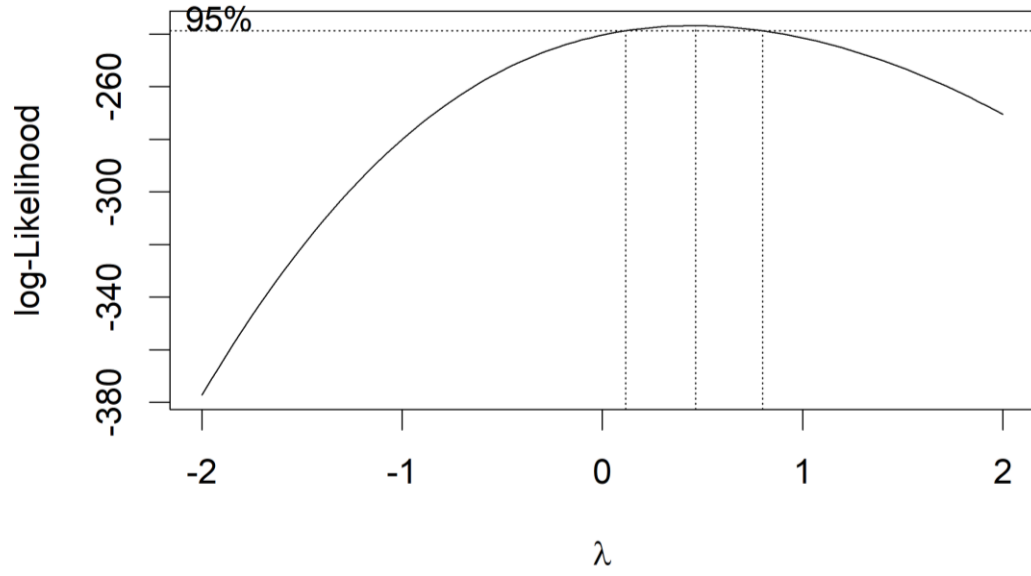


Figure A3. Lambda Box-Cox Plot for Balloons Completed

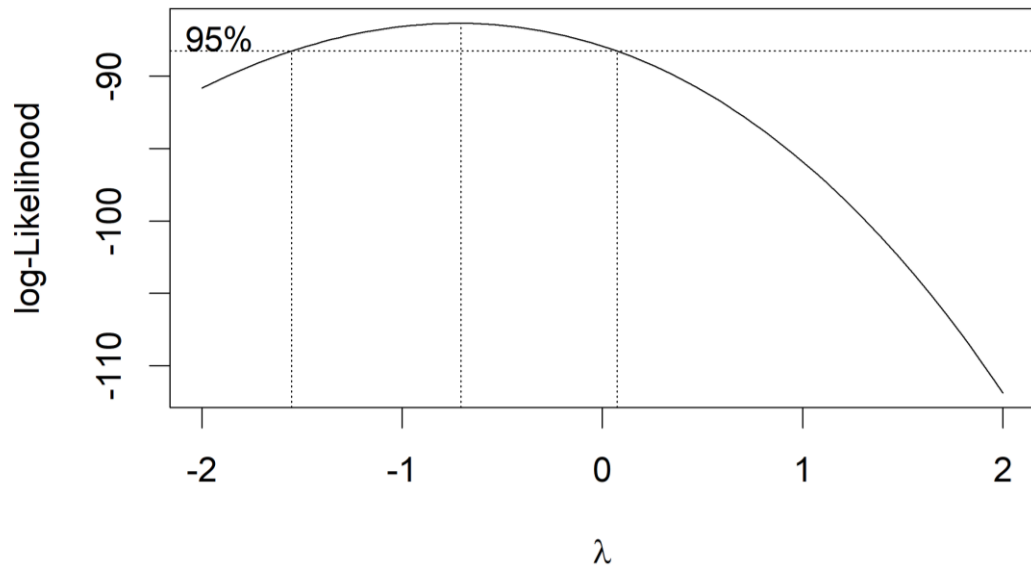
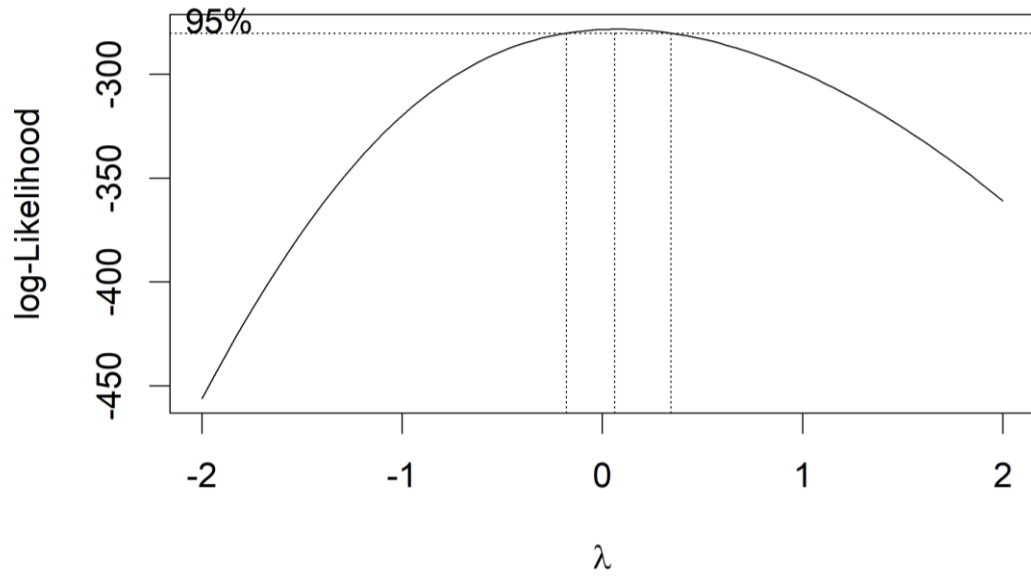


Figure A4. Lambda Box-Cox Plot for Reaction Time



Appendix A.3. Histograms of Behavior Variables' Distributions Before and After the Appropriate Box-Cox Transformation

Figure A5. Raw (Left) and Transformed (Right) Histograms for Choose Inflate Count

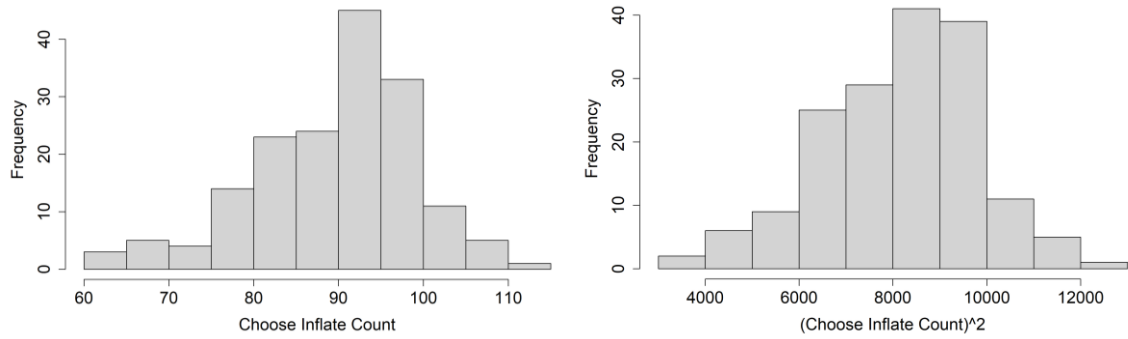


Figure A6. Raw (Left) and Transformed (Right) Histograms for Choose Win Count

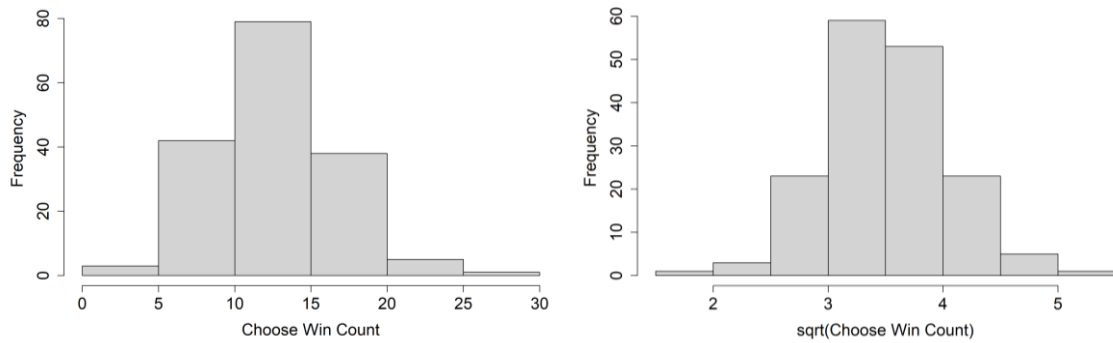


Figure A7. Raw (Left) and Transformed (Right) Histograms for Balloons Completed

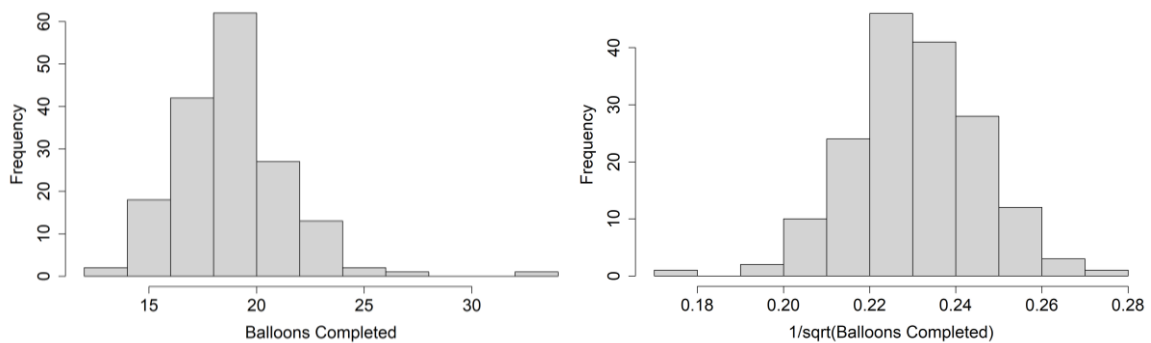
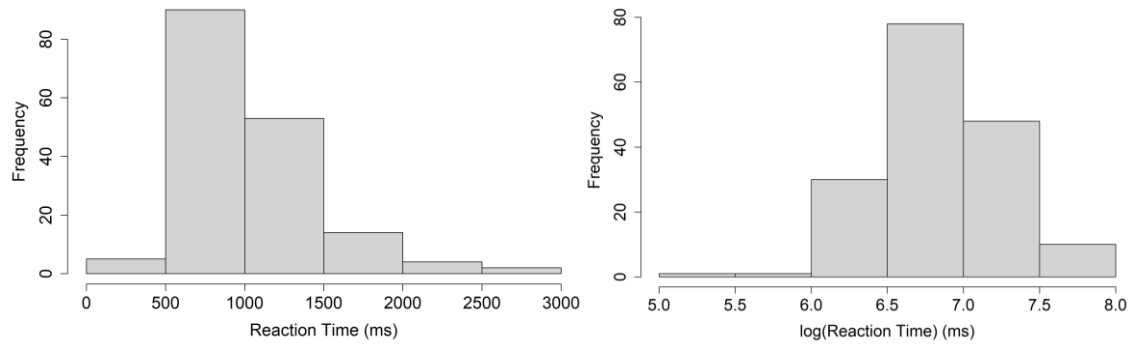


Figure A8. Raw (Left) and Transformed (Right) Histograms for Reaction Time



Appendix B: Stepwise AIC Model Selection Results

Akaike Information Criterion (AIC) stepwise model selection revealed the optimal, simplified model predicting problematic substance use included the z-score of average brain activation, sex, family history of SUD, the traumatic violence subscale of the Screen for Violence Exposure (SAVE), and the average score of parental monitoring. Each covariate besides family history of SUD was present in every model (as shown in Table A2 below), and due to family history of SUD's well-established genetic liability for SUD (178, 179), we included it as a covariate in the final model. Gender was excluded from the stepwise model selection due to the limited representation and unbalanced sample of gender diverse youth. An exploratory analysis was conducted to examine its effects in the main models and this was presented in the Supplementary Material.

Table A2: Unadjusted and Adjusted AIC for Each Contrast and Region of Interest (ROI)

<u>Contrast</u>	<u>ROI</u>	<u>Unadj.</u> <u>AIC</u>	<u>Adj.</u> <u>AIC</u>	<u>Sex</u>	<u>FH</u> <u>of</u> <u>SUD</u>	<u>SES</u>	<u>SAVE</u> <u>TV</u>	<u>SAVE</u> <u>IV</u>	<u>PM</u>
CICW_mod	left sgACC	248.04	238.59	1	0	0	1	0	1
CICW_mod	left NAc	249.47	238.67	1	0	0	1	0	1
CICW_mod	right sgACC	248.93	238.32	1	0	0	1	0	1
CICW_mod	right NAc	243.71	232.92	1	0	0	1	0	1
CICW_unmod	left sgACC	248.18	238.05	1	0	0	1	0	1
CICW_unmod	left NAc	249.64	238.80	1	1	0	1	0	1
CICW_unmod	right sgACC	249.39	238.48	1	0	0	1	0	1
CICW_unmod	right NAc	247.24	234.74	1	0	0	1	0	1
OEOI_mod	left sgACC	249.00	238.17	1	0	0	1	0	1
OEOI_mod	left NAc	248.60	237.79	1	1	0	1	0	1
OEOI_mod	right sgACC	249.59	238.36	1	1	0	1	0	1
OEOI_mod	right NAc	248.38	237.45	1	1	0	1	0	1
OEOI_unmod	left sgACC	247.39	238.63	1	0	0	1	0	1
OEOI_unmod	left NAc	249.70	238.80	1	1	0	1	0	1
OEOI_unmod	right sgACC	249.37	238.81	1	1	0	1	0	1
OEOI_unmod	right NAc	249.24	237.87	1	0	0	1	0	1

FH of SUD = family history of substance use disorder, SES = socioeconomic status, proxied here with maximum parental education, SAVE TV = traumatic violence exposure, SAVE IV = interpersonal violence exposure, PM= parental monitoring; NAc = nucleus accumbens, sgACC = subgenual anterior cingulate cortex, CICW = Choose Inflate—Choose Win contrast, OEOI = Outcome—Outcome Inflate contrast, mod = parametrically modulated activation with probability of balloon explosion, unmod = not parametrically modulated/averaged across all events; 1 = that covariate was included in the adjusted model for that ROI/contrast, 0 = that covariate was *not* included in the adjusted model for that ROI/contrast

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316. Miller AP, Baranger DAA, Paul SE, Garavan H, Mackey S, Tapert SF, et al. Neuroanatomical variability associated with early substance use initiation: Results from the ABCD Study. *medRxiv* (2024) doi: 10.1101/2024.03.06.24303876

Curriculum Vitae

Olivia Kay Murray

EDUCATION

Indiana University School of Medicine Indianapolis, IN
Medical Scientist Training Program June 2020-Present
M.D. Expected May 2027

Indiana University

Ph.D. in Medical Neuroscience May 2025

Washington University in St. Louis St. Louis, MO

B.A. in Biology: Neuroscience May 2020

Minors: Medical Humanities, Sociology

HONORS AND AWARDS

Indiana University School of Medicine Indianapolis, IN

- 2021 IUSOC Research Team Member of the Year May 2021
- Jack Bauer Honor Fund Travel Award July 2023
- IUSM Graduate Division's Student Volunteer of the Year Award April 2024
- Addiction, Grief, Attachment Recovery Conference: October 2024

Medical Student Scholar Award

- Inclusive Excellence Travel Grant February 2025

American Academy of Addiction Psychiatry September 2022

- John Renner Travel Award to the 33rd Annual Meeting and Scientific Symposium

College on Problems of Drug Dependence March 2024

- 2024 CPDD NIDA Women & Sex/Gender Junior Investigator Travel Award

National Center on Youth Prevention, Treatment, and Recovery February 2025

- Registration award for 2025 Joint Meeting

Washington University in St. Louis St. Louis, MO

- Arts and Sciences Honors: Magna Cum Laude with Thesis May 2020
- Phi Beta Kappa

RESEARCH EXPERIENCE

Indiana University School of Medicine Indianapolis, IN

PI: Leslie Hulvershorn June 2021, June 2022-Present

Ph.D. graduate student

- Adolescent ADHD and substance use risk, neuroimaging

PI: David G. Clark July 2021

Research Assistant: MSTP summer research rotation

Student Outreach Clinic November 2020-May 2023

- Analyze longitudinal patient data for quality improvement
- Organized project to track clinic's care of housing insecure patients

Laboratory of Neurophenomics June-July 2020

PI: Alexander B. Niculescu III, M.D., Ph.D.

Research Assistant: MSTP summer research rotation

Washington University in St. Louis St. Louis, MO

Biology Department May 2020

PI: Jonathan Peelle, Ph.D.

Research Emphasis in Biology with Thesis:

Assessing Long-Term Perceptual Learning in Normal Hearers with Noise-Vocoded
Speech

Washington University School of Medicine

St. Louis, MO

Department of Otolaryngology

August 2017-May 2020

PI: Jonathan Peelle, Ph.D.

Research Assistant: Cognitive Neuroscience Lab

- Worked with subject data analysis and entry
- Analyzed and organized results with Excel
- Planned experiment and ran participants
- Honors project in Biology-Neuroscience

Albert Einstein College of Medicine

Bronx, NY

Dominick P. Purpura Department of Neuroscience

June-July 2018

PI: Jose Pena, M.D., Ph.D.

Research Assistant: Summer Undergraduate Research Program

- Recorded multi-electrode arrays in barn owls
- Wrote MATLAB code for multi-electrode data analysis
- Attended two conferences with the Neuroscience department

PUBLICATIONS

1. Crum KI, Aloi J, Zimet GD, Aalsma MC, Smoker MP, Korin TE, **Murray OK**, Marimirofa CE, Hulvershorn LA. Profiles of HIV-Related Knowledge and Self-Regulation Factors in At-Risk PreAdolescents. *Children's Health Care*. July 2023. DOI: 10.1080/02739615.2023.2231339.

2. Hulvershorn LA, Weinstein S, Bixler K, Smoker MP, **Murray OK**, Hammond C. Identifying Cannabidiol (CBD) Research Priorities Relevant to Child and Adolescent Psychiatry. *Adolescent Psychiatry*. October 2023. DOI: 10.2174/2210676613666230901143219.
3. Aloï J, Korin T, **Murray OK**, Crum KI, Dziedzic M, Hulvershorn LA. 3.46 Latent Profiles of Impulsivity and Emotion Regulation in Children with Externalizing Disorders are Associated with Altered Striatocortical Connectivity. *Journal of the American Academy of Child & Adolescent Psychiatry*. October 2023. DOI: 10.1016/j.jaac.2023.09.211.
4. Hill MD, Gill SS, Le-Niculescu H, MacKie O, Bhagar R, Roseberry K, **Murray OK**, Dainton HD, Wolf SK, Shekhar A, Kurian SM, Niculescu AB. Precision Medicine for Psychotic Disorders: Objective Assessment, Risk Prediction, and Pharmacogenomics. *Molecular Psychiatry*. February 2024. DOI: 10.1038/s41380-024-02433-8.
5. Smoker MP, **Murray OK**, Peck M, Hulvershorn LA. Earlier Substance Use and Differential Rates by Substance Class for Youth With Combined Externalizing Disorders and Family History of Substance Use Disorders. *Drug and Alcohol Dependence*. July 2024. DOI: 10.1016/j.drugalcdep.2023.110739.
6. **Murray OK**, Matthey-Mora PP, Aloï J, Abu-Sultanah M, Smoker MP, Hulvershorn LA. Sex Differences in Cingulo-Opercular Activation During Risky Decision-Making in Youth with Externalizing Disorders. *Psychiatry Research: Neuroimaging*. April 2025. DOI: 10.1016/j.psychresns.2025.111965.

ABSTRACTS AND PRESENTATIONS

1. **Murray OK**, Ferger R, Beckert MV, Fischer BJ, Pena, JL. *Population Coding and Spectrotemporal Tuning in the Owl Optic Tectum*. Albert Einstein Summer Research Poster Session and Washington University Fall Undergraduate Research Symposium. July 2018 & October 2018. **Poster Presentation**
2. Symposia, Case Conference, Medical Update, and Case Summaries. Symposium I summary authors: Cignarella AG, **Murray O**, Nguyen F. *The American Journal on Addictions*. 2023;32(2):211-6.
3. Smoker MP, Crum KI, Oliver AP, **Murray OK**, Chemilis-Santiago JR, Finn PR, Aalsma MC, Hulvershorn LA. *Earlier Substance Use and Differential Rates by Substance Class for Youth with Combined Externalizing Disorders and Family History of Substance Use Disorders*. The College on Problems of Drug Dependence 85th Annual Meeting in Denver, Colorado. June 2023. **Poster Presentation**
4. Aloï J, Korin TE, **Murray OK**, Crum KI, Dziedzic M, Hulvershorn LA. *Latent Profiles of Impulsivity and Emotion Regulation in Children with Externalizing Disorders are Associated with Altered Striatocortical Connectivity*. American Academy of Child and Adolescent Psychiatry 70th Annual Meeting in New York, New York. October 2023. **Poster Presentation**
5. **Murray OK**, Matthey-Mora PP, Aloï J, Smoker MP, Hulvershorn LA. *Sex Differences in Risky Decision-Making Brain Activity in Youth At-Risk for Substance Use*. The College on Problems of Drug Dependence 86th Annual Meeting in Montreal, Canada. June 2024. **Oral Presentation**

6. **Murray OK**, Matthey-Mora PP, Aloï J, Abu-Sultanah M, Smoker MP, Hulvershorn LA. *Sex Differences in Risky Decision-Making and Brain Activation in Youth at Risk for Substance Use*. 2025 Joint Meeting on Youth Prevention, Treatment, and Recovery in Baltimore, Maryland. March 2025. **Poster Presentation**

NON-RESEARCH PUBLICATION

Murray O. Girls must learn to see themselves as scientists. Northwest Indiana Times. 2018. https://www.nwitimes.com/opinion/columnists/guest-commentary/guest-commentary-girls-must-learn-to-see-themselves-as-scientists/article_c97ccb9b-19bc-567e-9855-17c876ee11f3.html

CODING LANGUAGES

R, MATLAB, Linux, AFNI

CLINICAL EXPERIENCE

IU Health

Indianapolis, IN

Family Medicine Shadowing Participant

August-December 2021

- 12 hours total
- Interviewed patients, reported to attending physician, wrote SOAP notes
- Observed clinical decision making and relationship building in outpatient setting

Barnes-Jewish Hospital, Emergency and Trauma Center

St. Louis, MO

Emergency Department Shadowing Participant

January-May 2019

- 5 hours per week, every other week

- Observed patient histories, physical examinations, and triaging of patient care
- Discussed emergency cases with residents and medical students
- Shadowed a variety of trauma and emergent care procedures

Barnes-Jewish Hospital, Department of Neurology

St. Louis, MO

Shadowing Participant-10 hours total

August-December 2018

Associated Neuro & Psychological Specialties

Valparaiso, IN; June-August 2016

- Worked one-on-one with patients ages 5-80
- Daily administered and scored neuropsychological and intelligence tests
- Integrated patient information into new Electronic Health Records system

LEADERSHIP AND ACTIVITIES

Psychiatry Student Interest Group

Indianapolis, IN

Co-President of Events

May 2024-Present

- Oversee all executive board positions, plan executive board meetings, connect medical students with opportunities to explore interest in psychiatry, organize service/volunteer projects, complete all compliance documentation necessary, including end-of-year reports, to re-register as a student interest group
- Plan and promote career development events, organize service/volunteer projects, and organize networking events

Co-President Overseeing Mental Health Clinic

May 2022-May 2024

- Oversee all executive board positions, plan executive board meetings, connect medical students with opportunities to explore interest

in psychiatry, organize service/volunteer projects, complete all compliance documentation necessary, including end-of-year reports, to re-register as a student interest group

- Run the free mental health clinic at the Student Outreach Clinic: coordinate with psychiatrists and schedule licensed coverage for each clinic, train and serve on-call for clinic managers, facilitate student volunteer sign-ups, and communicate with patient referrals about upcoming clinic days and coordinate patient visits to the clinic sometime during the week prior to clinic.

Vice President of Events May 2021-May 2022

- Plan and promote lunch talks, communicate with speakers for career development events, organize service/volunteer projects

IU MSTP Diversity Equity and Inclusion Committee Indianapolis, IN

Vice President May 2022-Present

Secretary May 2021-May 2022

Interview Process Analysis Sub-committee November 2020-Present

- Led sub-committee on the development of post-interview survey

IU MSTP Combined Degree Student Council Indianapolis, IN

Co-President February 2023-Present

- Interface with directors and MSTP students to improve program experience
- Plan, organize, and execute annual summer retreat

Vertical Mentoring Team Captain June 2022-Present

- Organize mentoring events, coordinate reimbursement for events, facilitate networking for fellow MD/PhD students

Class Representative

June 2020-February 2023

WashU Alumni and Parents Admissions Program

Chair of the Indianapolis Committee

May 2022-March 2024

- Oversee committee of 14 volunteer interviewers, assign interviews to interest-matched volunteers, address interviewee or interviewer concerns, work in-person recruitment events, personally interviewed 50 applicants for the 2022-2023 and 80 for the 2023-2024 cycles

Volunteer Interviewer

May 2020-Present

Addiction Awareness Student Interest Group

Indianapolis, IN

Member and Narcan Packing Volunteer

October 2021-Present

VOLUNTEER EXPERIENCE

Overdose Lifeline

Indianapolis, IN

Narcan Kit Packing

July 2022-Present

IUSM Student Outreach Clinic

Indianapolis, IN

Patient Navigator

November 2020-February 2023

- Call 5-6 clinic patients weekly to help patients establish health insurance and primary care

Mental Health Day Coordinator (with Psych SIG)

July 2021-May 2024

- Take histories and perform psych screeners for patients presenting with mental health concerns

- Recruit volunteer psychiatrists and medical students to provide free mental health services

Indiana University School of Medicine

Indianapolis, IN

Growth Through Guidance

April 2023-Present

- Present to high school classrooms and small groups about medical careers
- 1-1 mentorship with students to grow interest and answer questions regarding careers in medicine and STEM

Community Outreach and Engagement

March-May 2021

Administered COVID vaccines to public