# EXAMINING BIOPSYCHOSOCIAL RISK FACTORS FOR ADULTHOOD DEPRESSION: INVESTIGATING THE ROLE OF CHILDHOOD TRAUMA, ADOLESCENT REWARD-RELATED NEUROCIRCUITRY, AND REWARD LEARNING

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CERTIFICATE OF APPROVAL

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This is to certify that the Ph.D. Dissertation of

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# Abbreviations

ACC – Anterior Cingulate Cortex
AFNI – Analysis of Functional Neuroimage
ASR – Adult Self Report
BA – Behavioral Activation
BDI-2 – Beck Depression Inventory, 2nd edition
BOLD – Blood-Oxygen-Level-Dependent
CBT – Cognitive Behavioral Therapy
CDI – Childhood Depression Inventory
CTQ – Childhood Trauma Questionnaire
DBS – Deep Brain Stimulation
DMN – Default Model Network
DSM-V – Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EEG – Electroencephalogram
EPI – Echo-Planar Imaging
GAD – Generalized Anxiety Disorder
fMRI – Functional Magnetic Resonance Imaging
FD – Framewise Displacement
FDA – Food & Drug Administration
FSL – FMRIB Software Library
HiTOP – Hierarchical Taxonomy of Psychopathology
ICA – Independent Component Analysis
iFC – Intrinsic functional connectivity
IQ – Intelligence Quotient
lme – Linear Mixed Effects
mm – Millimeters
ms – Milliseconds
MDD – Major Depressive Disorder
MDE – Major Depressive Episode
MNI – Montreal Neurological Institute
mOFC – Medial Orbitofrontal Cortex
mPFC – Medial Prefrontal Cortex
MRI – Magnetic Resonance Imaging
NIMH – National Institute of Mental Health
NAcc – Nucleus Accumbens
OLS – Ordinary Least Squares
PFC – Prefrontal Cortex
rACC – Rostral Anterior Cingulate
RCT – Randomized Control Trial
RDoC – Research Domain Criteria
ROI – Region of Interest
rsFC – Resting-State Functional Connectivity
RT – Reaction Time
SES – Socioeconomic Status

SSRI – Selective Serotonin Reuptake Inhibitors
SNRI – Selective Norepinephrine Reuptake Inhibitors
STAR*D – Sequenced Treatment Alternatives to Relieve Depression
TE – Time to Echo
TI – Inversion Time
TR – Time to Repetition
VS – Ventral Striatum
VTA – Ventral Tegmental Area
WOF – Wheel of Fortune

# Abstract

Depression rates have been on the rise and represents one of the leading causes of disability worldwide. Not only has the rise of depression rates impacted adults significantly, but the trend of depression starting at younger ages, peaking during adolescence to early adulthood, adds to the severity of this mental health crisis. While depression itself is problematic, experiencing depression also increases the risk of suicide by three-fold, which is the second leading cause of death in the adolescent to young adult age group. It is essential to identify risk prior to disease onset, as simply experiencing a single episode of depression has been shown to associated with subsequent risk for other psychosocial and biological impairments. To stifle this alarming trend, a shift in the mental health field needs to be refocused on prevention, because despite considerable empirical efforts, the efficacy of gold-standard treatment for depression remains low, with only a marginal percentage of adults and adolescents retaining remission. One way to perhaps foster improved preventative strategies is to identify those with potential risk factors and identify the developmental origins of psychopathology to assist in decreasing the odds for the development of future, long-term consequences of depression.

For these reasons, research has aimed to identify early biopsychosocial markers related to depression onset and increased severity. Progress in the field of neuroimaging has identified aberrant reward circuitry as a potential endophenotype for depression and substantial developmental research has highlighted prominent reward-related neurodevelopment occurring during this time. While there are a multitude of influences taking place during this adolescence to emerging adulthood period (i.e., hormonal, neurodevelopmental, and psychosocial changes) that may increase susceptibility for psychopathology development, it also represents an optimal window to study, as it may provide opportunities for resiliency due to greater brain plasticity.

Yet, depression etiology is not solely neurobiological and to improve our understanding of the pathogenesis of depression, the interaction among biological and environmental influences for increased risk of depression will better represent the multi-factorial nature of the disease. Fortunately, advancements in the understanding and value of an integrative developmental approach, coupled with prospective longitudinal study designs, enhance our ability to examine biopsychosocial features of risk and resiliency markers of psychopathology.

The overarching goal of the present work is to examine specific neurobiological and psychosocial risk factors across adolescence to young adulthood to improve our understanding of factors that may contribute to psychopathology risk. Chapter 1 outlines the potential for developmental origins of psychopathology and summarizes the extant literature on adolescent neurodevelopment, and select neurobiological and psychosocial risk factors (i.e., reward-related circuitry and childhood trauma) of future depression. Chapter 2 introduces the original study sample, re-recruitment strategies, study and neuroimaging protocols, and clinical measures assessed to longitudinally predict depression symptoms in adulthood. Chapter 3 details the results of the dissertation aims focusing on: 1) neurobiological risk factors of depression (implementing both task-based functional magnetic resonance imaging (fMRI) and resting-state functional connectivity (rsFC)), 2) childhood trauma, a psychosocial risk factor of depression, and 3) the integrative role of childhood trauma on the identified neurobiological and depression relationships. The findings from these aims are discussed in depth in Chapter 4. Together, the results from this project demonstrate the importance of incorporating biopsychosocial risk factors in future research in order to improve our understanding of pathways to future depressive symptoms in adulthood. It is hoped that these findings will help to inform future work and underscore the importance of biopsychosocial approaches for identifying risk factors.

# Chapter 1. Introduction

*(Portions of this chapter are currently under review for publication)*

## 1.1 Defining a global health problem

Depression rates in adults continue to climb and represent a significant public health problem (Mojtabai & Olfson, 2020; Weinberger et al., 2018), with depression being one of the leading causes of disability worldwide (Ferrari et al., 2013; Friedrich, 2017; Vos et al., 2012). An estimated 21 million adults have been impacted by depression (Bromet et al., 2011; Strashny et al., 2023; U.S. Department of Health and Human Services, 2021). Depression rates continue to rise in adolescents, as well (McGrath et al., 2023; Merikangas et al., 2010), with the peak onset for depression being during adolescence to emerging adulthood (15 to 20 years) (McGrath et al., 2023). Experiencing a depressive episode is a substantial risk factor for suicide, and by the year of 2018, suicide became the second leading cause of death in 10–24-year-olds (CDC, 2021; Heron, 2019, 2021). In 2023, a steep incline in suicidal ideation was also observed among adolescents, largely in assigned females at birth, with a significant increase in annual emergency visits for suicidal ideation being the highest recorded (128 per 10,000) (Strashny et al., 2023; Weinberger et al., 2018). Although this steep increase in rates of depression and suicide among youth has led to a national state of emergency in mental health, following the COVID-19 pandemic (American Academy of Pediatrics, 2021), there remains substantial room for improvement in the field of mental health care. These alarming statistics in adolescents underscore the importance of studying developmental risk factors of depression during a time when risk may be heightened and before the onset of clinical-level symptoms for improved preventative intervention.

It is particularly important to study risk factors and support prevention efforts prior to the onset of a full major depressive disorder (MDD) (as opposed to intervention), because simply experiencing a single depressive episode has significant negative impacts on future health

outcomes (Murray et al., 2015). For example, people who experience depressive disorders have increased risk for cardiovascular disease, hypertension, diabetes, stroke, obesity, and increased risk of mortality after a cardiovascular event (Joynt et al., 2003; Lespérance et al., 2002; Penninx et al., 2013), advanced aging – measured via telomere length often studied as a marker of cellular aging (Müezzinler et al., 2013; Schutte & Malouff, 2015), and earlier cognitive decline (Rapp et al., 2011). All of these physical health problems place greater stress on family systems and federal assistance programs (i.e., Medicare) (Joynt et al., 2003; Lynch & Clarke, 2006). Some hypothesize that physical health concerns in individuals with depression may be a consequence of the depressive symptoms themselves (i.e., psychomotor slowing, lack of motivation to engage in pleasurable activities); yet, emotional and physical sequela of depression may also be partly due to the underlying biological changes that make up an individual, such as alterations in brain structure and function, (see section 1.4 for more details), as well as macro- and micro-level systems that impact a person's developmental environment (Cui et al., 2024).

Depression occurs within a complex system and is often overlooked or conflated by typical developmental changes (i.e., hormones, brain development, social environment) during the adolescent to young adulthood period. While many significant relationships between depression and lowered social functioning (i.e., impaired family, peer, and romantic relationships), greater psychosocial impairments (i.e., higher rates of unemployment, poor academic success), and altered biological mechanisms (i.e., genetic and brain circuitry) exist (Avenevoli et al., 2008; Clayborne et al., 2019; Hammen et al., 2008; Pine et al., 1998; Zisook et al., 2007), these relationships are often bi-directional (Arnaud et al., 2022; Demidenko et al., 2022; McEwen & Akil, 2020). For example, greater exposure to early life stress has been shown to be associated with blunted reward response (McCrory et al., 2017), yet blunted reward

response has also been shown to predict life stressors and interpersonal conflict (Mackin et al., 2019). The interactions among these factors often go unexplored (Tang et al., 2020; Zajkowska et al., 2021), even though we have identified the importance of implementing an integrative biopsychosocial approach to improve our understanding of psychopathology (Cui et al., 2024). A lack of understanding of these complex systems, and lack of associated prevention strategies targeting such understanding, may be partially to blame for the continued rise in depression symptoms.

### *1.1.1 Depression heterogeneity, beyond simple diagnoses*

Depression is a multi-faceted mental health concern and impacts individuals in a variety of ways. The clinical symptoms that are associated with a full MDD diagnosis include: at least one of the primary core symptoms, either depressed mood or diminished interest or pleasure in activities that were once enjoyable (otherwise referred to as anhedonia). The core symptoms need to be accompanied by at least four other symptoms including: significant weight loss or gain, sleep difficulties (hypersomnia or insomnia), psychomotor agitation or slowing, fatigue or loss of energy, feeling of worthlessness, inappropriate guilt, trouble with concentration, and recurrent thoughts of death or suicide (American Psychiatric Association & Association, 2013), over a span of two contiguous weeks. It is important to understand that symptom clusters and severity can vary tremendously across individuals and over time and are defined by arbitrary lines that indicate “clinically significant” diagnostic categories; yet, this may limit generalizability of findings as they may only pertain to a very severe or specific group of individuals (Buch & Liston, 2021). While diagnostic categorizations are helpful in their practicality, they also often fall short in many regards. Currently, the DSM-V represents a syndrome-based, categorical approach targeted for clinicians. The benefits of the categorical

framework, such as the DSM-V, include: (1) common terminology that aids in communication across specialties, (2) providing a way to identify others with similar psychological phenomenon, and (3) helping to provide and guide specific recommendations or treatment strategies. However, researchers and clinicians in the field recognize that working within the confined, simple approximations and "clear-cut" diagnoses often ignore the heterogeneity across individuals and suggests that symptoms are unchanging. For these reasons, many initiatives have been set forth by the National Institute of Mental Health (NIMH), such as the Research Domain Criteria (RDoC) and Hierarchical Taxonomy of Psychopathology (HiTOP) frameworks, to improve our understanding of symptom clusters and different domains of human neurobehavioral functioning and to better capture heterogeneity of psychopathology symptoms. Thus, investigating symptoms of depression on a continuum, as well as co-morbid psychopathology symptoms and corresponding biopsychosocial features, may provide more insight into the heterogeneity in clinical presentations, better represent the community, and offer an improved understanding of the multiple systems within which interventions may intervene.

Both positive and negative affect are relevant for depression and clinically present very differently. For instance, increased negative affectivity (associated with the core symptoms of persistent sadness, guilt, worthlessness) and increased sensitivity to negative situations or feelings are common presentations seen in depression. On the other hand, diminished positive affect (i.e., anhedonia) and illustrated challenges with feeling positive reinforcement from activities traditionally shown to illicit positive emotions (i.e., rewards) is also observed in individuals with depression. Even though these two symptoms are core features of a "clinically significant" MDD, understanding how these symptoms differ from a neurobiological, psychosocial, and behavioral standpoint will help with improving tailored treatments for each

individual. Both adults and adolescents have been shown to commonly present with clinical symptoms of negative affect, such as persistent sadness or feelings of worthlessness (Rice et al., 2019), which from a neurobiological perspective is directed by serotonergic circuitry centered around the amygdala and medial prefrontal cortex (mPFC) (Phillips et al., 2015). Yet, it is worth noting that depression symptom presentations differ among adults and adolescents (Rice et al., 2019), with adults commonly displaying diminished positive affect, or anhedonia, more consistently than adolescents (Rice et al., 2019). Deficits in positive affective systems are thought to be modulated by dopamine and centered around the ventral striatum (VS) and mPFC regions (Phillips et al., 2015) (see section 1.4), and investigating disruptions in positive affective systems during adolescence through young adulthood are worthwhile, as this represents a sensitive time for significant reward-related behavioral and neurodevelopment changes (see section 1.2 for details). Namely, reward-related and affective systems are still largely undergoing significant changes, in parallel with significant hormonal changes that take place during puberty (Blakemore et al., 2010; Forbes & Dahl, 2010).

### *1.1.2 Treatment efficacy*

The gold-standard treatment for depression consists of a combination of medication (intervening at the neurobiological level) and psychotherapy (targeting cognitions and behaviors). The first line pharmacological treatment for depression is selective serotonin reuptake inhibitors (SSRIs); however, selective norepinephrine reuptake inhibitors (SNRIs) have been approved by the Food and Drug Administration (FDA) to treat treatment-resistant depression in adults. As reuptake inhibitors, SSRI and SNRIs are pharmacological interventions that act by inhibiting the reuptake or reabsorption of different neurotransmitters, chemical messengers that help neurons send signals to other nerve cells in the brain (Shelton, 2019). This

leads to a higher concentration and availability of neurotransmitters in the synaptic cleft, which in part works to improve depressive symptoms. That said, the impact of these pharmacologic interventions is slow and can take several weeks before patients notice positive benefits and may come with unpleasant side effects (i.e., gastrointestinal upset, fatigue, headaches, dizziness, sweating) (Strawn et al., 2023). Findings from a longitudinal study assessing the efficacy of treatments for depression, Sequenced Treatment Alternatives to Relieve Depression (STAR*D), also revealed that approximately half of the adults with MDD responded to first-line SSRI interventions and nearly a third failed to response to two or more alternative antidepressants (Rush et al., 2006; Souery et al., 2006), highlighting the need for better individualized treatment efforts based on objective markers in order to predict treatment response to different psychotropic medications.

Pharmacological therapy seems to improve quality of life via different mechanisms than psychotherapy (Hilt et al., 2014; Hofmann et al., 2017), thus the combination of the two has the strongest supported efficacy. Cognitive behavioral therapy (CBT) (Beck, 1970), an evidence-based psychotherapy intervention has been shown to provide amelioration of depressive symptoms in adults and adolescents (Hofmann et al., 2012; March et al., 2004; Méndez et al., 2021). A specific form of CBT and therapeutic skill taught to individuals with depression is behavioral activation (BA), coined by psychologist Peter Lewinsohn (Lewinsohn, 1974; Lewinsohn & Shaffer, 1971). This treatment focuses on behavioral principles set out by Skinner and colleagues (Skinner, 1963; Skinner, 2019) and focuses on the connection between behaviors and feelings through positive reinforcement. Specifically, this line of treatment promotes interactions with situations that may provide potential reinforcement, while decreasing avoidance behaviors. Of note, while there is a large focus on CBT, as it has received the most empirical

support, there are many other psychotherapeutic strategies that may improve symptoms of depression that are worth further exploring.

Despite these considerable empirical efforts and findings on treatment outcomes, the efficacy of gold-standard treatment for depression remains low; treatment of adult depression has been shown to be only 20-50% effective (Fournier et al., 2010; Trivedi et al., 2006), treatment of adolescent depression 55-70% effective (Brent et al., 2008; March et al., 2004), and remission rates also remain low (approximately 30% for adults) (Papakostas et al., 2008). Treatment response seems to vary tremendously by the individual, initial depression severity, (Fournier et al., 2010; Kirsch et al., 2008), and developmental age (Driscoll et al., 2005; Gregory E. Simon & Roy H. Perlis, 2010; Zhang et al., 2019), suggesting that studying individual differences across a transitional developmental period may be of benefit. Given low rates of treatment success, moving toward treatment strategies based on neurobiology and behavior, across a wider developmental period, such as adolescence to young adulthood, may improve treatment efficacy and diminish long-term consequences of depression.

With these notions in mind, this dissertation seeks to examine specific neurobiological and psychosocial risk factors across adolescence to young adulthood to gain a better understanding of factors that may contribute to depression risk and treatment success. The following sections of this introduction chapter will describe: the importance of studying predictors of depression during adolescence, a unique developmental period (Section 1.2), and a general overview of risk factors for depression (Section 1.3). Then in greater detail, there will be discussion of *two* key adolescent risk factors of adulthood depression, including: 1) neurobiological risk features (reward-related circuitry) (Section 1.4) and 2) the influence of other psychosocial risk factors, childhood trauma (Section 1.5), as well as the importance of

understanding potential brain-behavior relationships (Section 1.6). Finally, the objectives of the current study will be detailed in (Section 1.7).

## 1.2 Transitional period of adolescence and developmental origins of psychopathology

The peak age of first onset for any mental health disorder is approximately 15 years old, with depression, anxiety, and alcohol use disorder being the most prevalent (McGrath et al., 2023). Yet, the age range for onset of many mental health disorders spans young adolescence into young adulthood (12-36 years) (McGrath et al., 2023), which makes this an especially unique time to study the development of a significant mental health concern, such as depression. This developmental age range represents not only the peak time of onset for depression, it is also a time characterized by significant neurodevelopmental changes (Casey et al., 2008; Mills et al., 2021; Spear, 2013) and represents a unique time for environmental and psychosocial changes (i.e., increased autonomy, risk tasking), as well. Studying neurobiological and psychosocial factors across this developmental period may assist with identifying predictive features among those who go on to develop greater risk for psychopathology.

### *1.2.1 Adolescence is a unique transitional period*

Adolescence is defined broadly as the developmental phase between childhood and adulthood and is unique in that is represents a period of development characterized by distinct physical, cognitive, behavioral, and social changes (Blakemore & Mills, 2014; Forbes & Dahl, 2010; Fuhrmann et al., 2015; Knoll et al., 2015; Mills et al., 2014). Increased risk-taking behaviors and shifting social landscapes (i.e., shifting focus away from the immediate family and caregivers to social relationships) are both developmentally appropriate and essential for adapting and gaining skills to make a successful transition to autonomy in adulthood; however,

increased sensation seeking and risk taking, greater desire to explore novel situations (i.e., social interactions with peers), and changes in motivated, goal-directed behavior, to obtain more rewards may also make this developmental time period particularly relevant when studying the emergence of depression.

The beginning of adolescence is typically agreed upon as the time of puberty onset (Blakemore et al., 2010; Herting et al., 2015; Spear, 2000; Susman et al., 1987), with the onset of puberty notably occurring earlier and earlier in recent generations (Ledford, 2018). The end of the adolescent window is more unclear and is largely dependent on cultural, social, and individual factors, as there is no single physical marker to indicate the onset of adulthood. Sociocultural values primarily indicate the beginning of adulthood, as this is when adolescents attain certain milestones or achieve social roles (i.e., moving out of their childhood home, reaching legal ages to make individual choices (drinking age, voting), marriage, and parenthood (Sawyer et al., 2018; Steinberg & Icenogle, 2019). Although the end of adolescence is proposed to occur at a time evidenced by increased autonomy set by societal standards, this framework tends to disregard the neurodevelopmental research suggesting that critical brain regions continue to develop well into the third decade of life (Giedd et al., 2015; Miller et al., 2015; Mills et al., 2014; Sowell et al., 2001; Tamnes et al., 2017). Given the societal changes and delays in these transitional roles – such as increased age upon completing a college education, moving out of a childhood home permanently at a later age, and postponed marriage and parenthood (Dasen, 2000; Galván, 2021), research across this unique transition period should mirror these societal changes and incorporate the findings from neurodevelopment research. Studying the window of adolescence to young adulthood will be important, given the unique changes in goal-directed behavior, as well as evolving psychosocial influences. This window of

development represents both a time of increased susceptibility to the onset of psychopathology and an optimal time for intervention due to greater brain plasticity and opportunities for resiliency (Crone & Dahl, 2012; Do et al., 2017; Telzer, 2016).

### *1.2.2 Adolescence is a unique period for neurodevelopment*

Advances in the field of magnetic resonance imaging (MRI) have allowed researchers to improve our understanding of the developing brain. Seminal structural MRI studies on adolescent brain development have largely demonstrated a linear increase in white matter from childhood through adolescence, and cortical gray matter demonstrated non-linear, "U-shaped" decreases that were regionally specific (Giedd et al., 1999; Jernigan & Tallal, 1990; Sowell et al., 2001). For instance, somatosensory and visual cortices matured earlier than higher-order cortical gray matter, such as the PFC (Gogtay et al., 2004). Similarly, cortical and subcortical structure and volumes display a pattern of non-linear development, which varies as a function of brain region and sex assigned at birth (Jones et al., 2023; Mills et al., 2016; Mills et al., 2021). Importantly, understanding typical neurobehavioral features and how they might contribute to greater risk for depression is crucial to explore across this unique period, as there are large heterogeneities and individual differences in these neurodevelopmental processes that may make some individuals more prone to the development of mental health disorders compared to others.

Functional magnetic resonance imaging (fMRI) is a method used to indirectly measure neuronal activation underlying brain organization and function. FMRI is grounded in the assumption that when the brain is active, it requires more energy in the form of glucose or oxygen which increases the blood flow to specific neurons through a process called hemodynamic response (Ogawa, Lee, Kay, et al., 1990; Ogawa, Lee, Nayak, et al., 1990). Thus, fMRI measures fluctuations in blood-oxygenation (oxyhemoglobin and deoxyhemoglobin)

through the blood-oxygen level dependent (BOLD) signal (Bandettini et al., 1992; Fox & Raichle, 2007; Posner & Raichle, 1994). BOLD signal can be measured while engaged in a cognitive tasks (task-based fMRI) or "stimulus-free" (i.e., resting-state fMRI, rs-fMRI), which is measuring brain activation under limited demands to understand correlated fluctuations of BOLD signal across different brain regions (Biswal et al., 1995). Using this non-invasive tool to visualize and collect information about brain activity and neural communication patterns during adolescence may help shed light on typical brain development, as well as how these processes may go awry to help identify at-risk populations and improve our knowledge of the development of psychopathology.

### *1.2.3 Adolescence is a unique period for heightened sensitivity to reward*

As part of this underlying neurodevelopmental period, adolescence is often characterized by heightened sensitivity to reward and greater tendency for risk-taking, as hypothesized by several neurodevelopmental model heuristics of adolescence (imbalance model, dual systems (Casey et al., 2008; Steinberg, 2008), suggesting the typical brain system maturation may be in part contributing to adolescent behaviors. Broadly, these heuristics highlight that typical adolescent brain development is defined by a protracted maturation of top-down, cognitive control systems compared to bottom-up, reward-related brain systems, which may potentially explain some of the observed heighted drive by rewards and sensation seeking seen during this time; however, it should be noted that these models do not entirely capture the complexities of adolescent behavior (Sherman et al., 2018). While some reward seeking behaviors are adaptive and developmentally appropriate (Crone & Dahl, 2012; Dahl et al., 2018), increased risk taking can also lead to consequential behaviors (i.e., substance use, reckless driving) (Braams et al., 2016). Adolescent researchers have illustrated consistently that reward sensitivity exhibits a

curvilinear pattern across age with a peak in reward sensitivity during mid-adolescence and then stabilization thereafter (Blankenstein & van Duijvenvoorde, 2019; Braams et al., 2015; Ernst et al., 2005; Galván, 2010; Galvan et al., 2006; Shulman et al., 2016; van Duijvenvoorde et al., 2016; van Duijvenvoorde et al., 2022). The timing of these reward-related neural sensitivities also coincides with a rise in depression risk and suggests reasons to study how reward-driven mechanisms may confer vulnerability for depression. Similarly, typical adolescent mesocorticolimbic reward system development occurs within the context of the environment, and individual experiences may alter the developmental trajectory of the brain resulting in long-term changes in reward-associated behaviors. Since adolescent reward-related behavior is developmentally unique, (van Duijvenvoorde et al., 2014) and young adulthood is a period during which the majority of psychopathology first onsets, seeing how the neurobiological features of adolescent reward circuitry predict adult behavior may provide insight to first-line treatment targets.

### 1.3 Biopsychosocial risk factors for adulthood depression

The etiology of depression is still largely unknown, yet the field has agreed that the pathogenesis of depression is complex and multi-factorial. Depression has been shown to be associated with specific genetic factors (PCLO, piccolo presynaptic cytomatrix protein, dopamine receptor D2, DRD2, positive family history) (Gotlib et al., 2014; Howard et al., 2019; Ike et al., 2023; Joormann et al., 2009; Kendall et al., 2021; Sullivan et al., 2000), temperamental traits (negative affectivity, neuroticism) (Kendler & Gardner, 2011), neurobiology (reward-related and fronto-limbic dysregulation) (An et al., 2024; Phillips et al., 2015), and stressful environments (family conflict, low income, maltreatment) (Chapman et al., 2004; McLaughlin et al., 2020), and chronic disease (Moussavi et al., 2007). Studying the development of

psychopathology then should not solely be based on biological and environmental influences *separately,* but rather the interaction between risk factors and how psychosocial and neurobiological features might shape different paths to elevated psychopathology risk and protection (Bronfenbrenner & Ceci, 1994; Dennison et al., 2019). As demonstrated through the multiple iterations of the DSM diagnostic manual, phenotypes of mental illnesses are ever changing, nonlinear, and discontinuous (Hayes et al., 2007), which emphasizes that there may be multiple contributing factors that impact overall mental health and disrupted behavior. Investigation among multiple levels of risk, including neurobiological and psychosocial factors, illustrates the transactional nature of these relationships and need to study them in combination.

While the underlying pathological mechanisms of depression are complex and depression is rather heterogeneous, it is rare that a single biological and psychosocial measure can predict all individuals at risk. However, for the purposes of this dissertation and based on the availability of data in our lab, the present study will focus on reward-related neurocircuitry, a biological risk factor of depression, and childhood trauma, a psychosocial risk factor of depression, to achieve better clarity on the predictive capability of the integration of these factors to confer adulthood depression risk and severity.

### 1.4 Reward-related neurobiology as a risk factor for depression

Despite known negative effects of depression on quality of life and future productivity, the neurobiological features associated with depression onset are just beginning to be understood (Nielson et al., 2021). Core features of depression involve reduced pleasure, decreased goal-motivated behavior, and persistent low mood which have been proposed to be reflective of underlying neurobiological differences in reward processing and network circuitry. To that end, dysfunctional reward circuitry (as measured via fMRI) has been consistently implicated in adult

depression (Russo & Nestler, 2013), and this system withstands changes that are developmentally unique to adolescence (as described above), making this an optimal time to investigate risk, prior to disease onset. For example, the neurobiological phenotype of blunted neural response to reward has been shown to be more pronounced in depressed individuals under 18 years old (Keren et al., 2018), suggesting this timeframe may offer greater opportunities for discovery and impact.

The mesocorticolimbic system is heavily implicated in depression, as this brain network sets the groundwork for interpreting expected and experienced rewards, as well as regulating emotional responses to rewarding stimuli (Behrens et al., 2007). The VS engages in multiple aspects of reward processing, such as encoding expected rewards and motivation to obtain future rewards (Haber & Knutson, 2010). The nucleus accumbens (NAcc), part of the VS, receives excitatory afferents from the ventral tegmental area (VTA) of the mid-brain (Albertin et al., 2000; Berridge & Kringelbach, 2008; Berridge et al., 2009; Morrison et al., 2017), as well as cortical signals from the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) (Haber & Knutson, 2010). The VS-VTA connection is essential for anticipation and encoding of rewards (i.e., drug, food, social engagements). The connections between the VS and the ACC and medial OFC, which are typically implicated in regulatory, attentional, and affective neural circuitry, reward-related decision making, and emotion regulation when facing behavioral outcomes, are also pivotal in reward circuitry (Rushworth et al., 2007; Rushworth et al., 2011; Rushworth & Behrens, 2008). Broadly the medial PFC is crucial for regulating reward-directed behaviors and assessing information about outcomes within the decision-making process. More specifically, the medial OFC has been shown to be involved in evaluating environment-centered or externally driven reinforcers (Bouret & Richmond, 2010), modulating bottom-up activity from reward

responses, and guiding behavioral selection based on predicted reward outcomes (Izquierdo et al., 2004; Ongür & Price, 2000). The ACC plays important roles in monitoring and integrating information about behavioral consequences and encoding reward expectation, which warrants its strong connection to the VS (Behrens et al., 2007; Haber, 2016; Haber & Knutson, 2010; Van Leijenhorst et al., 2010). Dampened response to rewards leading to disruptions in one's ability to use rewards to guide and regulate behavior, as may be the case in specific depression presentations, might represent an important neural feature to investigate when aiming to identify future risk.

### *1.4.1 Reward response and anticipation in depression*

Disruptions in reward processes are central neurobiological mechanisms shown to be associated with depression (Phillips et al., 2015; Pizzagalli, 2014; Russo & Nestler, 2013). Though reward processing is multidimensional, working within the domains of affective, motivation, and learning processes (Berridge et al., 2009), blunted reward response during reward anticipation and outcome have commonly been identified in adults and adolescents with present depressive symptoms and have been used to predict later depression risk and severity (Forbes, 2020; Forbes et al., 2006; Pizzagalli et al., 2009).

Studies utilizing fMRI in adults with current MDD illustrated a blunted VS response to anticipation of reward (Eckstrand et al., 2019; Greenberg et al., 2015; Weinberg et al., 2015; Weinberg & Shankman, 2017), as well as reward outcome (Guyer et al., 2006; Satterthwaite et al., 2015; Smoski et al., 2011; Steele et al., 2007; A. E. Whitton et al., 2016). Adults with depression also have been shown to exhibit a decreased ability to *sustain* positive affect in the NAcc, with a lessened reward positivity response (Burkhouse et al., 2018; Heller et al., 2009). Together, meta-analyses showed concordance among studies in adults with depression, such that

compared to healthy controls, adults with depression showed decreased activity in areas, such as the striatum (caudate, putamen, accumbens), thalamus, insula, and cerebellum during reward processing (Ng et al., 2019; W.-N. Zhang et al., 2013). Additionally, this phenotype is present even in adults with *remitted* MDD, (Boger et al., 2014; Rzepa et al., 2017; Weinberg & Shankman, 2016; Alexis E. Whitton et al., 2016) providing some support that this neurobehavioral phenotype *may act as a trait level* difference in depression trajectories. Yet notably many of the previous studies conducted in adults did not indicate whether their samples had experienced a single episode or multiple episodes of depression. This lack of specificity may be limiting our understanding of symptom chronicity and potential differentiation of underlying neurobiology. While there are limitations with the interpretation of previous methods, the depression literature in adults has consistently outlined disruptions in VS mediated reward processes across the spectrum of depression severity. Though useful, it remains difficult to identify if these neurobiological features were present prior to disease onset, as they are often measured during concurrent or past symptoms. Investigating adolescent neurobiology before depression onset is critical in this regard.

There is evidence to suggest that this blunted neural VS response is replicated in adolescents with concurrent depressive symptoms, evidenced by less VS activation during fMRI tasks involving anticipation (for review see; O'Callaghan & Stringaris, 2019; Rappaport et al., 2020; Stringaris et al., 2015) and receipt of reward (Bress et al., 2013; Bress et al., 2012; Chantiluke et al., 2012; Forbes et al., 2006; Luking et al., 2016; Steele et al., 2007) compared to healthy controls. Similarly, adolescents at-risk for depression (i.e., biological parent with history of MDD), but no current symptoms, reveal a similar blunted reward response within the striatum compared to low risk adolescents (Gotlib et al., 2010; Joormann et al., 2009; Luking et al., 2016;

Olino et al., 2014; Olino et al., 2015; Sharp et al., 2014). Whether these reward-related neural markers precede depression onset and represent a vulnerability marker or if they are a consequence of the disorder remains up for debate. As noted earlier, previous studies have not differentiated between single or multiple depressive episodes, yet the reward-related markers of blunted reward processing, have been illustrated in *both* first onset and reoccurring or remitted depressive symptoms suggesting it may have at least some overlap in affected neurobiological processes. Although some of these findings in high-risk adolescents are promising and suggest the blunted VS response may be a precursor to the onset of a MDE, it would have great impact on prevention efforts if the findings were shown in healthy adolescents who go on to develop depression at a later timepoint.

### *1.4.2 Predictive capacity of blunted ventral striatum reward response on depression*

Few prospective studies in adolescents have examined the predictive capacity of reward-related circuitry dysfunction on later depression. Diminished reward positivity, measured via event-related potentials electroencephalogram (EEG) monitoring, (Bress et al., 2013; Nelson et al., 2016) and dampened VS reward anticipation and gain measured using fMRI (Luking et al., 2016; Morgan et al., 2013), in healthy children and adolescents without pre-existing risk, predicted increased depressive symptoms later in adolescence. Another large community-based sample of adolescents, including those with sub-clinical depression, clinical depression, and healthy controls revealed reduced VS activation during reward anticipation predicted the transition from healthy control to clinical depression category at a 2-year follow-up (approximately 16 years old) (Stringaris et al., 2015). Although these findings showed specificity to depression and not to other co-morbid psychopathology symptoms (i.e., anxiety) (Nelson et al., 2016), one study showed these effects only in adolescents at mid to late pubertal stages

(Morgan et al., 2013), and all studies showed the predictive effects over a narrow follow-up range (~2 years). The potential value of this neural marker to predict depression in adulthood has not been studied.

*1.4.3 Broader reward-related neural circuitry involved in depression*

While blunted VS reward processing seems to be consistently reported in depressed adults and adolescents, broader reward-related brain regions and their association with depression seem to remain up for debate regarding hyper- or hypo-activation of these regions. In both adults and youth with MDD, greater reward response in areas such as OFC, ACC, middle and inferior frontal gyri, subgenual cingulate, and dorsomedial, dorsolateral and ventromedial PFC were reported (Dichter et al., 2012; Forbes et al., 2006; Forbes et al., 2009; Pizzagalli et al., 2009). Yet, the opposite effect, with less neural activity in response to reward in MDD, has also been shown – lesser OFC, ACC, and middle frontal gyrus (Forbes et al., 2009; Forbes et al., 2010; Smoski et al., 2009; Stringaris et al., 2015). This effect was similar in a sample of never depressed adolescents to young adults (16-21 years) at high risk for depression, evidenced by biological parent with depression; high-risk individuals showed dampened reward response in OFC and blunted reward response in the ACC compared to low-risk individuals (McCabe et al., 2012). While the literature demonstrates inconsistencies about how other reward-related regions are differentially engaged in depressed individuals, a recent meta-analysis highlighted that across multiple studies (both in adolescents and adults), greater activity in response to reward in the OFC was consistently implicated (Ng et al., 2019). Together, these findings suggest there may be a neural phenotype of depression, such that there is a combined effect of dampened VS activation and heightened medial PFC activation to rewards (Lichenstein et al., 2016; J. K. Morgan et al., 2016; Ng et al., 2019; Stringaris et al., 2015). In support of this, greater task-

dependent connectivity between NAcc and medial PFC during reward receipt was observed in adolescents boys with depression compared to peers without psychiatric concerns (J. K. Morgan et al., 2016), and greater ACC, dorsomedial PFC, and ventromedial PFC involvement, and frontal-limbic connectivity during reward processing in adolescents was associated with increased depressive symptoms (Jin et al., 2017; Morgan et al., 2013). Importantly, these neural aberrations in reward processes seem to also impact reward-learning behavior, the ability to use rewards to guide decision making, evidenced by adults with and adolescents at risk for depression showing a diminished ability to develop a response bias toward more frequently rewarded stimuli (Admon et al., 2015; Belleau et al., 2021; Kumar et al., 2008; Pizzagalli et al., 2009; Pizzagalli et al., 2008; Pizzagalli et al., 2005). However, replicability of these findings in adults with varying levels of depression symptoms, not specifically MDD, were difficult to demonstrate (see Appendix 1). The reward-related neural disruption and potentially impaired reward-learning behavior may be underlying mechanisms contributing to the clinical presentation of diminished positive affect often seen in depression.

*1.4.4 Reward network resting-state connectivity and depression*

Measuring BOLD fluctuations irrespective of a task or demand placed on the participant may help to assess spontaneous fluctuations in functionally related or connected brain regions. These brain regions that are connected often work in tandem to form a network with a level of *coactivation* reflecting an intrinsic design of the brain (Biswal et al., 1995). In its simplest form, BOLD time series are extracted from region of interests (ROIs) or 'seeds,' and the time series is then correlated among other extracted seeds or all other brain voxels (Fox & Raichle, 2007). Seed-based connectivity methods allow the researcher to generate a resting-state correlation matrix that represents the communication between ROIs, otherwise referred to as resting-state

functional connectivity (rsFC). This method may assist in gaining information about how the VS interacts with other regions within the reward circuit irrespective of reward-based behavioral processes.

Depression has not only been associated with dampened VS reward response, but also aberrations in reward circuit connections. The VS is an essential node within the mesocorticolimbic system and is highly connected to regions, such as the VTA, ACC, and medial OFC (Haber, 2016; Haber & Knutson, 2010) (see section 1.4). As with task-based fMRI results illustrating neural recruitment of the extended regions of the reward circuit, the literature is mixed in terms of greater or lesser communication between these ROIs. In adults with depression, hypoconnectivity during rsFC has been observed between areas such as the ventral NAcc and dorsal striatum (caudate, putamen), ACC, and ventromedial PFC (see recent meta-analysis; Ding et al., 2022; Fan et al., 2021; Furman et al., 2011; Satterthwaite et al., 2015; Strikwerda-Brown et al., 2015). These findings are partially supported by meta-analyses illustrating hypoconnectivity among regions in affective and salience networks (e.g., NAcc, ACC, ventromedial PFC) in both adolescents and adults with current and remitted MDD (Ding et al., 2022; Kaiser et al., 2015) and in select longitudinal studies (Hirshfeld-Becker et al., 2019; Luking et al., 2011; Malhi et al., 2019). In fact, one of these longitudinal studies showed that hypoconnectivity among the subgenual ACC and inferior parietal lobule as well as hypoconnectivity among regions of the PFC was evident in healthy children, with family risk for depression (Hirshfeld-Becker et al., 2019). In contrast, studies have shown hyperconnectivity among reward-related circuitry (e.g., striatum and ACC, dorsomedial and medial PFC) in adults (Davey et al., 2012; de Kwaasteniet et al., 2013) and adolescents with depression (Gabbay et al., 2013; Rolls et al., 2018). Multiple longitudinal studies in depressed adolescents also support

these hyperconnectivity findings (Callaghan et al., 2017; Davey et al., 2015; Jin et al., 2020; Langenecker et al., 2018). Specifically, a large-scale longitudinal study demonstrated that greater VS functional connectivity to other regions within the reward network (including areas such as ACC, VTA, and ventral medial PFC) in 9-year-old children was predictive of greater risk of developing depression at a three-year follow-up (Pan et al., 2017), even when youth with elevated baseline rates of depression were removed from analyses. These latter findings suggest *hyper*connectivity in reward-related circuitry might be a risk factor for developing depression, as it has been replicated in children who go on to develop depression and since the resting-state findings are contrary to each other, it highlights the need for more investigation.

*1.4.5 Treatment changes neurobiology and predicts improvements in depression symptoms*

If alterations in reward processing represent a causal mechanism of depression, altering reward circuitry function should, in theory, change clinical presentation of depressive symptoms (Nielson et al., 2021). While treatment studies have illustrated promising interventions capable of manipulating reward processes, the impact on clinical change and applicability has been less clear. For example, adults with MDD receiving behavioral psychotherapy demonstrated normalization and even improvements in reward-related neurobiological responses (i.e., VS reward response, sustaining positive reward response in ACC, cingulate-putamen connectivity) in addition to reductions in depression symptoms (for review see, Carl et al., 2016; Mori et al., 2016; Nagy et al., 2020; Smoski et al., 2009; Walsh et al., 2017). Degree of increased positive reward responsivity and normalization of blunted VS during reward processing (anticipation and outcome) in adults with MDD following pharmacological interventions (12- and 6-week SSRI interventions) correlated with depressive symptom decreases (Burkhouse et al., 2018; Stoy et al., 2012). Further, a randomized control trial (RCT), which utilized optimal ways to monitor causal

effects of treatment (pharmacological versus placebo), showed that higher rsFC between the NAcc and rostral ACC (rACC) was associated with better treatment response to anti-depressant medications (specific to bupropion over sertraline) (Ang et al., 2020). Yet, others have noted minimal clinical impact following neurobiological reward-related changes following treatment intervention (Admon et al., 2017; Krystal et al., 2020). Specifically, implementation of an acute-dose trial to increase dopamine signaling illustrated increased striatal activation and corticostriatal functional connectivity to reward in depressed adults, compared to depressed adults without dopamine enhancement (Admon et al., 2017), and k-opioid receptor antagonist improved VS activation during reward anticipation (Krystal et al., 2020), but, neither study showed strong evidence of improvement in reward-related behavior or depressive symptoms. Although some of these findings highlight treatment's impact on neurobiology and improvements in depressive symptoms as a result, more research needs to be done to see if changing neurobiological processes will sustainably reduce depressive symptoms to measure the true clinical impact.

### 1.5 Childhood trauma as a psychosocial risk factor for adulthood depression

Individual differences in neurobiological mechanisms are not sole factors impacting depression risk, and the field lacks an understanding of the combined effect of neural phenotypes and other risk factors associated with depression onset. Children facing adversity are approximately twice as likely to develop a mental health diagnosis, with this relationship increasing with severity (Lewis et al., 2019; McLaughlin et al., 2019). Adolescence is also a time for increased vulnerability to stress (Andersen & Teicher, 2008), and increased experiences of childhood maltreatment in youth have been shown to increase risk for psychiatric disorders in adulthood (i.e., MDD, substance use disorders, and posttraumatic stress disorder) (Guyer et al.,

2006; Heim et al., 2008). Experiencing childhood trauma is a well-established risk factor for depression (Goff & Tottenham, 2015), with trauma-exposed children at two times greater odds of developing depression in young adulthood (Li et al., 2016), at elevated risk for early onset of depression, and with greater likelihood of treatment resistance (Nanni et al., 2012). Exposure to traumatic experiences may also play a crucial role in shaping depression-relevant neurodevelopmental trajectories (VS reactivity and global dysfunction across reward-related circuitry) and course of psychopathology (McLaughlin et al., 2014). Examining how these early life experiences of childhood trauma are associated with changes in brain response to external stimuli as well as how they may impact connectivity within reward-related circuitry may further help to delineate individualized risk and guide prevention efforts for those at elevated risk. Of note, negative childhood experiences are wide ranging and represent differing severities, therefore it is important to take into consideration that not all adversities should be treated with the same magnitude and that the impact on neurodevelopmental mechanisms may vary based on type of maltreatment (McLaughlin & Sheridan, 2016; McLaughlin et al., 2014).

### *1.5.1 Childhood trauma and reward-based disruptions*

Conceptually, exposure to early life trauma impacts reward-related contingencies that a child acquires through parent-child relationships. For example, when a relationship is abusive, inconsistent, or sparse, the system by which a child learns from various cues in their environment (i.e., rewards) understandably is often impaired (Pollak, 2015). While behavioral changes and attachment styles have been studied extensively in the developmental psychology literature (Bowlby, 1979; Goldberg, 2014; Harlow & Zimmermann, 1959), the role of childhood trauma on developing brain systems has more recently been explored. Overlap between the neurobiology of stress response and reward processing has led to an interest in the neurobiological similarities

among childhood trauma and depression and potential ties between these biopsychosocial variables. Gaining an improved understanding of how the underlying neurobiological mechanisms contribute to or augment the significant relationship between childhood trauma and future depression would inform prevention strategies.

Childhood trauma experiences have been shown to impact both structure and function in frontal and reward-related brain networks (Backhausen et al., 2023; Hanson et al., 2015; Hanson et al., 2018; Kennedy et al., 2021). Volumetric reductions in the mPFC (Edmiston et al., 2011; van Harmelen et al., 2010), hippocampus and amygdala (Hanson et al., 2017), and VS (Edmiston et al., 2011) have been illustrated in children who experienced adversity and maltreatment. Greater early life adversity is related to neurobiological alterations, such as decreased accumbofrontal tract integrity (white matter connection between the medial PFC and VS) (Kennedy et al., 2021) and weaker reward anticipation brain response (in regions including globus pallidus, putamen, thalamus, caudate, medial PFC) (Boecker et al., 2014; Dillon et al., 2009; Romens et al., 2015). The consistently supported predictor of depression onset and severity – dampened VS reward response – has also been replicated in individuals who experienced emotional neglect (Hanson et al., 2015) and youth who experienced early life institutionalization (Goff et al., 2013). Longitudinally, higher levels of early life stress exposure (7 years of age) predicted lower brain response during reward anticipation (in the caudate, NAcc, putamen, and globus pallidus) 3 years later, and greater brain response during reward anticipation (in the mPFC and ACC) predicted higher stress reactivity (Vidal-Ribas et al., 2019), suggesting that early life stress may alter reward processes, yet these associations appear bidirectional, as neurobiology also was associated with altered stress response. These findings highlight that while dysfunctional reward circuitry has been illustrated in both those with

depression and exposed to trauma, gaining an understanding of how early life experiences increase or decrease potential risk or alter outcomes is warranted.

The identified reward-related aberrations in those exposed to childhood trauma may also contribute to alterations in reward-related behaviors. Individuals exposed to maltreatment demonstrated decreased overall positive ratings of rewards (Dillon et al., 2009), a diminished ability to learn from rewards (Hanson et al., 2017; Kamkar et al., 2017; Kennedy et al., 2021), and adjustments in decision making under varying levels of risk and reward, where maltreated children demonstrate increased risk-taking, reduced sensitivity to varying reward values, and greater impulsivity in choices (Pechtel & Pizzagalli, 2013; Weller & Fisher, 2013); yet maltreated children *with combined depressive features* selected safe more often than risky choices (Guyer et al., 2006). Further, the identified deviations in associative reward-related learning, in adolescence, partially explained the positive relationship between early childhood adversity and reported psychosocial and behavioral problems (Hanson et al., 2017). Together, these study findings suggest limbic reward-related regions may be susceptible to change when under stressful early life experiences.

### *1.5.2 Childhood trauma and reward circuitry differences*

Similar to the literature in depression, childhood maltreatment impacts broader reward circuitry. Hyperconnectivity between reward-related regions (e.g., VS/NAcc and medial PFC) in older adolescents and adults exposed to childhood trauma was related to increased depressive symptoms (Hanson et al., 2018; Olson et al., 2018). Adults exposed to childhood trauma showed decreased rsFC between the NAcc and orbital middle frontal gyrus, decreased rsFC between the ventral caudate and orbital frontal gyrus (Fan et al., 2021), and blunting of mPFC response to positive stimuli (van Harmelen et al., 2014). Greater trauma exposure was significantly

associated with greater activation in the ventral ACC and lesser connectivity between ACC and other reward related regions (frontopolar cortex, fusiform gyrus, superior temporal gyrus, middle temporal gyrus) during reward prediction error, a form of reward learning (Eckstrand et al., 2019). These findings suggest the potential for reward-related neurobiological alteration in those exposed to childhood maltreatment, and these changes may also be associated with later internalizing symptom presentation, yet the direction of connectivity (greater or lesser) within regions of reward circuitry has shown to vary.

### 1.6 Childhood trauma and reward circuit dysfunction contributions to depression

While reward dysfunction has been identified as an underlying mechanism associated with depression risk and prognosis, as mentioned above, similar neurocircuitry is altered in individuals who have experienced childhood maltreatment. Thus, reward-related neurobiology may act as an intermediary phenotype connecting the trauma-depression link. A few important studies have aimed to examine the underlying mechanisms of these associations (childhood trauma, reward-related neurobiology, and depression), though it continues to be elusive. For example, some have hypothesized that early traumatic and stressful experiences impact reward system dysfunction, yet it is important to highlight, again, that these relationships are bidirectional (McEwen, 2017; Vidal-Ribas et al., 2019).

While the literature thus far suggests that childhood trauma impacts neurodevelopment during adolescence and subsequently alters trajectories of psychopathology, inferring causality has been challenging due to conflicting results, and studies predicting psychopathology into adulthood are scarce. The intermediatory role of altered neural reward-processing has been replicated in resting-state, such that VS-OFC rsFC in adulthood mediated the relationship between childhood trauma and adulthood depressive symptoms (Fan et al., 2021), and is further

supported by studies of white matter integrity between fronto-striatal tracts (Bick et al., 2017; Bick & Nelson, 2016; Bick et al., 2015; Dennison et al., 2019). A longitudinal resting-state study, found greater childhood trauma was associated with increased within SN connectivity (from 16 to 19 years), and this hyperconnectivity mediated the association between childhood trauma and depressive symptoms in adolescence (Rakesh et al., 2023). Similarly during fMRI, greater reward response and reward-learning behavior during adolescence moderated the association between childhood maltreatment and depression symptoms later in adolescence (2 years later), such that these reward processes (i.e., greater reward response, and faster reaction time (RT) to rewarded stimuli) were protective and associated with lower depressive symptoms in adolescents exposed to trauma (Dennison et al., 2016). These findings have been shown in a sample of young adults as well, where increased VS reactivity to reward buffered the negative effects of anhedonia after experiencing early life stress (Corral-Frías et al., 2015); yet, the temporality of these studies have been mixed and whether childhood trauma, shown to alter reward-processes in adolescence, longitudinally predicts depression extending to adulthood has yet to be investigated.

A recent international systematic review in search of studies that included both biological and environmental risk factors in the context of MDD found a total of 21 studies examining the both factors (Zajkowska et al., 2021), highlighting the necessity to continue studying the combined effect of biopsychosocial risk factors of psychopathology. In that regard, though the association between childhood trauma and later internalizing problems appears strong, the underlying neurobiological mechanisms that are shown to differentiate individuals exposed to trauma and presenting with depression (either as a consequence of or perhaps pre-existing neurobiological differences) are still largely debated. A gap in the literature is a limited understanding if the reward-related alterations in adolescence extend into adulthood, as most

studies have only looked over short-term (2-3 year) follow-up periods. Further to our knowledge there have been no studies investigating the predictive capacity of these reward-related neural markers, prior to depression onset, or depression symptoms in adulthood. Additionally, the impact of the *combined* effects of childhood trauma and reward-related neurobiology on adult depression requires further investigation.

### 1.7 Summary and study objectives

Identification of biopsychosocial vulnerability factors that put individuals at higher risk of developing depression, before onset, is critical due to the detrimental effects early onset depression may have on lifelong physical and psychosocial health. With increased understanding of risk and protective factors via a biopsychosocial, developmental lens, it is hoped that this information may be used to develop and guide prevention efforts to thwart youth from going on to develop adverse health outcomes. Experiencing depression with combined features of low positive affect has been shown to make people more prone to treatment-resistant depression and poorer recovery after using first-line therapies such as SSRIs (McMakin et al., 2012). Improving our understanding of depressive symptoms, as they present through reward-related processing (low positive affect), may help assist the most vulnerable of patients. Due to the strong evidence on reward-related deficits as promising endophenotypes for depression risk and escalating severity (Keren et al., 2018), and predictors of depressive symptom change following treatment (Burkhouse et al., 2018), as part of this dissertation, the primary focus will be on better conceptualizing relationships between adolescent neurobiological mechanisms of reward-related circuitry and adulthood depression severity, as well as corresponding psychosocial factors associated with depression risk (specifically, childhood trauma).

With this in mind, this dissertation will use a biopsychosocial model to understand the developmental origins of risk factors for depression in adulthood. The current work will focus on depressive symptoms on a continuum as the outcome variable of interest to gain insight into depression symptoms more broadly. Also, the current work did *not* exclude individuals in adulthood with other existing mental health symptoms, so as to increase the generalizability of the findings and to allow for specificity analyses for specific psychopathology or general psychopathology symptoms. This dissertation seeks to address two specific aims. First, to advance our understanding of the role of adolescent reward response and circuitry in adult depression, in the current study, we used a longitudinal design and an *a priori* seed-based approach to 1) investigate whether adolescent brain response to rewards and rsFC of mesocorticolimbic circuitry (prior to the onset of mood-related concerns) prospectively predict depressive symptoms in adulthood, and 2) test the role of childhood trauma in potential adolescent brain-adult behavior associations. In regard to Aim 1, I used a series of regression analyses, with appropriate covariates (baseline depression symptoms, age, sex assigned at birth), to examine if adolescent brain response during reward outcome (measures via fMRI) and adolescent rsFC between mesocorticolimbic ROIs predicted a continuous measure of adult depressive symptoms. These analyses were corrected for multiple comparisons and post-hoc sensitivity analyses were conducted to see if the significant brain-behavior results also predicted other psychopathology symptoms (anxiety, externalizing). Based on previous literature demonstrating that *blunted* reward response during reward outcome (Bress et al., 2013; Luking et al., 2016; Nelson et al., 2016; Steele et al., 2007) and *hyperconnectivity* in reward-related circuitry was predictive of depressive symptom severity and greater risk for depression (Morgan et al., 2013; Pan et al., 2022; Pan et al., 2017; Stringaris et al., 2015), I hypothesized that lesser

VS reward response and greater functional connectivity between reward circuitry during adolescence would be associated with greater depressive symptoms in young adulthood.

For Aim 2, I ran similar regression analyses, including the same covariates as above, to investigate if childhood trauma predicted adulthood depression symptoms and if childhood trauma predicted adolescent mesocorticolimbic reward response and rsFC. The same correction for multiple comparisons and post-hoc sensitivity analyses were implemented. For significant brain-behavior relationships among all three variables (childhood trauma, adolescent brain, and adult depression), post-hoc mediation and moderation analyses were explored to better understand the inter-related associations. As shown previously (Hanson et al., 2015; Hanson et al., 2018), I hypothesized that greater exposure to childhood trauma would be related to greater depression symptoms in adulthood, dampened VS response to reward, and heightened connectivity among reward-related brain regions. With the study objectives aiming to understand neurobiological and psychosocial precursors of adult depression during childhood and adolescence, this work hopes to shed light on the potential factors that elevate risk and may inform early prevention strategies.

# Chapter 2. Methods and Materials

*(Portions of this chapter are currently under review for publication)*

## 2.1 Adolescent recruitment and exclusionary criteria at baseline

All participants took part in a longitudinal study approved by the Oregon Health & Science University (OHSU) Institutional Review Board investigating adolescent development. Adolescents were originally recruited from the local Portland Metro Area through outreach fliers, community clinics, and prior study involvement at OHSU at ages 10-16 years at baseline. Following a telephone prescreen assessing initial eligibility, parental written consent and youth assent were collected at the time of enrollment. As the goals of the longitudinal study were to investigate the *emergence* of psychopathology, baseline exclusionary criteria were stringent. Exclusionary criteria for adolescent enrollment included probable DSM-IV psychiatric diagnosis (assessed using the Diagnostic Interview Schedule for Children Predictive Scales (DPS, (Lucas et al., 2001), serious medical problems, significant head trauma, intellectual or learning disabilities, biological parents with schizophrenia or bipolar I, known prenatal exposure to substances, and MRI contraindications (i.e., left-handedness (Oldfield, 1971) and irremovable metal). Participants were also excluded from the baseline study entry if they had reported consuming >10 lifetime alcoholic drinks, >2 alcoholic drinks on any one occasion, or any other drug use, measured via the Customary Drinking and Drug Use Record (CDDR; (Brown et al., 1998)). Participants were initially followed until age 21 years and were given the option to opt-in to being re-contacted for future studies, following the completion of their participation in the original study.

## 2.2 Adulthood inclusion criteria and final sample

Adolescent participants from the above study were re-contacted to complete follow-up, adult data collection. Inclusion criteria for re-contacted adults were: 1) had completed a wheel of fortune (WOF) scan, a reward-based decision-making fMRI task (described in section 2.4.3),

between the ages of 12-16, 2) were currently aged 21-27 years old, and 3) had reconsented to be re-contacted. The age range for scan data was chosen based on prior literature illustrating a quadratic pattern of brain activation in relation to reward sensitivity during adolescence (Braams et al., 2015) and suggests a peak in reward activity during this time, as well as based on the greatest availability of potential participants for re-enrollment.

A total of 154 individuals were identified to fit the inclusion criteria and were re-contacted. Of those re-contacted, 78 individuals were reconsented; however, 1 participant who had completed the WOF task-based fMRI study did not complete all the adult study measures, resulting in a final sample of 77 participants for whom we had adolescent WOF scans and adult behavioral data. Additionally, 12 participants were excluded from the resting-state sample due to insufficient resting-state imaging quality (see section 2.2.4), resulting in a final sample of 66 participants with usable resting-state scans and adult behavioral data.

## 2.3 Adolescent behavioral and psychosocial measures

### *2.3.1 Children's Depression Inventory (CDI)*

Though participants were excluded for psychiatric diagnoses at enrollment, the Childhood's Depression Inventory (CDI) (Kovacs; M Kovacs, 1985) was collected to quantify adolescent depression symptoms at baseline. The CDI is a self-report measure that has been used across research studies and in clinical settings to assess cognitive, affective and behavioral impacts of depression on school-aged children and adolescents, 7-17 years of age. Each of the individual items consists of 3 statements that increase in graded severity (scored 0-2), with a total score range between 0 and 54. The scale further breaks down into a five factor structure representing typical presentations of depressive symptoms in youth, including negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self-esteem (Kovacs, 1992). CDI total scores were computed and then converted to total score T-scores based on age- and

sex-based norms. Clinical cut-offs for elevated depression are represented by a T-score greater than or equal to 65. This is a reliable 27-item (Cronbach's alpha = 0.86) measure that has been validated for measuring depressive symptoms (M. Kovacs, 1985).

### *2.3.2 Socioeconomic status (SES)*

Socioeconomic status (SES) has been shown to relate to psychopathology symptoms in adulthood, early childhood experiences, and neurobiological development (D. Barch et al., 2016; McLaughlin et al., 2020; McLaughlin et al., 2019). Though a cursory assessment of SES, adolescents' parents completed the Hollingshead Index of Social Position, a measure utilizing educational attainment and occupation of each parent (Hollingshead, 1957; Hollingshead & Redlich, 2007). The ratings were measured on a 7-point Likert scale with lower scores representing attainment of a professional degree or occupation and 7 representing attaining less than 7 years of education or work. Total scores ranged from 11 to 77 with lower scores representing higher parental education and occupational attainment.

### *2.3.3 Intellectual functioning (IQ)*

Adolescents completed the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI-II) (including Vocabulary and Matrix Reasoning subtests) (Wechsler, 1999, 2011). The abbreviated Full-Scale IQ measure was used to estimate each individual's cognitive abilities, with higher scores indicating greater estimated intellectual functioning. This abbreviated format parallels the full Wechsler battery; while it is not a comprehensive measure of intelligence, it is a quick method to assess a combination of verbal and nonverbal skills to generate a general cognitive abilities composite.

## 2.4 Adolescent neuroimaging measures

### *2.4.1 Scan Acquisition*

Brain imaging data were collected on a 3.0 Tesla Siemens Magnetom Tim Trio scanner at OHSU's Advanced Imaging Research Center. Each subject underwent a high-resolution T1-weighted anatomical MPRAGE structural scan, acquired in the sagittal plane (time to repetition [TR] = 2300 ms, time to echo [TE] = 3.58 ms, inversion time [TI] = 900 ms, flip angle = 10°, voxel size 1 x 1 x 1.1 mm, total acquisition time = 9:14). Blood-oxygen-level-dependent (BOLD) signal during the WOF task was assessed using a functional T2*-weighted gradient echo-planar imaging (EPI) sequence collected in axial slices parallel to the anterior-posterior commissure line (TR = 2000 ms, TE = 30 ms, flip angel = 90°, field of view [FOV] = 240 $mm^2$, voxel size = 3.75 x 3.75 x 3.8 mm, acquisition time = 10 minutes per run). Whole-brain resting-state functional images were acquired over two runs (TR = 2500 ms, TE = 30 ms, flip angle = 90°, voxel size = 3.75 x 3.75 x 3.8 mm, acquisition time for each run was dependent on protocol and approximately 4:17-5:17), and participants were instructed to fixate on a white cross presented on a black background.

### *2.4.2 General image processing*

Analysis of Functional NeuroImages (AFNI) (Cox, 1996) (v19.0.26) was used for preprocessing of task-based and resting-state connectivity data, as described previously (Jones & Nagel, 2019; Morales et al., 2021), and included visual inspection for artifacts, removal of pre-steady state volumes, and slice time correction. Additional steps included spatial transformations for head motion, co-registration of the BOLD image to the high-resolution structural image, and final registration to standard coordinate space. Data were then smoothed (using a 6-mm, for task-based data, and 4-mm, for resting state, Gaussian kernel) and demeaned. Finally, images were

resampled to 3 $mm^3$ voxels prior to group-analyses. To remove potential head motion-related artifacts, censoring was used to remove volumes with framewise displacement (FD) that exceeded a certain threshold (0.7 mm for task-based data and 0.3 mm for resting-state data) or data with < 5 contiguous frames (Siegel et al., 2014).

*2.4.3 Wheel of fortune (WOF) reward response task*

To assess the neurobiological underpinnings of adolescent reward response, data were analyzed from participants who completed a modified version of the WOF task (Figure 1) during fMRI (Cservenka et al., 2012; Ernst et al., 2004; Morales et al., 2018). The task consisted of three phases: selection, anticipation, and feedback. In the selection phase, participants viewed a wheel that provided a visual illustration of the percentage associated with each of the two options for monetary reward available on that trial (probability of winning $7 (10%) versus $1 (90%); probability of winning $2 (30%) versus $1 (70%); and probability of winning $2 (50%) versus $2 (50%)). During the anticipation phase, participants indicated how sure they were of winning on a scale of 1–3. Finally, during feedback, participants learned whether they won or not ('Win' versus 'No Win') and saw their cumulative earnings. Participants were asked to select the portion of the wheel they believed would win them the most money, because at the end of the task they would receive a portion of their earnings. The outcome for each trial was based on whether the participants' choice for a given trial matched that of a predetermined probability. A total of 72 trials were presented over two 10-minute runs. Trials were 10.5 seconds long with intertrial fixation jitter between 1 and 11 seconds (Morales et al., 2018). Given our interest in how reward circuitry is associated with future depression and extensive work showing dampened reward response as a marker for future depression (Forbes et al., 2006), the third feedback phase (reward receipt), was analyzed. As outlined previously (Cservenka et al., 2015; Cservenka & Nagel,

2012; Morales et al., 2018), regressors of interest for the WOF task included 'Win' and 'No Win' trials, contrasted to generate a measure of reward response. Selection and anticipation phases of the task, as well as motion parameters and linear drift were modeled as regressors of no interest. The main contrast of interest was 'Win' versus 'No Win', as this contrast was shown to elicit VS reward response previously (Alarcón et al., 2017).

*2.4.4 Additional resting-state preprocessing*

Additional preprocessing steps for resting state analyses included the use of FreeSurfer (Dale et al., 1999) (v6.0.0) to segment the structural image and create gray matter, white matter, and ventricle masks. Additionally, linear regression was used to apply a high-pass filter, to remove signal correlated with timeseries extracted from the white matter, ventricular, and whole brain masks. Participants containing less than 5-minutes of quality resting-state data following motion censoring (as described in section 2.3.2) were excluded from group-level analyses.

*2.4.5 Reward-related brain response and network connectivity*

Neural reward response and seed-based rsFC were used to test *a priori* hypotheses about reward response and connectivity between ROIs within the mesocorticolimbic reward circuit and its association with future depressive symptoms. The Oxford-GSK-Imanova structural striatal atlas was used to generate the VS seed mask (Tziortzi et al., 2013), and the VTA was generated using a probabilistic subcortical atlas and was dilated (Bo et al., 2017; Pauli et al., 2018; Tyszka, 2021). The remaining mesocorticolimbic ROIs, the rACC and mOFC, were selected from the Desikan-Killiany Atlas (Desikan et al., 2006). The average brain activation from the 'Win' vs. 'No Win' contrast was extracted from each ROI, otherwise representing reward response within each brain region. Similarly, the average timeseries across all voxels in every individual ROI was

extracted and correlated with each other ROI to generate a connectivity matrix for each subject and to improve normality, the connectivity values underwent Fisher's r to z transformations.

## 2.5 Adult psychopathology follow-up measures

At follow-up, participants completed the Beck Depression Inventory – Second Edition (BDI-2; (Beck et al., 1996)), the Generalized Anxiety Disorder 7-Item (GAD-7; (Spitzer et al., 2006)), and the Adult Self-Report (ASR; (Achenbach, 2003)). The Childhood Trauma Questionnaire (CTQ; (Bernstein et al., 2003)) was also administered to retrospectively assess childhood maltreatment exposure prior to 18 years of age. The GAD-7 total score and ASR externalizing subscale T-score were utilized in specificity analyses (see section 3.2.2). Although participants were excluded from enrollment (during adolescence) for the presence of probable psychiatric diagnoses, at adult follow-up, we did not complete full psychiatric diagnostic screening. During follow-up visits, all participants denied current visual and/or auditory hallucinations and major head injuries that may have impacted their participation and ability to accurately complete self-report measures.

### *2.5.1 Beck Depression Inventory – Second Edition (BDI-2)*

At follow-up, participants completed the Beck Depression Inventory – Second Edition (BDI-2; (Beck et al., 1996)). Adult depression symptoms were assessed using the Beck Depression Inventory – Second Edition (BDI-2), which is a 21-item self-report questionnaire assessing depressive symptoms on a 4-point scale (0 = "not present" and 3 = "severe"), with higher scores denoting greater depressive symptoms. For example, the statements range from a '0' response "I do not feel sad" to a '3' response "I am so sad and unhappy I can't stand it". The BDI-2 is utilized in adult samples >18 years old and is a reliable measure (Cronbach's alpha range = 0.83-0.96) (Beck, 1996; Beck et al., 1996; Wang & Gorenstein, 2013). A total BDI-2

score was created by summing each item response; typically labeled ranges are: minimal depression (0-13), mild depression (14-19), moderate depression (20-28), and severe (29-63). The scale followed standardized administration procedures, and participants were asked to report their depressive symptoms in the past two weeks.

*2.5.2 Childhood Trauma Questionnaire (CTQ)*

The Childhood Trauma Questionnaire (CTQ; (Bernstein et al., 2003)) was administered to retrospectively assess childhood maltreatment exposure and severity prior to 18 years of age. The CTQ consists of 28 items across five dimensions of maltreatment including emotional neglect, emotional abuse, physical neglect, physical abuse, and sexual abuse. Each question was answered using a five-point scale (1 = "Never True" and 5 = "Very Often True") with higher scores indicative of greater experiences of trauma in childhood and each subscale ranges from 5-25. The CTQ has good convergent and discriminant validity, with clinician interrater reliability for the majority of subscales intraclass correlation above 0.90 (Bernstein et al., 1997; Bernstein et al., 2003; Fink et al., 1995). Childhood experiences of maltreatment were operationalized for the current study using a CTQ total score, which was generated by summing each subscale (i.e., emotional neglect, emotional abuse), as has been utilized in previous studies of childhood maltreatment (Gorka et al., 2014; Hanson et al., 2018). Additional post-hoc analyses were conducted to investigate associations with specific trauma subscales.

*2.5.3 Generalized Anxiety Disorder (GAD-7)*

The Generalized Anxiety Disorder 7-Item (GAD-7; (Spitzer et al., 2006)) was administered at adulthood follow-up, since depression and anxiety are often highly co-morbid, and specificity analyses (section 3.2.2) were carried out to see if the risk factors identified to be

associated with depressive symptoms are similarly related to anxiety symptoms in young adults. The Generalized Anxiety Disorder 7-item (GAD-7) is an abbreviated self-report questionnaire that measures the severity of generalized anxiety symptoms on a four-point 0-3 (0 = "Not at all" and 5 = "Nearly Every Day") with total scores ranging from 0 to 21. Higher scores represented greater anxiety symptoms and typical clinical labeled ranges are: mild anxiety (5-9), moderate anxiety (10-14), severe anxiety (>15). This measure has excellent internal consistency (Cronbach alpha range = 0.92), good intraclass correlation, and strong construct validity (Spitzer et al., 2006). Similar to the BDI-2, the questions on the GAD-7 were given following standardized administration procedures, and participants were asked to report their symptoms in the past two weeks.

*2.5.4 Adult Self Report (ASR)*

The Adult Self Report (ASR) was administered to assess for a range of mental health symptoms in adulthood, particularly externalizing disorder symptoms. The ASR assesses behavioral, emotional, and social concerns, as well as adaptive functioning in adults aged 18-59 years old. It is a 126-item self-report questionnaire, and each item is rated on a three-point scale (0 = "Not true" and 2 = "Very true or often true") (Achenbach, 2003). The items are grouped according to syndrome categorizes that are correlated with DSM diagnoses and include: depressive problems, anxiety problems, somatic problems, avoidant personality problems, attention-deficit/hyperactivity problems (inattention and hyperactivity/impulsivity subscales), and antisocial personality problems. Similarly, as used with the GAD-7, the ASR externalizing subscale T-score was utilized in specificity analyses (section 3.2.2) to assess if underlying mechanisms associated with depression were similarly associated with externalizing symptoms.

This is particularly important to assess in adulthood, as children with externalizing disorder behaviors often go on to develop increased rates of depression (Loth et al., 2014).

### 2.6 Summary of analytic strategy

All statistical analyses were carried out using R (v 4.3.2). Demographics variables are presented in Table 2.1. Baseline demographic variables, as well as follow-up variables were examined for normality. Correlation analyses and parametric t-tests were used to assess associations between potential covariates. Given the unequal number of females and males in the samples, nonparametric t-tests were used to assess sex differences in depression and trauma. Sex differences across all baseline and follow-up measures were assessed due to strong evidence suggesting differences between internalizing symptoms across sexes (Kessler, Chiu, et al., 2005; Kuehner, 2017). Multiple linear regression analyses were conducted to examine the association between adolescent mesocorticolimbic reward response and connectivity among *a priori* ROIs and adult depression symptoms, controlling for baseline CDI, scan age, and sex at birth. Additionally, linear regression was used to investigate the associations between childhood trauma and both adult depression symptoms and mesocorticolimbic neurobiology (adolescent task-based fMRI reward response and rsFC). For analyses investigating associations between neurobiology and depression, thresholds for significance were Bonferroni corrected for multiple comparisons (separately for reward response ROIs and rsFC predictors). That is, for task-based regression analyses (adolescent ROI reward response predicting BDI & CTQ predicting adolescent ROI reward response), significance values were corrected for four (each ROI) comparisons, Bonferroni corrected p-values (0.05/4 = 0.0125). For rsFC analyses (adolescent rsFC predicting BDI & CTQ predicting adolescent rsFC), regression analyses were corrected for six (each ROI to ROI connection) comparisons, Bonferroni corrected p-values (0.05/6 = 0.008).

To test the specificity of reward-related brain response and connectivity and adult depression symptom effects, models with significant associations between neurocircuitry and depression were re-run to investigate relationships among mesocorticolimbic reward response and rsFC and anxiety (GAD-7) and externalizing (ASR, externalizing T-Score) symptoms.

# Chapter 3. Results

*(Portions of this chapter are currently under review for publication)*

### 3.1 Sample characteristics

Participants were selected from a larger study (as discussed in section 2.1) and included 77 young adults (53 assigned female at birth) who completed WOF scans between the ages of 12-16 years. Additionally, of those with task-based scan data, 66 young adults (45 assigned female at birth) also completed resting-state scans. The majority of participants were white (86% white, 3% Native American/Alaskan Native, 1% Asian, 1% Native Hawaiian/Pacific Islander, 8% Multiracial, and 9% Hispanic/Latinx). Briefly, on average, participants were approximately 15 years old at the time of their scans and 25 years old at the time of their follow-up visit. Childhood trauma total scores and subscales, adolescent CDI ratings, and adult BDI-2 scores were not significantly different among female and males at birth ($p$'s > 0.05), with the exception of CTQ sexual abuse, where females reported higher incidence than males ($t = 2.1$, $p = 0.04$). Even though sex differences were not demonstrated specifically in BDI-2 and CTQ total scores, sex was retained as a covariate and used to test interaction effects given previous literature suggesting internalizing symptoms and trauma rates impact females more often than males (Kessler, Berglund, et al., 2005), as well as neurodevelopmental differences as a function of sex demonstrated during adolescence (Jones et al., 2023; Mills et al., 2021). Similarly, scan age was another covariate added to models, as the age of adolescent neuroimaging data ranged from 12-16 years, a time when typical developmental change would occur (Casey et al., 2019; Larsen et al., 2020). Notably, compared to the 154 individuals initially identified as meeting eligibility criteria for the current study, the 78 recruited/enrolled did not differ on race/ethnicity, socioeconomic status, or adolescent CDI ratings ($t = -1.57$, $p$-value = 0.11) (See Table 2.1 for further sample details).

The depression outcome variable of interest, BDI-2 total scores in the WOF sample, was related to adolescent CDI scores at the time of scan ($r = 0.23$, $p = 0.04$); however, adolescent CDI scores in the resting-state sample were not significantly associated with BDI-2 at follow-up ($r = 0.19$, $p = 0.14$). It is likely the decreased sample size in the resting-state sample contributed to this association no longer being significant, and therefore it was kept as a covariate across task and resting-state analyses. Other demographic variables (i.e., age at follow-up, SES, IQ) were not significantly related to BDI-2 or CTQ total scores ($p$'s > 0.05).

### 3.2 Adolescent neurobiology and adult depressive symptoms

#### *3.2.1 Adolescent WOF reward response association with adult depressive symptoms*

There were no significant associations between adolescent reward-related WOF brain ROI response and symptoms of depression in adulthood (BDI-2 total scores), controlling for sex at birth, scan age, and adolescent CDI scores (See Table 3.2.1) (corrected $p$'s > 0.05). There were no significant sex, scan age, or baseline CDI score effects on adult BDI-2 scores ($p$'s > 0.05).

#### *3.2.2 Adolescent mesocorticolimbic rsFC association with adult depressive symptoms*

There was a significant positive association between adolescent VS-rACC rsFC and adult BDI-2 scores, controlling for sex at birth, scan age, and adolescent CDI scores ($\beta = 0.34$, $p = 0.04$, corrected) (Figure 2B, Table 3.2.2). There were no significant effects between connectivity within other mesocorticolimbic ROIs and adult BDI-2 scores (corrected $p$'s > 0.05). As was the case in the task sample, there were no significant sex, scan age, or baseline CDI scores effects on adult BDI-2 scores ($p$'s > 0.05). To establish specificity in this finding, we conducted the same analysis with anxiety and externalizing symptoms as the outcome variables of interest, and no significant relationships were found between VS-rACC rsFC and these other types of

psychopathology symptoms (GAD-7: $\beta = 0.12$, $p > 0.05$, ASR externalizing T-Score: $\beta = 0.13$, $p > 0.05$).

### 3.3 The role of childhood trauma on brain-behavior relationships

#### *3.3.1 Adult depressive symptoms, adolescent WOF reward response, and childhood trauma*

There was a significant positive association between adult BDI-2 scores and CTQ total scores in the task-based sample ($r = 0.56$, $t = 5.80$, $p < 0.001$). There was also a significant positive association between adolescent rACC WOF reward response and CTQ total scores ($\beta = 0.33$, $p = 0.04$, corrected), controlling for sex at birth, scan age, and adolescent CDI scores (Figure 3B, Table 3.3.1). There were no significant associations between WOF reward response (in other ROIs, refer to Table 3.3.1) and CTQ total scores (corrected $p$'s > 0.05). There were also no significant main effects of sex, scan age, or baseline CDI scores on the rACC WOF reward response ($p$'s > 0.05). Follow-up investigation of CTQ specific subscales showed that while all subscales were significantly associated with BDI-2 total scores ($p$'s < 0.05), only emotional neglect (Figure 3C) was positively associated with rACC WOF activation, with the same covariates as above ($\beta = 0.35$, $p = 0.02$, corrected for 5 subscale comparisons).

#### *3.3.2 Adult depressive symptoms, adolescent mesocorticolimbic rsFC, and childhood trauma*

The significant positive association between adult BDI-2 scores and CTQ total scores was also demonstrated in the smaller resting-state sample ($r = 0.52$, $t = 4.82$, $p < 0.001$) (Figure 2C). There was also a positive relationship between VS-rACC rsFC and CTQ total scores ($\beta = 0.47$, $p < 0.01$, corrected), controlling for sex at birth, scan age, and adolescent CDI scores (Figure 2D, Table 3.3.2). There were no other significant mesocorticolimbic rsFC relationships with CTQ total scores and no significant main effects of sex, scan age, or baseline CDI scores ($p$'s > 0.05). Upon follow-up investigation, all CTQ specific subscales showed positive

associations with VS-rACC rsFC ($p$'s < 0.01, corrected after controlling for 5 subscale comparisons), except for physical abuse.

### 3.4 Additional exploratory analyses with task-based sample

Since we did not observe a blunted reward response in association with depression symptoms, as was hypothesized and previously shown (Auerbach et al., 2022; Stringaris et al., 2015), but found a significant association between rACC reward response (rACC WOF) and CTQ total scores, we explored the moderating effects of adolescent rACC WOF on the CTQ to adult BDI-2 relationship, as similarly shown (Fassett-Carman et al., 2023). The rACC WOF by CTQ total interaction effect on adult BDI-2 scores was not significant, controlling for sex at birth, scan age, and adolescent CDI scores ($\beta$ = -0.04, $p$ > 0.05). However, investigation of the specific CTQ subscale, emotional neglect, which was significantly associated with rACC WOF reward response, showed a *trend level* interaction between rACC WOF and CTQ emotional neglect (emotional neglect: $\beta$ = 0.60, $p$ = 0.05, Figure 4, Table 3.4.1). These findings suggest that individuals who showed heightened rACC reward response showed a stronger positive relationship between childhood neglect and adult depression symptoms; however, these analyses were entirely exploratory for the purposes of the dissertation and interpretation should carefully consider the interaction between reward response and differences in specific trauma experiences on depression (see sections 4.3 and 4.4).

Given the strong relationship between childhood trauma and depression, as well as a relationship between rACC WOF and CTQ total and emotional neglect scores, we used structural equation modeling, via the lavaan package in R, to investigate whether rACC WOF mediated the association between childhood trauma (CTQ total and emotional neglect) and adult BDI-2 scores, as shown previously (Romens et al., 2015). Overall model fit was evaluated using fit

indices: comparative fit index (CFI) (values closer to 1 represent better fitting models, CFI > 0.9 indicates good model fit) (Bentler, 1990), Root Mean Square Error of Approximation (RMSEA) (Steiger, 1990) (RMSEA < 0.05 indicate excellent model fitting, and RMSEA between 0.05-0.08 indicated adequate fit) (Kline, 2023), Akaike Information (AIC) and Bayesian Information Criterion (BIC) (generally lower values indicate better model fit), (Akaike, 1974; Bentler, 1990; Kuha, 2004), and standardized root mean square residual (SRMR) (lower values represent better fit) (Jöreskog, 1971).

The fully constrained mediation model (1a) had a non-significant indirect path from CTQ total scores, to rACC WOF, to adult BDI-2 scores ($\beta$ = -0.005, $p$ = 0.89), controlling for sex at birth, scan age, and adolescent CDI scores. Next, a mediation model (1b), CTQ total score, to rACC WOF, to adult BDI-2 scores was conducted, but the paths were allowed to vary differently by assigned sex (i.e., moderated mediation), which resulted in non-significant effects for both females and males (Females: indirect $\beta$ = -0.04, $p$ = 0.41; Males: indirect $\beta$ = 0.02, $p$ = 0.64). Utilizing emotional neglect scores in the mediation model (1c) still resulted in a non-significant indirect path ($\beta$ = -0.009, $p$ = 0.78), as was the moderated mediation (1d) with emotional neglect for females and males (Females: indirect $\beta$ = -0.04, $p$ = 0.42; Males: indirect $\beta$ = 0.02, $p$ = 0.73)). These findings suggest that although a significant relationship was found among CTQ total scores and rACC WOF reward response, as well as a significant relationship between CTQ and BDI-2 scores, it appears rACC *reward response* does not statistically explain the direct association between childhood trauma on depression. Together, the exploratory task-based results do not support a causal relationship between childhood trauma, adolescent reward response, and adult depression; rather, the task findings show some *preliminary* support for moderation in that,

individuals with heightened reward response in the rACC show a stronger relationship between childhood emotional neglect and adult depression symptoms.

### 3.5 Additional exploratory analyses with resting-state sample

Based on the previous findings suggesting potential moderation (the interaction of reward-related neurobiology and childhood emotional neglect on depression) on adulthood depression; the same moderation analyses were investigated in the resting-state sample. The interaction effect of adolescent rsFC (VS-rACC) and CTQ total scores on BDI-2 scores in the resting-state sample was not significant ($\beta = 0.19$, $p > 0.05$). Even though the majority of CTQ subscales (except for physical abuse) were related to VS-rACC rsFC, to keep analyses consistent with the task-based results, a separate moderation analysis with CTQ emotional neglect (specifically the interaction of CTQ emotional neglect and VS-rACC rsFC) was examined. Again, the moderation revealed a non-significant interaction effect ($\beta = 0.32$, $p > 0.05$). These findings do not support a statistically significant interaction of VS-rACC rsFC and childhood trauma on depressive symptoms in adulthood.

Given that childhood trauma, VS-rACC connectivity, and adult depression were all found to be inter-related and to keep analysis consistent across neuroimaging modalities, analyses were conducted to explore whether VS-rACC connectivity mediated the association between CTQ and BDI-2 scores, controlling for sex at birth, scan age, and adolescent CDI scores. The constrained mediation model (2a) had a non-significant indirect path from CTQ total scores, to VS-rACC, to BDI-2 scores ($\beta = 0.07$, $p = 0.22$), suggesting this rsFC marker did not help to statistically explain the CTQ to BDI-2 score association for the full sample. Notably, there was a trend-level CTQ total by sex interaction effect on adult BDI (interaction effect: $\beta = 0.60$, $p = 0.05$), suggesting that the direct effect of CTQ on BDI was modestly different between males and

females (See table 3.4.1). Next, a mediation model (2b), CTQ total score, to VS-rACC, to adult BDI-2 scores, was conducted but the paths were unconstrained and allowed to vary differently by assigned sex (i.e., moderated mediation). The results of model (2b) demonstrated *trending* mediation effects for *females* but not males (Females: indirect $\beta = 0.17$, $p = 0.07$; Males: indirect $\beta = 0.004$, $p = 0.82$, see Figure 5, Table 3.5.1). This finding suggests that VS-rACC rsFC may assist in explaining the CTQ total score to adult BDI-2 score relationship, primarily in females. Then, a constrained mediation model (2c) was examined using CTQ emotional neglect, specifically, however, this resulted in a non-significant indirect effect ($\beta = 0.06$, $p = 0.17$). Finally, the unconstrained moderated mediation (same as model 2b above) was replicated using CTQ emotional neglect. Model (2d) demonstrated a similar trending mediation effect for females, but not males (Females: indirect $\beta = 0.14$, $p = 0.06$; Males: indirect $\beta = 0.01$, $p = 0.69$). Model fit comparisons revealed that model 2b (unconstrained moderated mediation with CTQ total scores) was a better fitting model than model 2a (constrained mediation with CTQ total scores, see Table 3.5.2). There was no statistical support to suggest the moderated mediation using the CTQ emotional neglect subscale was better fitting than the constrained model (see Table 3.5.2). In sum, these *preliminary* results suggest VS-rACC rsFC may help to explain the relationship between childhood trauma and adult depression in females only; however, it should be noted that this sample had a greater number of females than males, so investigation of sex differences are entirely exploratory for the purposes of the dissertation and caution should be taken when interpreting these findings (see section 4.3.2).

# Chapter 4. Discussion

*(Portions of this chapter are currently under review for publication)*

### 4.1 Summary of aims and findings

The current study set out to examine longitudinal associations between adolescent mesocorticolimbic brain response during winning of monetary rewards and rsFC and depression symptoms in adulthood, as well as explore the role of childhood trauma in these associations. By utilizing a biopsychosocial approach and investigating the effect of multiple potential risk factors of depression, this project aimed to underscore the importance of an integrative lens and provide early groundwork for future research investigating risk and resiliency markers of psychopathology. Together, this project lends new insights on the developmental origins of psychopathology to better support preventive mental health efforts.

The dissertation's overachieving goals were to study the predictive capacity of two risk factors, one neurobiological (reward-related circuitry) and one psychosocial (i.e., childhood trauma), and their role in the development of depressive symptoms in adults. The current study sought to address two major aims including 1) how adolescent reward response and reward-related circuitry, at ages 12-16 years, relates to depression symptoms in adulthood, at ages 21-27 years, and 2) how childhood trauma relates to adult depression symptoms, as well as to adolescent reward response and reward-related circuitry. Contrary to Aim 1 hypotheses, a blunted VS adolescent reward-related brain response was *not* predictive of depression symptoms in adulthood. However, in line with hypotheses, there was a positive relationship between adolescent rsFC and adult depression. Specifically, hyperconnectivity among mesocorticolimbic regions (VS-rACC) was predictive of increased depression symptoms in adults. There was also some specificity to these findings, as adolescent VS-rACC rsFC was not predictive of other adult psychopathology symptoms (externalizing and anxiety).

Findings confirmed part of our Aim 2 hypotheses and revealed a significant positive association between adult depression symptoms and childhood trauma. The present results did not show support for a negative relationship among VS reward-related brain response and childhood trauma scores (i.e., blunted VS reward response and greater childhood trauma). Though not specific to our hypotheses, we demonstrated adolescent rACC reward response was positively related to childhood trauma scores, primarily childhood emotional neglect. As hypothesized, results revealed heightened adolescent mesocorticolimbic rsFC was associated with childhood trauma in the *same* adolescent VS-rACC rsFC that was related to adult depression. Exploratory task-based analyses suggested preliminary support for an interaction effect of childhood emotional neglect and rACC reward response on adult depression symptoms, such that the childhood trauma to adult depression relationship was altered as a function of adolescent rACC reward response. Moreover, those with greater rACC reward response showed a stronger relationship between childhood trauma and depression. Exploratory rsFC analyses suggested that adolescent VS-rACC rsFC may in part help to explain the childhood trauma to adult depression relationship, specifically in assigned females at birth. Together, these findings provide novel information on how adolescent aberrations in brain response to rewards and reward-network connectivity may be used to identify risk phenotypes of depression in adulthood and highlight the importance of incorporating other risk factors, such as childhood trauma, to best understand pathogenesis.

### 4.2 Mesocorticolimbic WOF reward response

#### *4.2.1 Mesocorticolimbic WOF reward response associations with depression*

Although blunted VS activation during reward anticipation and outcome has been repeatedly identified as a neurobiological risk phenotype and characteristic of depression in

adolescents and adults (for review; Keren et al., 2018; Ng et al., 2019; O'Callaghan & Stringaris, 2019; Toenders et al., 2019), our results did not support this hypothesis, nor replicate previous findings. Historically, in healthy adults and adolescents, the striatum has demonstrated an increased response to reward (Forbes et al., 2009; Haber, 2016; Haber & Knutson, 2010; Schultz et al., 1997); however, depressive symptoms have been negatively linked to VS reward activation in adults and adolescents. Multiple studies in adults with concurrent depressive symptoms found reduced activation to striatal areas (NAcc, caudate, putamen) compared to non-depressed counterparts, and these findings have been similarly replicated among currently depressed youth and adolescents (Forbes et al., 2009; Forbes et al., 2010; Lichenstein et al., 2016; Morgan et al., 2013; Judith K. Morgan et al., 2016; Pechtel et al., 2013; Pizzagalli et al., 2009; Whitton et al., 2015). Similar to the present study objectives aiming to utilize neurobiological risk factors prior to disease onset to predict future depression symptoms, select studies in at-risk and healthy youth have shown that this neurobiological phenotype (i.e., dampened VS reward response) is predictive of future increases in depression symptoms at a later timepoint (Bress et al., 2013; Gotlib et al., 2010; Morgan et al., 2013; Nelson et al., 2016; Stringaris et al., 2015); yet, all of these mentioned studies were investigating *both* the neural marker and depressive symptoms during the *adolescent* period (i.e., follow-up within 1 to 3 years). This might explain, at least in part, why the current project was not able to replicate previous associations between adolescent reward response neurobiology at 12-16 years (i.e., VS response during monetary reward receipt) and future depressive symptoms in adults 21-27 years, a much later follow-up. Notably, although previous studies demonstrated blunted reward response fluctuated as a function of current depression symptom severity (greater severity, lesser reward response), as well as first onset depression, perhaps length of symptoms presentation alters the impacted underlying

neurobiological mechanisms (Alexopoulos et al., 2012; Bartova et al., 2015; Kaiser et al., 2015). That said, it is important for future studies to disentangle whether this neurobiological phenotype of blunted reward response truly represents a risk phenotype.

While it is well understood that the reward system is still undergoing significant changes during adolescence (Telzer, 2016), with greater activation shown in the VS for adolescents (ages 13 to 17 years) when compared to children (ages 7 to 11 years) and adults (ages 23 to 29 years) (Galvan et al., 2006), developmentally, the VS shows a reward-related peak in middle adolescence (ages 15 and 16 years) (Van Leijenhorst et al., 2009) and normalization once the adult stage is reached (Braams et al., 2015; Cao et al., 2021). Therefore, studying reward response during this peak developmental period could potentially offer greater likelihood of detecting a blunted reward response in those at risk for depression, since there should be room for more variation from expected high levels of brain response. Although the present study did not find adolescent age to be associated with differences in adolescent reward-related brain response in our cross-sectional sample, it may be that unique developmental differences in the timing of reward response peak (i.e., data collected during an adolescent's peak reward response window, or before/after this peak) may perhaps be overshadowing potential findings, especially with the large span of adolescent ages included in the present study. As such, recent studies found relationships among depression symptoms and reward circuitry to vary significantly as a function of age (i.e., preschool vs. adolescence) as well as depression symptom status (i.e., current, past, and cumulative) (Luking et al., 2021; Rappaport et al., 2020). Future work would benefit from having multiple timepoints of neuroimaging data, from childhood to late adolescence, as well as multiple measures of depression symptoms to appropriately model reward system neural trajectories and psychopathology development.

Previous studies have also shown conflicting findings based on the reward processes under examination. For instance, some have shown blunted VS response during reward anticipation exclusively (Gotlib et al., 2010; Morgan et al., 2013; Rappaport et al., 2020; Stringaris et al., 2015), while others demonstrated these effects only upon reward receipt (Bress et al., 2013; Luking et al., 2016). Studies utilizing both reward anticipation and outcome have even shown opposing findings among the different reward processes (Fassett-Carman et al., 2023; Smoski et al., 2009), as well as similar findings among these processes (Luking et al., 2021). Potential differences in the specific reward-related processes (i.e., anticipation, receipt) studied during fMRI and different reward-related tasks (i.e., WOF, monetary incentive delay, MID) might explain our inconsistences and lack of findings during reward receipt. It might be argued that reward anticipation better captures diminished positive affect during adolescence, whereas dampened hedonics, measured via reward receipt, might be better representative of a younger sample, since hedonics is an automatic process and reward anticipation represents a more advanced developmental skill adapted through repeated environmental exposure (Fassett-Carman et al., 2023; Rappaport et al., 2020). Reward anticipation might also better capture specific depression subtypes, such as anhedonia, as it represents a motivational drive to gain rewards. Overgeneralizations have been made suggesting that depression dampens one's ability to feel pleasure; yet studies have shown similar consummatory pleasure (i.e., rating sweets) across depressed and non-depressed adults (Treadway & Zald, 2011). Additional neurobiological evidence suggests that the dopaminergic system is heavily involved in reward anticipation due to necessary motivational aspects required to predict a salient reward; whereas reward consummation may rely more heavily on opioid receptors (Berridge & Robinson, 1998; Berridge & Robinson, 2003; Smith et al., 2010). Another piece of evidence that may help conceptualize

the inconsistencies when measuring dampened hedonics in depression comes from the literature on comorbid substance use disorders and depression, which demonstrates that individuals with chronic substance use show intact hedonics during drug consumption even with current depressive symptoms (Baskin-Sommers & Foti, 2015), perhaps due to opposing actions on reward circuitry (e.g., hyper-response due to drugs and hypo-response due to depression), much like what may be the case during the heightened time of reward response during adolescence. Unfortunately, there were methodological issues with the anticipation phase of the WOF task in this particular sample, so direct examination of differences among reward receipt and anticipation were not possible. That said, reward anticipation and receipt are *only* two reward-related processes and future work should incorporate other domains, such as reward-based decision making and effort expenditure, as these may map on to other associated symptom clusters of depression.

*4.2.2 Rostral anterior cingulate WOF reward response and childhood emotional neglect*

Childhood emotional neglect is characterized by limited emotional responsiveness, lesser interactive time between caregiver and child, and limited emotional availability (Glaser, 2002; McLaughlin et al., 2019). This type of trauma has the highest incidence rate, with approximately 76% of children impacted by emotional neglect (Child Welfare Information Gateway, 2022). It is suspected that childhood emotional neglect decreases the opportunities a child has for the development of associative learning, particularly reward responsivity (Hanson et al., 2017; Kaplan et al., 1999; Sheridan et al., 2018). Experiencing childhood maltreatment (emotional abuse and neglect) has been shown to increase the risk for depression and suicide by 3-fold (Brown et al., 1999; Chapman et al., 2004). While reductions in VS reward activation and anticipation have consistently been shown in children and adolescents exposed to early life

emotional neglect and early life stress (institutionalized maltreatment) (Goff et al., 2013; Hanson et al., 2015; M. A. Mehta et al., 2010), our findings did not replicate this, perhaps not surprising given the null findings between VS reward response and depression.

Though our results seem contrary to the typical hypo-reactivity characterization of reward dysfunction in MDD (i.e., blunted VS to reward), and suspected neurobiological findings replicated in trauma-associated reward dysfunction (Dillon et al., 2009; Hanson et al., 2015; M. A. Mehta et al., 2010; Takiguchi et al., 2015), it should be noted again that the reward process is more complex than simply dampened hedonics. The extended reward network integrates both *affective* and *regulatory* information in order to recognize reward, respond to stimuli, and alter behavior based on previous outcomes. Both dampened activation in areas of the extended reward network (i.e., mPFC, posterior cingulate, and precuneus), as well as increased activation of these areas (i.e., mPFC, ACC, inferior frontal gyrus) have been shown to be related to childhood maltreatment (Birn et al., 2017; Hanson et al., 2018; Kumar et al., 2015; Quevedo et al., 2017); however, the directionality has varied as a function of the reward process under examination, as well as type of trauma measured (Boecker et al., 2014).

Our results did indeed reveal a positive association between reward response in the rACC and childhood trauma. Additionally, preliminary findings suggest that rACC reward response moderated the relationship between emotional neglect and adult depression, such that those with heightened rACC reward response showed a stronger emotional neglect to depression association. Viewing childhood emotional neglect as increased exposure to violated environmental expectations, in line with what others have coined as the conceptual model of ‘deprivation’ as opposed to ‘threat’ (McLaughlin & Sheridan, 2016), may assist with understanding how increased activation in this reward-regulatory region of the rACC might have

developed. For example, Kim-Spoon and colleagues found higher rates of emotional neglect to be associated with increased insula and dorsal ACC activation during risk processing (Kim-Spoon et al., 2021), suggesting this type of trauma may affect the neurodevelopment of the salience and reward circuits. Adolescents with high exposure to childhood trauma (CTQ total across domains) showed similar increased rACC, mPFC, and insula activation when viewing emotionally valanced cues (Elsey et al., 2015; Zhai et al., 2019). Using structural and rsFC modalities, others showed that exposure to emotional neglect was associated with larger bilateral ACC as well as alterations in SN rsFC (middle frontal gyrus, ACC, supramarginal gyrus) in neglected children compared to typically developing children (Kawata et al., 2024). Further, a positive relationship between lifetime trauma and rACC reward responsivity was shown to be associated with negative affectivity in young adults (Eckstrand et al., 2019). Together with this past work, our findings may suggest that increased rACC recruitment and *over-monitoring* during winning of rewards may represent an altered neural process as a consequence of unclear expectations in early childhood environments and might be involved in the progression of depression psychopathology. The extra recruitment of these regulatory regions perhaps represents increased conflict monitoring due to the learned inconsistencies in predictability of rewards; therefore, the combination of growing up in an emotionally neglectful environment and recruiting more rACC when receiving rewards might increase one's risk for depression in adulthood. Due to the significant influence of the childhood environment on trajectories of neurodevelopment and the potential role it plays in adult psychopathology, continued investigation of how early childhood trauma relates to underlying neurobiological mechanisms is important. Notably, a recent study invested the different roles specific trauma types play on trajectories of neurodevelopment and found that varying trauma exposures were differentially

related to changes in risk and reward processes (Kim-Spoon et al., 2021). Future work should aim to implement greater dimensional modelling strategies to compare discrete types of maltreatment (i.e., physical and emotional threat/abuse and deprivation/neglect) instead of a cumulative approach (Kim-Spoon et al., 2021; McLaughlin & Sheridan, 2016).

### 4.3 Mesocorticolimbic resting-state functional connectivity

#### *4.3.1 Striatal-rostral anterior cingulate rsFC and depression*

Although blunted VS activation during reward anticipation and outcome has been repeatedly identified as a neurobiological risk phenotype and characteristic of depression in adolescents and adults (for review; Keren et al., 2018; Ng et al., 2019; O'Callaghan & Stringaris, 2019; Toenders et al., 2019), the results for rsFC studies have been less consistent. Generally, based on a recent rsFC review, adolescents with MDD showed patterns of hyperconnectivity within the salience network (SN), hyperconnectivity between the default mode network (DMN) and SN, and hypoconnectivity within the cognitive control network (CCN) (Macêdo et al., 2022). Our results align with select prior work showing hyperconnectivity between reward circuitry predicting greater depressive symptoms (Jin et al., 2020; Pan et al., 2022; Pan et al., 2017; Rolls et al., 2018). In accordance with hyperconnectivity in the SN findings, a longitudinal study demonstrated increased amygdala-rACC connectivity to be associated with greater internalizing psychopathology (i.e., depression and anxiety symptoms) in late adolescence and early adulthood (Jalbrzikowski et al., 2017). Given the relevance of reward-related dysfunction in depression risk and severity, Pan and colleagues extended these findings to the larger reward network and found that greater VS connectivity to a number of reward-related regions (e.g., VTA, ACC, and ventromedial PFC) in childhood was predictive of future depression in early adolescence (Pan et al., 2017)); however, follow-up studies by their group (Pan et al., 2022)

found that greater VS intrinsic functional connectivity (iFC), a network-based measure of resting-state connectivity between the VS and other reward-related regions, was *only* associated with a higher probability of depressive symptoms at 14 years, not at 16 or 18-year timepoints. Our findings complement these more recent reward-based rsFC results and showed it has the capacity to predict depressive symptomology at a later time point, extending into adulthood.

More specifically, we found hyperconnectivity between the VS-rACC to be associated with greater depressive symptoms at follow-up. Previous rsFC literature has demonstrated increased connectivity between the NAcc, ventral ACC, and OFC in adolescents and adults with MDD compared to health controls (Fan et al., 2021; Gabbay et al., 2013) and greater inflexibility, quantified as less efficiency in connectivity changes as a function of task modality resting-task versus behavioral inhibitory task, between dorsal ACC to middle frontal gyrus in depressed adolescents (Ho et al., 2017). Similarly, others have illustrated hyperconnectivity primarily among frontal/cognitive control regions, such as the rACC and middle frontal gyrus in depressed participants (Davey et al., 2012; Langenecker et al., 2018). Utilizing an independent component analysis (ICA), data-driven approach, greater connectivity between the ACC and ventromedial PFC was associated with current and future depressive symptoms (Jin et al., 2020). Studies investigating the predictive capability of *dynamic* functioning of neural rsFC markers (standard deviation in rsFC over a series of sliding windows) found individuals with MDD exhibited increased dynamic (greater variability) rsFC between salience network regions (mPFC, including ACC and insula) (Kaiser et al., 2016), greater dynamic rsFC time spent in DMN and SN, and decreased time spent in ventral limbic networks (Kaiser et al., 2022). Further, the dynamic rsFC markers were shown to mediate the relationship between sertraline response and depressive symptoms (Kaiser et al., 2022), suggesting these altered rsFC markers might help to

explain treatment response. Together, the previous rsFC work and our findings suggests greater coupling of regulatory regions, such as the rACC, and limbic regions, such as the VS, may again represent *over-functioning* of this affective regulatory region which may, in part, contribute to blunted reward response in the VS, so often observed in depression (O'Callaghan & Stringaris, 2019). The over-regulatory hypothesis is further supported by intervention studies showing that *decreasing* VS-ACC connectivity demonstrated an immediate reduction in depressive symptoms and long-term treatment success (Elias et al., 2021; Mayberg et al., 2005; Salomons et al., 2014). That said, greater VS-rACC rsFC may represent a precursor to depression risk, particularly as these results were in adolescents before the development of significant depression symptoms; however, the reliability of this finding may be limited due to the original study recruitment excluding adolescents with pre-existing mood-related symptoms. Future work may aim to enroll adolescents with varying levels of depressive symptoms (clinical, at-risk, and typical levels) at baseline to understand causal predictors of depression.

*4.3.2 Striatal-rostral anterior cingulate rsFC and childhood trauma*

Understanding biopsychosocial risk factor associations with depression is important since individuals who have experienced childhood trauma are at elevated risk of developing depression, and these early life experiences may help in understanding the pathogenesis of depression (Nelson et al., 2017). Our results demonstrate that the *same* adolescent mesocorticolimbic resting-state connection (VS-rACC) shown to be associated with adult depression was also positively associated with childhood trauma. These findings are supported by previous studies showing reward-related behavioral alterations and neural aberrations in children and adolescents who suffered from early life stress and maltreatment (Goff et al., 2013; Guyer et al., 2006; Hanson et al., 2015; Mehta et al., 2010; Vidal-Ribas et al., 2019). Further,

hyperconnectivity between reward-related regions (e.g., VS, mPFC, amygdala, ACC) in older adolescents and young adults exposed to childhood trauma was related to increased depressive symptoms and rsFC markers were shown to mediate the childhood maltreatment to internalizing severity and depression association (Hanson et al., 2018; Rakesh et al., 2023), suggesting a potential causal neurobiological link between childhood experiences and adult internalizing psychopathology.

We demonstrated preliminary findings in support of VS-rACC as a neurobiological link from childhood trauma to adult depression symptoms, particularly in assigned females at birth. Some have argued that experiences of childhood trauma in fact alter the reward circuit and associative learning processes (Sheridan et al., 2018) in support of an underlying causal mechanism to future depression. There have also been studies illustrating that the consequences of early life trauma on alterations in rsFC are different among assigned males and females (Bath, 2020). Although some studies have shown support for an intermediary role for this altered reward-related rsFC marker on the childhood trauma to later depressive symptoms link (Fan et al., 2021; Rakesh et al., 2023), one such study was cross-sectional therefore making causal links difficult and the other had limited distribution of trauma exposure. The sex specificity of the present findings may be related to differences in puberty and hormonal changes occurring during adolescence, which in and of themselves may confer greater risk (Goddings et al., 2019). For example, females with higher levels of testosterone showed greater NAcc to ACC and insula connectivity during reward anticipation, whereas male adolescents did not (Ladouceur et al., 2019), suggesting sex specific hormonal changes may contribute to differences in reward-related brain development. Notably, physiological responses to early life adversity, as well as rsFC, have been shown to vary as a function of biological sex and type of adversity (Gupta et al., 2017).

Although our work provides early support of childhood trauma playing a role in altering neurodevelopmental trajectories of reward circuitry, which may be linked to increased risk for the development of depression symptoms, these findings are preliminary. Our study did not recruit enough assigned males at birth to thoroughly investigate how reward-related circuitry in those exposed to trauma might be different as a function of sex assigned at birth. Of note, there will need to be more evidence beyond simply a binary category of sex and approximations of brain maturation measured by age and self-reported pubertal development in future work, particularly as typical pubertal changes have been shown to alter rsFC, independent of early psychopathology (Ojha et al., 2022).

### 4.4 Integrated results and potential underlying mechanisms of childhood trauma, reward-related circuitry, and adult depression

The rACC has also been highly implicated in the current study findings. In alignment, prior studies of depression have shown *greater* recruitment of the dorsal and rACC in adults with MDD during reward anticipation (Knutson et al., 2008; Walsh et al., 2017) and upon reward outcome in adults and adolescents (Admon et al., 2015; Morgan et al., 2013; Nelson et al., 2016). This increased ACC monitoring during reward processes and greater coupling of rACC to VS at rest might represent a neurobiological sequala of childhood emotional neglect, at least for some individuals. To explain, if one's environment does not align with expectations or results in conflicting outcomes (i.e., completed chores results in both rewards and punishments), this may recruit greater monitoring from the rACC. This is supported by evidence that depressed individuals experience more affective conflict (rACC recruitment) during anticipation of *attainable rewards* versus healthy controls recruiting rACC during *avoidable losses* (Knutson et al., 2008). Conceptually, perhaps over time these individuals learn that a typically rewarding environment no longer holds rewarding property (Wacker et al., 2009), which again could help to

explain why some individuals go on to develop depression and dampened VS reward response during reward outcome.

The ACC is a target region often studied in relation to multiple psychopathologies, but particularly depression, as it is highly involved in integrating inputs from multiple systems (i.e., affective, social, cognitive). It is also involved in many behaviors that characterize depressive symptoms, such as difficulty regulating negative affect and decreased goal-directed behaviors (Lichenstein et al., 2016; Newman et al., 2015). Given the ACC's position and role in connecting cortical and subcortical brain regions, it is an especially important region to study during adolescence, as the integration of communication between top-down and bottom-up pathways is still undergoing significant developmental changes (Casey et al., 2008; Casey, 2015). As mentioned above, the rACC is involved in multi-functional regulatory processes and thus may be involved in updating and regulating future behaviors. Increasing regulation over bottom-up reward and affective response may be adaptive when in a traumatic environment, however, this may also lead to disruptions in reward-based decision making and unnecessary conflict monitoring in safe environments (Guyer et al., 2014; Guyer et al., 2006).

Together, our finding of increased brain response in the rACC during winning of rewards complements our rsFC findings showing increased connectivity between the VS-rACC in support of an over-regulatory role of the rACC in those at higher risk of developing adult depression. Investigation into the neurochemical mechanisms involved is warranted; however, perhaps childhood maltreatment plays a part in altering the dopamine transmission (Ironside et al., 2018), as well as the hypothalamic-pituitary-adrenocortical (HPA) axis (Kraynak et al., 2019) possibly leading to dysregulation of glucocorticoid secretion and interleukin (IL)-6, thus increasing depression risk and symptoms (for review, Goff & Tottenham, 2015; Zajkowska et al.,

2021). That said, greater rACC brain response to reward and increased VS-rACC rsFC may represent precursors to depression risk, particularly as the current study's results were in adolescents *before* the development of significant depression symptoms; however, the reliability of this finding may be limited due to the original study recruitment excluding adolescents with pre-existing mood-related symptoms. Future work may aim to enroll adolescents with varying levels of depressive symptoms (clinical, at-risk, and typical levels) at baseline to understand causal predictors of depression.

Our results may also have clinical implications for potential prevention efforts and future therapeutic interventions. Focus on both distal and proximal prevention efforts have been shown to promote resilience in populations affected by childhood maltreatment. Evidence suggests parent education programs focused on teaching parents how to promote a caring, consistent, and positive parenting environment, as well as home visiting programs (e.g., targeting parental skills and knowledge on the importance of child-parent relationships) and increasing social connectedness have been shown to prevent maltreatment and decrease the associated deleterious outcomes (Gubbels et al., 2019; Han & Oh, 2022; van der Put et al., 2018). Similarly, having access to a relationship with a trusted adult instills resiliency in children impacted by adverse childhood experiences (Ashton et al., 2021). Proximally, maltreated individuals with higher levels of temperamental traits such as self-reliance, perseverance, and future-oriented thinking were less likely to go on to engage in maladaptive behaviors (i.e., substance use) (Picci et al., 2023).

Manipulation of brain activation and circuit communication in intervention studies have shown success in depressive symptoms reductions. Specifically, decreases in VS-ACC connectivity demonstrated an immediate reduction in depressive symptoms and long-term

treatment success (Elias et al., 2021; Mayberg et al., 2005; Salomons et al., 2014) in adults with depression. Utilizing deep brain stimulation (DBS) to alter the functioning of the rACC, past research has shown significant symptoms improvement in adults with treatment-resistant depression and demonstrated that these effects were sustained long-term (Alagapan et al., 2023; Crowell et al., 2019). Even behaviorally focused interventions, such as BA, aimed at re-teaching cue-associative learning, was effective in increasing neural sensitivity to reward-related information in adolescents with MDD, which subsequently improved depressive symptoms as well (Webb et al., 2020). That said, future interventions may target symptoms reduction at both the neurobiological and behavioral level of reward-related processing as they both have been shown to improve symptoms and together might have the most impact on symptom improvement.

### 4.5 Limitations

Some limitations should be considered when interpreting our research findings. Although the study design was longitudinal, our study sample size was relatively small, and neuroimaging findings in small sample sizes may be difficult to replicate (Marek et al., 2022). Additionally, the current study utilized an *a priori* seed-based approach to assess rsFC, and there are several data-driven approaches to analyzing resting state data (i.e., whole-brain graph theory methods, and ICA) which may conclude different findings. Although these are limitations, Marek and colleagues indicated that utilizing a voxel-wise approach has demonstrated increased Type I errors, therefore an *a priori* hypothesis driven approach may help to slightly mitigate these concerns. Future research with larger, heterogeneous samples implementing these approaches may provide additional information about the involvement of reward-related network communication in the development of depression. Notably, our adult study sample was

comprised of re-contacted participants from an existing longitudinal study, for which adolescents originally were excluded for psychiatric disorders and risk factors. Though a strength of the study was illustrating a neurobiological precursor to depression prior to depression onset, our range of individualized risk trajectories and depressive symptomology at follow-up was likely constrained. Due to fairly limited power, we used a total trauma score, involving exposure to multiple types of trauma (i.e., emotional neglect, sexual abuse); however, future research should parse trauma types as it may provide improved specificity (Sheridan & McLaughlin, 2022). It should be noted that differing types of trauma may differentially impact neurodevelopment. Notably, the present study was not able to precisely ascribe the timing of trauma and therefore cannot thoroughly contribute to the ongoing debate regarding the impact of trauma timing (early versus later) on neurodevelopment. However, many in the field described that the impact of timing and type of trauma (threat versus deprivation) may create unique "sensitive periods" (McLaughlin et al., 2019). For instance, the first two years of life represent a critical window for language development, yet, if a child grows up in a less enriched environment (i.e., lacking cognitive input and spoken interactions, a form of deprivation), this may result in greater negative neurocognitive effects versus later in life. Improved measurement on the specificity of type, timing, and chronicity of traumatic experiences is warranted for future research. Low power precluded our ability to justify thorough examination of sex differences with these associations; future work may aim to enroll an equal sample of assigned males and females with and without elevated depression symptoms to do so. Also, to capture typical and atypical development of reward-related circuits, future studies may collect multiple waves of data to model neurobiological and psychopathological trajectories. Lastly, caution should be taken when generalizing our findings to more diverse samples, as the current study was not demographically

diverse and primarily included higher socioeconomically status, white, non-Hispanic individuals, such that findings may not be representative across other populations (LeWinn et al., 2017). Future work focused on biopsychosocial risk factors for depression should investigate these relationships among a sample with greater diversity.

### 4.6 Conclusions

The current dissertation set out to better understand the developmental origins of adult depression through examination of two specific biopsychosocial risk factors, childhood trauma and adolescence mesocorticolimbic circuitry. Implementing longitudinal data, the study demonstrated strengths in its ability to prospectively predict potential precursors of disease. The current work identified that heightened involvement of the rACC, a region involved in monitoring and encoding reward expectation, when receiving rewards in adolescence may be a neural phenotype associated with greater childhood trauma exposure. Specifically, youth exposed to early environments of emotional neglect coupled with this heightened conflict monitoring during reward may be at higher risk for adult depression. Complementary findings in rsFC, illustrated that both childhood trauma and adult depression show similar hyperactivation among mesocorticolimbic brain regions, VS-rACC, which may play a role in the often-revealed blunted reward response or anhedonic clinical presentation in depression. The greater coupling among mesocorticolimbic circuitry at rest may act as a link tying early childhood trauma to the progression of adult depression. However, the causal relationships are entirely speculative and potential future studies may find it relevant to understand the causal mechanism between childhood trauma, reward-related circuitry, and adult depression, and underlying neuromodulators associated with these connections as dysfunctional interactions of trauma exposure and reward mechanisms may be at play in the progression of depression. It is hoped

that these findings might encourage future research to consider biopsychosocial risk factors for depression to assist in guiding mental health prevention efforts.

# Appendix 1.

Evaluating the predictive capacity of adolescent reward neurobiology and reward-learning behavior and depression symptoms in young adults

## A.1 Introduction

Disruptions in reward-related processes have been repeatedly shown to be a critical factor underlying depression (Keren et al., 2018; Phillips et al., 2015; W. N. Zhang et al., 2013). Over several decades, substantial evidence has accumulated to suggest depression is characterized by a diminished ability to experience hedonics, measured through dampened VS response to the anticipation and receipt of reward (Eckstrand et al., 2019; Forbes et al., 2009; Guyer et al., 2006; Pizzagalli et al., 2009). Similar disruptions in reward-related networks have been demonstrated in both adolescents and adults with MDD, and based on a compilation of studies and meta-analysis, less striatal and greater PFC neural response to monetary rewards has been consistently shown (Lichenstein et al., 2016; Ng et al., 2019; Stringaris et al., 2015). That said, depression has not only been associated with dampened VS reward response but also aberrations in reward circuit connections. Although the directionality of these findings have been mixed in terms of greater or lesser connectivity (see section 1.4.3) between reward-related brain regions, multiple longitudinal rsFC studies in adolescents support a hyperconnectivity hypothesis (i.e., greater VS to ACC connectivity) (Jalbrzikowski et al., 2017; Jin et al., 2017; Pan et al., 2022; Pan et al., 2017). These recent findings suggest the potential for *over-functioning* of top-down prefrontal brain areas resulting in dampened VS reward response as a neurobiological marker for depression. There is also some evidence to suggest that these neural markers may precede MDD onset, supported by research in healthy adolescents showing greater ventromedial PFC activation during reward receipt and less VS activation during reward anticipation are predictive of greater increases in future depressive symptoms (Morgan et al., 2013; Stringaris et al., 2015). Yet, how these neural markers in adolescence are associated with depression in adulthood remains largely unknown, as past prospective studies examining the predictive capacity of these neurobiological

features on future depression symptoms have only done so over a short follow-up span (2-3 years).

Prior studies investigating neurobiological markers of depression have conceptually focused on a diminished hedonic response, whereas depression is more complex than simply an inability to experience pleasure (Keren et al., 2018). The key reward processes that have been studied in relation to depression include initial responsiveness to and expectancy of reward (i.e., anticipation and reward outcome). However, there are a variety of other decision-making processes at play when faced with a possible reward (e.g., amount of effort needed to obtain a reward, reward valuation to determine the probability of cost and benefits of the outcome, and using decision-making processes to guide future action selection) (Berridge & Robinson, 1998; Berridge et al., 2009). Rather than focusing solely on dampened hedonics, investigating how these underlying neurobiological deficits in hedonics (i.e., blunted VS, heightened PFC activation) may propagate and influence future reward-related learning, another reward process, may provide more useful information for targeted intervention strategies based on individual variability in neurobiology and reward-outcome behaviors. (D. M. Barch et al., 2016).

Studies investigating reward learning in adults using the probabilistic reward task (PRT) have shown that healthy controls develop a response bias to more frequently rewarded stimuli over time, whereas this effect is diminished adults with MDD (Admon et al., 2017; Esfand et al., 2024; Pizzagalli et al., 2009; Pizzagalli et al., 2008; Pizzagalli et al., 2005; Reilly et al., 2020; A. E. Whitton et al., 2016). Importantly, reward learning may be predictive of MDD diagnosis and treatment success (Eckstrand et al., 2019; Vrieze et al., 2013), as lower baseline reward learning predicted persistence of MDD diagnosis, and intervention improved reward learning to levels analogous to healthy controls (Vrieze et al., 2013). This highlights the potential importance of

investigating reward learning, as it may act as an intermediate behavioral phenotype between neurobiological reward deficits and depressive symptoms. Notably, depressive symptom profiles differ in adults and adolescents (Rice et al., 2019), yet, adolescents with high familial risk for depression, defined by positive biological parental history of MDD, also exhibited impaired reward learning, compared to those with low familial risk (Belleau et al., 2021). In combination, previous work suggests a relationship between reward-learning behavior and emerging depression risk, as well as current depression symptoms. Through the integration of underlying early neurobiology and resulting behavioral impact it is hoped that this research adds to the clinical understanding of depression and helps to identify key features involved in the risk and maintenance of depressive symptoms to diminish long-term consequences of this mental health concern.

The goals of the current study were two-fold. First, the present study aimed to determine whether current depressive symptoms in young adults were related to reward-learning behavior via *virtual* administration of the original PRT task. The initial PRT (Pizzagalli et al., 2005) study investigating reward-based learning in adults with MDD and adolescents at high risk for developing MDD (Belleau et al., 2021) was, for the purposes of this study, converted to an online format through the millisecond platform (Millisecond-Software, 2015), which to our knowledge was the first to test the virtual administration of this version of the task. The present approach was to further assess the validity of virtual administration of the PRT by replicating the same reward-learning effect across task blocks, and investigate whether reward-learning behavior was related to depression symptoms in young adults, as shown previously (Pizzagalli et al., 2008; Pizzagalli et al., 2005; A. E. Whitton et al., 2016). The second aim of this study set out to investigate if adolescent neurobiological reward circuitry (i.e., reward responsivity and rsFC of

the reward system) was predictive of adulthood reward-learning behavior and depression. If significant associations between adolescent reward neurobiology and adult reward-learning behavior are found, it may support the notion that reward learning acts as an intermediate behavioral phenotype between neurobiological reward deficits and depressive symptoms. There were three primary hypotheses for the current study. First, I hypothesized that adult participants would demonstrate adequate reward-learning behavior illustrated by a main effect of block on response bias, suggesting all young adults developed a response bias over time by learning reward associations. Second, I hypothesized that reward-learning behavior would differ as a function of depression, such that young adult participants with higher depressive symptoms would demonstrate poorer reward-learning behavior (measured by a reduced response bias to more frequently rewarded stimuli) compared to young adults with lower depressive symptoms, evidenced by a depression by block interaction (poorer response bias over time as a function of depression symptoms). Finally, I hypothesized that adolescent reward neurobiology (i.e., reduced VS response upon receipt of reward and increased VS rsFC to other reward regions) would be associated with impaired reward learning and higher depressive symptoms in young adulthood.

## A.2 Methods and Material

### *A.2.1 Participants*

For specific participant recruitment details see (see sections 2.1 and 2.2). Broadly, of the 154 individuals identified to be re-contacted as part of the lab's longitudinal study, 73 young adults completed the virtual PRT; however, 4 participants were excluded from this sample due to insufficient data after behavioral data cleaning parameters (described in section A.2.3 below) resulting in a final sample of 69 participants. Depression symptoms were assessed using the Beck Depression Inventory – Second Edition (BDI-2) (see section 2.5.1), as was used to assess depression in the primary dissertation analyses (see section 2.6). As previous studies have shown,

reward-learning behavior varies as a function of depression diagnosis, symptom severity, depression risk (family history positive), and remitted depression (Belleau et al., 2021; Pizzagalli et al., 2009; Pizzagalli et al., 2008; A. E. Whitton et al., 2016). Since the current study did not formally complete full psychiatric diagnostic screening (see section 2.5), depression groups were generated based on current endorsement of depression symptoms. As done previously (A. E. Whitton et al., 2016), participants who reported BDI-2 scores $\leq$13 were categorized as "non-depressed" and young adults with BDI-2 scores >13 were categorized as "depressed." This cutoff was chosen to include variability in depression symptom severity, ranging from mild to severe, as well as to increase power to investigate group differences.

*A.2.2 Experimental reward-learning task*

The PRT utilizes signal detection theory to assess participants' propensity to modulate behavior based on prior reinforcement history. The premise of the task is based on research demonstrating that unequal frequency of reward produces a systematic preference for a stimulus that was paired with the more frequent reward (Macmillan & Creelman, 2004; McCarthy & Davison, 1979). The PRT consisted of 3 blocks containing 100 trials each. Each trial began with a 500-ms fixation cross and then a 500-ms face missing a mouth. Next, either a short mouth (10mm) or a long mouth (11mm) was added to the face presentation and shown for 100-ms (see Figure 6). Following the 100-ms presentation of the target, the face stimulus was removed, and a white screen was shown until the participant's response was recorded. Participants were instructed to make a button response based on whether they perceived a long or short mouth. Each mouth length was presented with equal frequency. Unbeknownst to the participants, one mouth length was rewarded 3 times more frequently ("rich" stimulus) than the other ("lean" stimulus). Participants were *only* given reward feedback, not loss/error feedback, and this was

done so on an asymmetrical reinforcer ratio, such that rewards were administered on 40 correct trials out of the total 100 trials (30 rich and 10 lean). Reward feedback was displayed on the screen for 1750 ms after a correct trial, along with their cumulative earnings across the entire task. If a participant failed to make a correct response on a trial that was predetermined to receive reward feedback, the feedback was delayed until the next correct item for the same stimulus type. The more frequent reinforcement allocation and short/long button press locations were counterbalanced across participants. Participants were instructed to respond as quickly and as accurately as possible and that not all correct responses would be rewarded. The entire task took approximately 25 minutes with 30s breaks between runs, and participants could win up to $6 in total. Additional instructions for virtual administration included requesting participants turn off mobile device notifications to eliminate task distractions, verifying their battery life prior to task onset to decrease incidence of the task being terminated early, and requesting participants complete the task in a single sitting (i.e., participants could close out of the app which would discontinue/pause the task).

The outcome variable of interest for all analyses was response bias calculated using the formula below, like previous studies (Belleau et al., 2021; Vrieze et al., 2013; A. E. Whitton et al., 2016). Response bias represents the participants' inclination to choose the more frequently rewarded stimulus (Reilly et al., 2020; Vrieze et al., 2013), otherwise an indicator of reward-learning behavior, as it is suspected that an individual who changes their behavior based on learned reinforcement history therefore learned from the earlier experiences. Task performance was assessed using discriminability, a participants' ability to differentiate between the two stimuli, shown below as well. The formulas were calculated using four different trial type counts: 1) "rich correct" represented the number of trials the participant answered correctly for the more

frequently rewarded stimuli, 2) “rich incorrect” represented the number of trials the participants answered incorrectly for the more frequently rewarded stimuli, 3) “lean correct” represented the number of trials the participants answered correctly for the less frequently rewarded stimuli, and 4) “lean incorrect” represented the number of trials the participants answered incorrectly of the less frequently rewarded stimuli. To ensure all computations could be executed for participants with extremely high accuracy (e.g., ‘0’ rich incorrect), 0.5 was added to every variable in the response bias and discriminability equations to eliminate issues with zero in the formulas, as was done previously (Belleau et al., 2021; Pizzagalli et al., 2005; A. E. Whitton et al., 2016). Response bias and discriminability were calculated by block. Mean RT was calculated by block and condition (rich versus lean) to ensure adequate attention throughout and was also used in analyses to investigate reward-learning behavioral differences.

$$Response\ bias = 0.5 * \log \frac{(Rich_{correct} * Lean_{incorrect})}{(Rich_{incorrect} * Lean_{correct})}$$

$$Discriminability = 0.5 * \log \frac{(Rich_{correct} * Lean_{correct})}{(Rich_{incorrect} * Lean_{incorrect})}$$

*A.2.3 Behavioral data cleaning procedures*

A number of quality control checks were conducted on the PRT data prior to analyses, as done previously (Belleau et al., 2021; Pizzagalli et al., 2009; Pizzagalli et al., 2005; Reilly et al., 2020). Participants with too few correct responses to the rich stimulus (≤20) or to the lean stimulus (≤6) were removed from all analyses. Participants’ data were only used if their rewarded responses met a 2:1 ratio of correct rewarded rich trials to correct rewarded lean trials. Further, trials with reactions times < 150 or > 2500 ms were excluded, and trials with latencies greater than or less than 3 standard deviations from the individual participant’s average reaction

time across blocks were also removed. Only participants with a total number of trials per block equal to or greater than 80 were included in analyses after trial level exclusions.

*A.2.4 Statistical analyses and modelling approach*

Group differences in age, depression symptoms, and number of trial outliers were assessed using non-parametric t-tests given the unequal number participants in the samples. To test the validity of the virtual administration of the PRT and to examine reward-learning behavior across blocks and among young adult depression groups, linear mixed effects (lme) models, fitted using maximum likelihood estimate, were conducted (R package, *nlme*) (Pinheiro, 2022) with response bias as the main outcome variable of interest (see models below).

Main effects

```
lme(response bias ~ block+group, random = (~1|Subject))
```

Interaction effect

```
lme(response bias ~ block*group, random = (~1|Subject))
```

The choice to use this modelling strategy was selected in order to model block as a within-subject variable, and to appropriately capture between-subject variability (across all blocks) in response bias, by modelling random intercepts for each participant. The same lme models were used to investigate traditional PRT metrics such discriminability differences and condition specific reaction times (rich and lean correct RT) across blocks. Finally, follow-up analyses of simple effects were investigated (R package, *emmeans*) as appropriate. Like in prior studies (Vrieze et al., 2013; A. E. Whitton et al., 2016), a general increase in response bias across blocks is reflective of significant reward learning represented by a significant block effect, and a difference in reward-learning behavior by depression groups would be evidenced by a significant block by group interaction.

## A.3 Results

### *A.3.1 Participants characteristics and individual differences*

Overall participant descriptives and demographics can be found in section (Sample Characteristics, see section 2.1). Please reference (Table A1) below for specific reward-learning group reported differences and associated statistics. Broadly, there were significantly more assigned females than males in the sample. Adults in the depression group were younger than the non-depressed group. As a function of the grouping criteria, average BDI-2 scores in the depressed group were higher than in the non-depressed group.

### *A.3.2 Data cleaning results*

A total of 1.2% of the trial level data were removed from the sample due to not meeting data cleaning criteria. On average participants had a total of 98/100 trials per block after cleaning procedures. The number of removed outlier trials and mean accuracy did not differ across depression groups (see Table A2). The number of removed outlier trials did not differ across blocks (see Table A3).

### *A.3.3 Response bias*

There was no significant main effect of block on overall response bias (see Table A3), suggesting there was no change in reward-learning behavior across blocks. Additionally, there was no main effect of depression group on overall response bias (see Table A2), suggesting no difference in reward-learning behavior between depressed and non-depressed adults. The block by group interaction was also non-significant ($F = 0.76$, $p = 0.47$), illustrating that group differences did not emerge over the length of the task or differ across blocks (Figure 7).

*A.3.4 Discriminability*

There was a significant main effect of block on discriminability (see Table A3), suggesting there was a change in discriminability, a measure of a participant's ability to differentiate between stimuli, across blocks. Follow-up comparison of simple effects demonstrated that participants' discriminability improved from block 1 to block 2 ($t$ = -2.47, $p$ = 0.04), suggesting they improved in their ability to detect stimuli differences (i.e., short vs. long mouth distinctions) (see Figure 8). There was no main effect of depression group on discriminability, suggesting no differences in task discriminability across depression groups (see Table A2). The block by group interaction on discriminability was also not significant (F = 1.89, $p$ = 0.16), illustrating that group differences did not emerge across blocks.

*A.3.5 Reaction time*

The three-way interaction (block by depression group by condition) on RT was not significant ($F$ = 0.13, $p$ > 0.05), suggesting that the depression groups did not learn from the different conditional stimuli at different rates over time (see Figure 9). However, there was a significant two-way depression group by condition interaction ($F$ = 8.74, $p$ < 0.05), such that the depressed group had a greater difference in RT between rich compared to the lean condition trials ($t$ = -6.24, $p$ < 0.05) compared to non-depressed group ($t$ = -4.96, $p$ < 0.05) (see Figure 10). These findings may suggest both groups learned, but the depressed group showed a *larger difference* in RT as a function of condition which may in part represent *better* learning. There was significant main effect of block on RT ($F$ = 14.59, $p$ < 0.05) (see Table A3, Figure 11) which illustrates that participants' RT was faster as time went on (block 3 > block 1: $t$ = 2.98, $p$ < 0.05), which is what would be expected given practice effects. There was also a main effect of condition ($t$ = 54.98, $p$ < 0.05), such that participants were faster on rich trials (collapsed across

blocks and groups) compared to lean trials suggesting all participants learned from the different stimuli type.

*A.3.6 Adolescent reward-related neurobiology and reward-learning behavioral associations*

As the above results suggest, adult participants did not show adequate reward-learning behavior based on previous studies findings. Similarly, there was no main effect of depression group, main effect of block, or block by group interaction on response bias suggesting limited reward-learning differences based on traditional behavioral metrics. Therefore, the brain-behavior analyses are not reported here as it may not accurately depict a true brain-behavior association.

**A.4 Discussion**

*A.4.1 Summary of results*

The overachieving goal of the study was to better understand the associations of reward-learning behavior, reward-related brain circuitry, and depression symptoms. First, in order to study these relationships, the present study set out to validate the administration of the initial PRT on a virtual platform, which had not been done previously. Our results, however, did not provide strong support in favor of using the PRT via virtual administration. Contrary to previous findings (Belleau et al., 2021; Pizzagalli et al., 2009; Pizzagalli et al., 2008; Pizzagalli et al., 2005) and our hypotheses, there were no main effects of block, depression group, or block by group interactions on response bias (a metric of one's propensity to select the more frequently rewarded stimulus, a method of reward-related learning), suggesting no significant change in reward-learning behavior over time or differences in reward-learning behavior as a function of depression group. Yet, there was some evidence to suggest that participants' performance on the task progressed, higher discriminability, as well as reaction time to rich stimuli got faster;

however, there were limited depression group differences, which was the ultimate goal of the study, and there were limitations to these group findings (discussed below). In sum, our findings do *not* support using the original format of the PRT via virtual administration, as it appears the task was too simple and revealed minimal changes in reward-learning behavior while employing traditional metrics.

*A.4.2 Potential explanations and future directions*

While an increase in response bias across blocks did not emerge as would be expected to illicit reward-related learning, there was some evidence to suggest that participants learned how to accurately complete the task. Results showed an increase in discriminability from the first to second block, which was in line with previous studies using this task in the laboratory (Bogdan & Pizzagalli, 2006), and suggests participants' performance improved. Of note, discriminability is a measure of one's ability to differentiate between short and long mouthed stimuli and represents a general measure of task difficulty. Although this shows learning, participants' discriminability within the first block of the task was high, which might indicate participants quickly were able to discriminate between stimuli and approached a ceiling early on in the task. Future work may aim to investigate response bias differences on the trial level data within the first block as it might show when early reward-learning behavior emerged.

The current work also showed a general decrease in reaction time to the more frequently rewarded, "rich" trials. A decrease in reaction time to the rich trials was revealed by a main effect of condition (collapsed across all blocks) suggesting *all* participants were faster in responding to the rich trials. Further, a group by condition interaction revealed that reaction time varied as a function of depression group. These findings showed that participants were aware of the differential reinforcement types based on condition (rich or lean), and depressed participants

showed a greater *discrepancy* between rich and lean trial reaction times. In part, these results replicated previous studies, using both the laboratory-based PRT, as well as the novel virtual version, demonstrating significantly faster reaction times to rich versus lean stimuli (Esfand et al., 2024; Pechtel et al., 2013; Pizzagalli et al., 2008; Pizzagalli et al., 2005). Contrary to previous studies and our hypotheses, however, we did *not* show impaired reward learning in young adults with depression. Rather, our findings revealed that individuals with greater depressive symptoms perhaps learned *better* than non-depressed individuals, evidenced by the larger reaction time discrepancy between rich and lean condition trials. One argument to support these findings could be that depressed individuals showed less effort or were less inclined to perform quickly on trials that were not as often rewarded (lean trials) because the cost (i.e., cognitive effort and moving quickly) did not outweigh the benefit, as has been shown in cognitive effort-based decision making studies in individuals with schizophrenia and current depression (Barch et al., 2023; Vinckier et al., 2022); however, these interpretations are speculative and require more investigation. Notably, the depression group-by-condition interaction is difficult to interpret, because the non-depressed sample had extremely fast reaction times (~550 ms) across both conditions, therefore making it hard to know if they would have shown condition reaction time discrepancies if they were physically incapable of responding any faster. In sum, these results appear to illustrate that the task was, again, too easy for participants via the virtual platform, particularly because it was administered on a hand-held device (i.e., cell phone with quick finger responses), and participants reached reaction time floors.

Moving forward, future work may find it useful to investigate differences in reward-learning behavior as a function of assigned sex at birth. For example, in a new virtual version of the PRT, results similarly did not find a significant effect of depression group, but found a sex by

depression group interaction, where females with a lifetime history of MDD displayed lower response bias compared to females without MDD history (Esfand et al., 2024). The current dissertation project did not have enough depressed males to truly measure depression group by sex assigned at birth interaction effects in a meaningful manner. Additionally, the preliminary results of the present work may point to the limited utility of response bias as an optimal measure of reward-learning, particularly via online administration of the task, because it appears that across groups, response bias trended negatively. To help further explain, in order to obtain a "high" response bias (i.e., greater reward learning), the numerator needs to be large, while the denominator is small. This requires the numerator to have a large number of correct rich trials and large number of incorrect lean trials (i.e., choosing rich more often) in conjunction with the denominator including few incorrect rich trials (i.e., few rich misses) and few correct lean trials; however, since the task appeared too simple, participants had a high number of both rich and lean correct trials, possibly explaining the limited differential preference to rich stimuli. Notably, since the initiation of this dissertation study, a new, more engaging, and challenging virtual version of the PRT was created by Pizzagalli and colleagues and they replicated the main effect of block on response bias (Esfand et al., 2024), highlighting that perhaps with a more challenging task, response bias can show meaningful reward-learning behavior.

# Figures

**Figure 1. Wheel of Fortune Task.** The Wheel of Fortune Task (WOF) was used during fMRI to assess the neurobiological underpinnings of adolescent reward response. The task had three phases: selection, anticipation, and feedback. The feedback phase was utilized.

**Figure 2. Greater VS-rACC rsFC is associated with greater childhood trauma exposure and higher adult depression symptoms.** A. Masks containing regions of interest, with the rostral anterior cingulate (rACC) in green and ventral striatum (VS) in blue. B. Greater adolescent resting-state functional connectivity (rsFC) between the rACC and VS was associated with greater adult depressive symptoms. C. Positive association between childhood trauma total score and adult depressive symptoms. D. Greater childhood trauma was associated with greater VS-rACC rsFC.

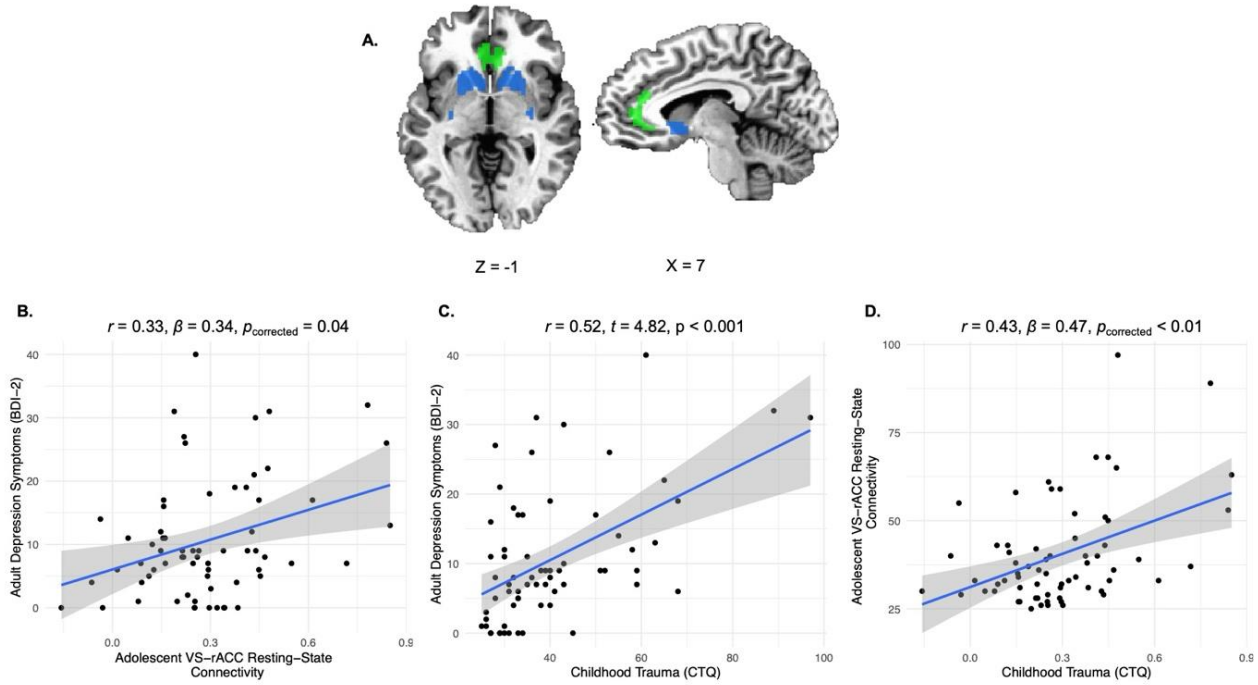


**Figure 3. Greater reward response in the rACC during task-based fMRI is related to greater childhood trauma.** A. Mask of region of interest in green the rostral anterior cingulate (rACC). B. Greater adolescent reward response, measured via a task-based functional magnetic resonance imaging (fMRI) wheel of fortune (WOF) task, during the outcome phase (rACC WOF) was associated with greater childhood trauma. C. Greater childhood emotional neglect was associated with greater reward response (rACC WOF).

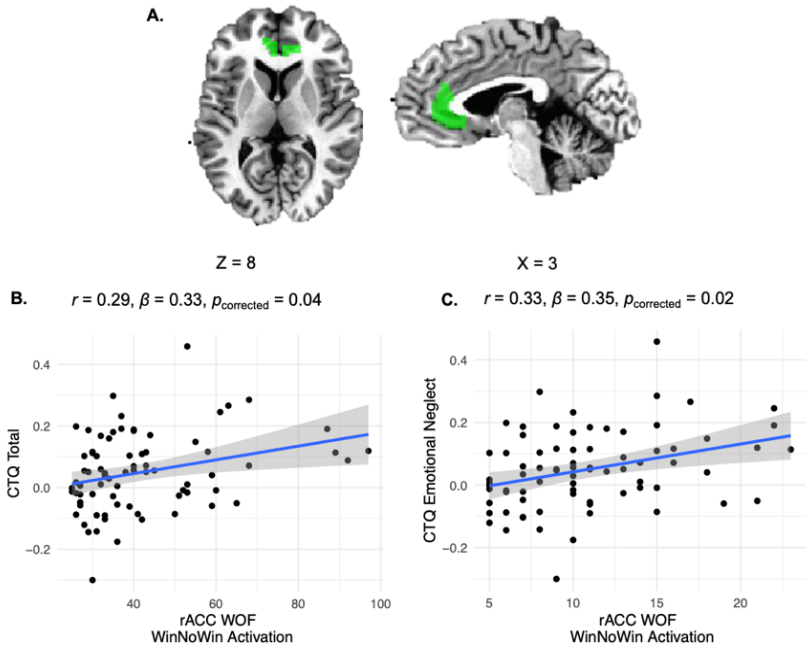


**Figure 4. Greater rACC reward response strengths the relationship between emotional neglect and adult depression.** Trend level moderating effect of childhood emotional neglect and rACC WOF reward response on adulthood depressive symptoms, suggesting the combined effect of greater childhood emotional neglect and heightened reward response in the rACC is associated with great depression symptoms in adults.

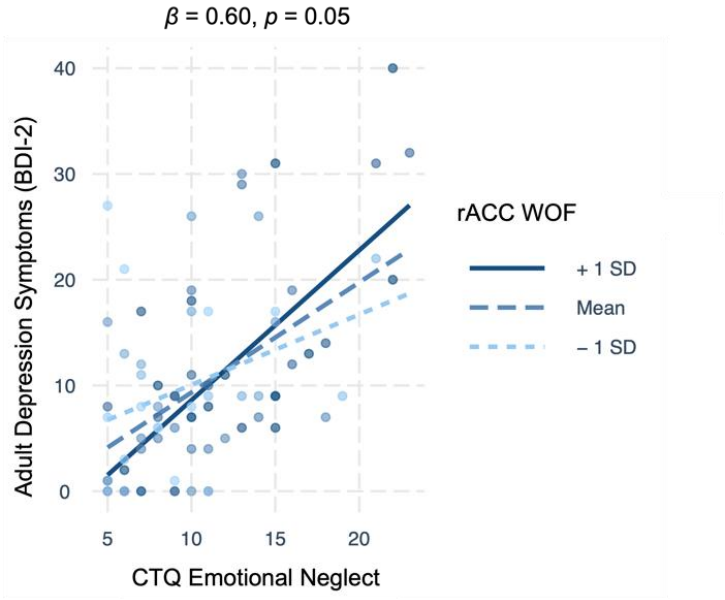


**Figure 5. Schematic representation of the mediating effect of VS-rACC rsFC in females.** A visual representation of the unconstrained moderated mediation model (female model displayed). The results demonstrated a *trending* mediating effect of VS-rACC rsFC. These findings suggest VS-rACC rsFC helps to explain the CTQ total score to adult BDI-2 score relationship.

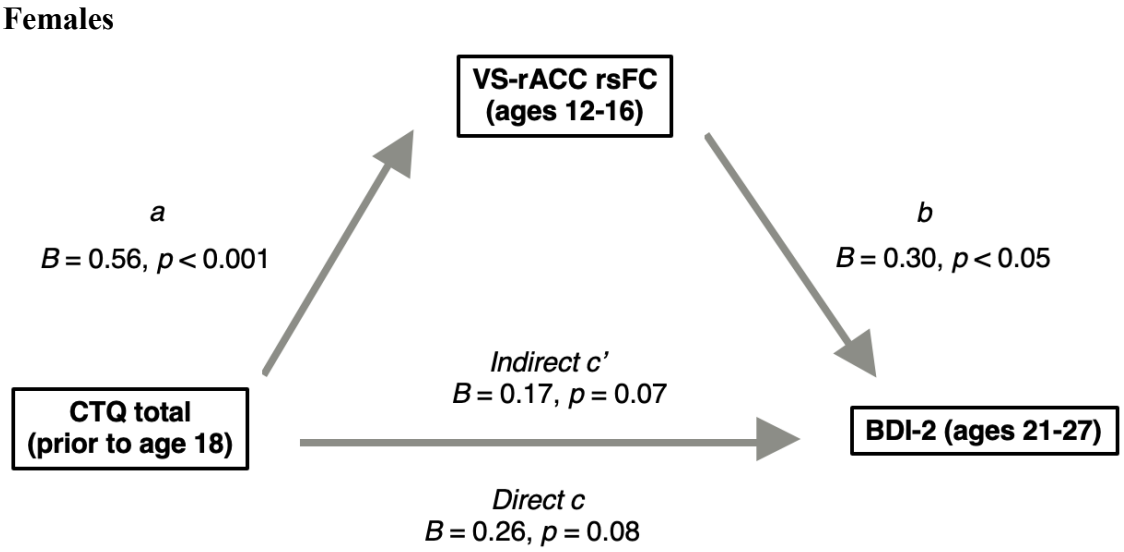


**Figure 6. An example trial of the Probabilistic Reward Task.** The PRT is a measure of reward learning such that participants change their behavior based on prior reinforcement history. Participants are told to differentiate between long and short mouth lengths; however unbeknownst to them one mouth length is rewards three times more frequently.

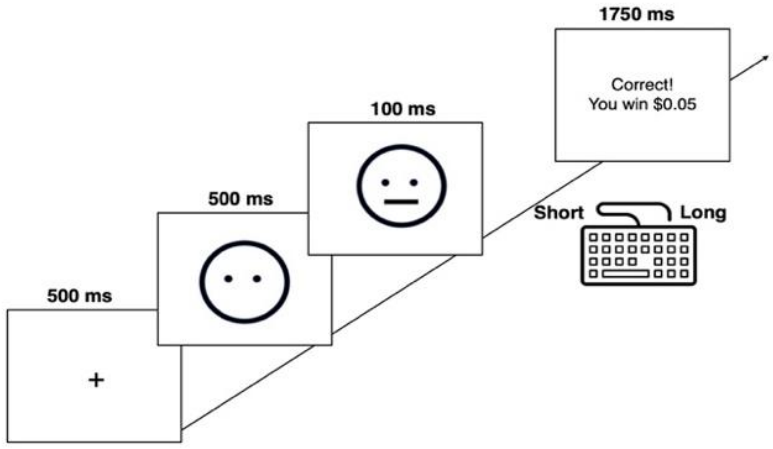


**Figure 7. No reward learning differences by block or group.** The average response bias comparisons between young adults with elevated depression symptoms and young adults with limited depression symptoms across blocks of the probabilistic reward task. There was no significant group effects or group by depression interaction effects suggesting there were no reward-related learning differences across block or between groups.

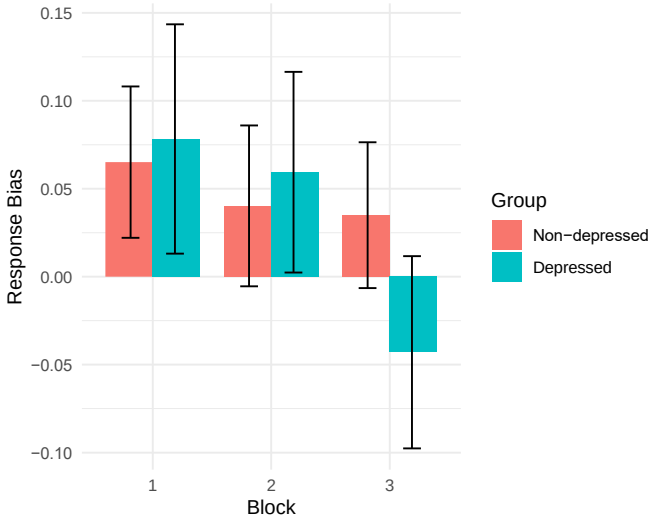


**Figure 8. Discriminability on the PRT is very high.** The average discriminability comparisons among young adults across blocks of the probabilistic reward task. There was a significant group effect. Follow-up simple effects showed there was a significant increase in discriminability from block 1 to block 2, however, it should be noted that discriminability was high beginning in block 1 (discriminability block 1 = 0.91).

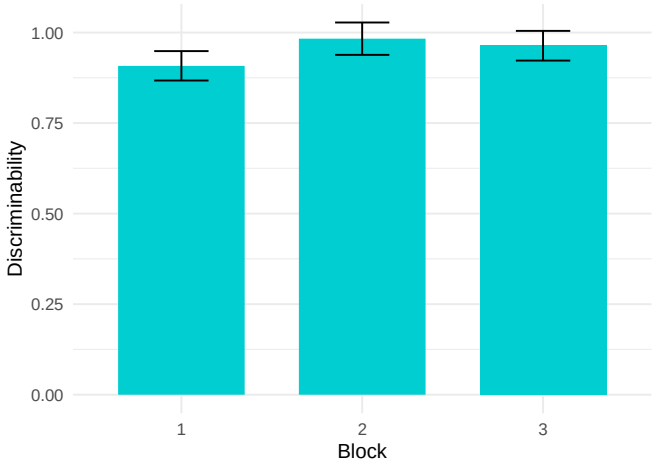


**Figure 9. Depressed and non-depressed groups did not show differences in reaction time as a function of block or condition.** There was a non-significant three-way interaction (group by block by condition). This suggests that depression groups did not differ in reaction time as a function of time (blocks) or condition (rich and lean).

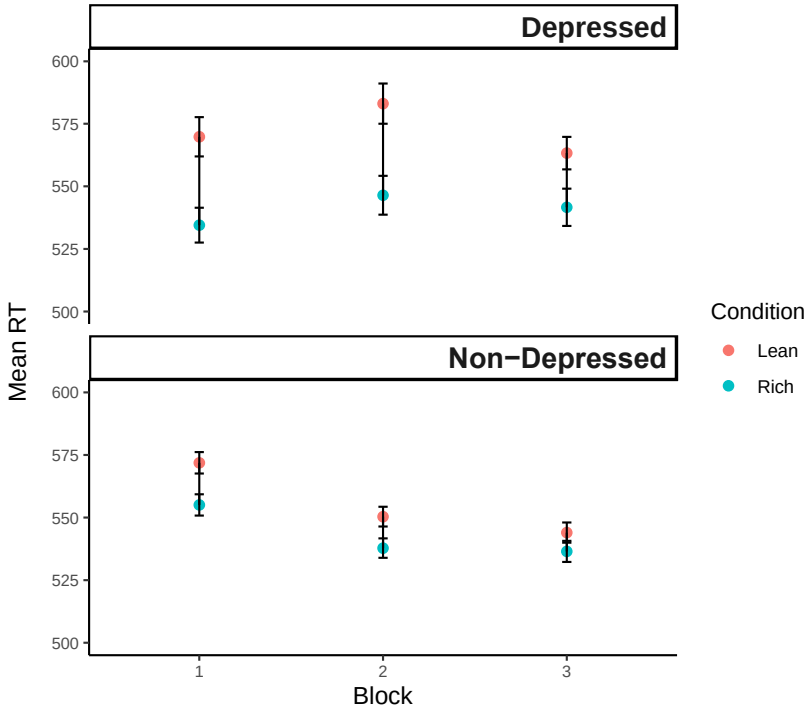


**Figure 10. Depressed group showed larger discrepancies in reaction time on PRT.** There was a significant two-way interaction (depression group by condition). These findings suggest the depressed group showed a larger discrepancy between rich and lean condition trial reaction times compared to the non-depressed group.

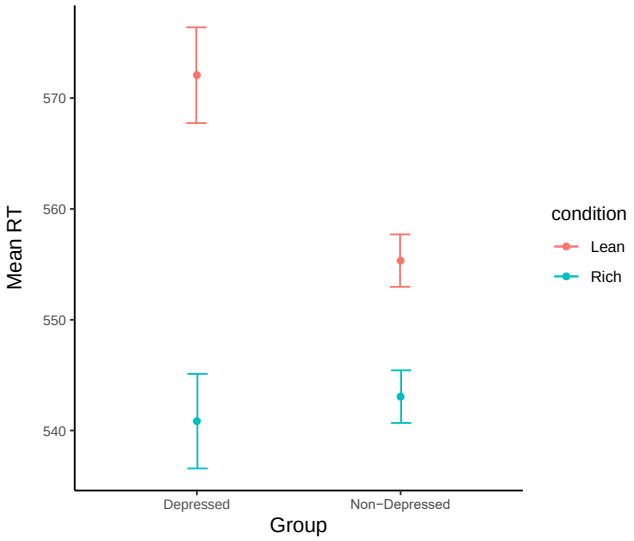
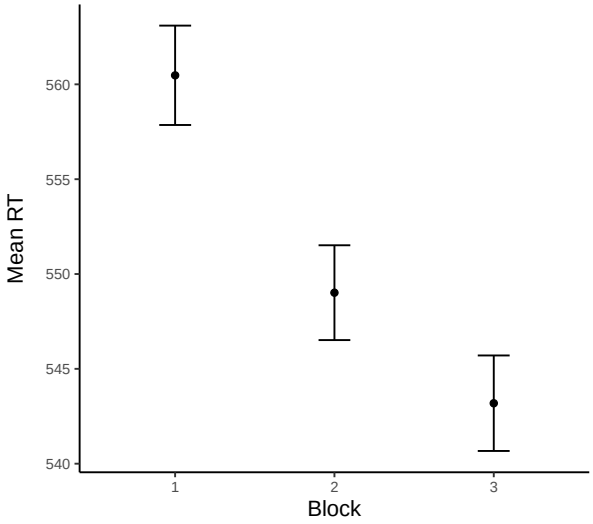


**Figure 11. Participants' reaction times were faster over time.** There was significant main effect of block on reaction time suggesting that participants' behavioral responses were faster as a function of time, which would be expected.



# Tables

**Table 2.1. Sample characteristics.**

| | Task-based sample | | Resting-state sample | |
|---|---|---|---|---|
| | Female | Male | Female | Male |
| N (%) | 53 | 24 | 45 | 21 |
| Scan Age: Mean (SD) | 14.5 (1.4) | 14.6 (1.3) | 14.6 (1.4) | 14.8 (1.2) |
| Follow-up Age: Mean (SD) | 24.5 (1.6) | 25.1 (1.6) | 24.5 (1.7) | 25.2 (1.6) |
| CDI T-Score: Mean (SD) | 44.4 (8.9) | 42.3 (5.4) | 44.2 (8.3) | 42.7 (5.7) |
| Index Social Position: Mean (SD) | 29.5 (14.3) | 30.5 (11.9) | 28.4 (13.7) | 31.5 (12.4) |
| IQ: Mean (SD) | 110.2 (10.8) | 112.5 (10.3) | 111.6 (10.2) | 111.1 (9.8) |
| BDI-2 Total: Mean (SD) | 11.4 (9.4) | 9.2 (8.9) | 11.2 (9.4) | 9.2 (9.5) |
| CTQ Total: Mean (SD) | 43.2 (18.0) | 38.5 (11.1) | 41.5 (16.1) | 37.8 (11.4) |
| *Emotional Neglect:* Mean (SD) | 10.9 (4.7) | 10.6 (4.7) | 10.7 (4.5) | 10.7 (4.8) |
| *Emotional Abuse:* Mean (SD) | 11.0 (5.7) | 9.2 (3.6) | 10.5 (5.1) | 8.7 (3.6) |
| *Physical Neglect:* Mean (SD) | 7.9 (3.9) | 6.7 (2.3) | 7.5 (3.5) | 6.7 (2.5) |
| *Physical Abuse:* Mean (SD) | 6.6 (2.9) | 6.5 (2.6) | 6.4 (2.7) | 6.3 (2.6) |
| *Sexual Abuse:* Mean (SD) | 6.8 (4.1) * | 5.5 (1.4) * | 6.4 (3.3) * | 5.3 (0.9) * |
| GAD-7 Total: Mean (SD) | 6.5 (5.4) | 5.7 (5.0) | 6.0 (4.9) | 5.3 (5.2) |
| ASR Externalizing T-Score: Mean (SD) | 51.5 (12.8) | 51.3 (9.5) | 51.4 (12.1) | 50.4 (9.7) |
| Native American/Alaskan Native | 3% | | 2% | |
| Asian | 1% | | -- | |
| Native Hawaiian/Pacific Islander | 1% | | 2% | |
| White | 86% | | 86% | |
| Multiracial | 8% | | 9% | |
| Hispanic/Latinx | 9% | | 6% | |

* $p < 0.05$

**Table 3.2.1 Linear regression model results for adolescent WOF reward response predicting adult depression.**

| | Std. Beta | *t*-value | *p*-value (corrected) | Partial $R^2$ | 95% Confidence Interval |
|---|---|---|---|---|---|
| **rACC WOF** | 0.14 | 1.26 | $p = 0.85$ | 0.02 | [-6.21, 27.39] |
| Scan Age | -0.06 | -0.49 | $p = 2.50$ | $3.0e^{-3}$ | [-1.97, 1.19] |
| Sex (male) | -0.09 | -0.76 | $p = 1.81$ | $8.4e^{-3}$ | [-6.22, 2.80] |
| Baseline CDI | 0.24 | 2.00 | $p = 0.20$ | 0.05 | [0.00, 0.55] |
| **mOFC WOF** | -0.06 | -0.05 | $p = 3.83$ | $3.8e^{-5}$ | [-2.21, 2.10] |
| Scan Age | -0.07 | -0.56 | $p = 2.31$ | $4.3e^{-3}$ | [-2.05, 1.15] |
| Sex (male) | -0.08 | -0.68 | $p = 1.00$ | $6.3e^{-3}$ | [-6.20, 3.05] |
| Baseline CDI | 0.24 | 2.00 | $p = 0.20$ | $5.3e^{-2}$ | [8.51, 0.56] |
| **VS WOF** | 0.08 | 0.73 | $p = 1.89$ | $8.2e^{-3}$ | [-6.99, 15.0] |
| Scan Age | -0.06 | -0.54 | $p = 2.36$ | $4.3e^{-3}$ | [-2.02, 1.16] |
| Sex (male) | -0.08 | -0.68 | $p = 2.00$ | $6.7e^{-3}$ | [-6.08, 2.99] |
| Baseline CDI | 0.23 | 1.99 | $p = 0.20$ | 0.05 | [0.00, 0.55] |
| **VTA WOF** | 0.18 | 1.60 | $p = 0.85$ | 0.03 | [-3.07, 28.12] |
| Scan Age | -0.06 | -0.51 | $p = 2.50$ | $4.8e^{-3}$ | [-1.97, 1.16] |
| Sex (male) | -0.08 | -0.72 | $p = 1.81$ | $7.0e^{-3}$ | [-6.08, 2.87] |
| Baseline CDI | 0.25 | 2.10 | $p = 0.20$ | 0.06 | [0.02, 0.56] |

**Table 3.2.2 Linear regression model results for adolescent mesocorticolimbic rsFC predicting adult depression.**

| | Std. Beta | *t*-value | *p*-value (corrected) | Partial $R^2$ | 95% Confidence Interval |
|---|---|---|---|---|---|
| **VS-rACC** | 0.34 | 3.31 | $p = 0.04$ | 0.12 | [4.75, 27.06] |
| Scan Age | -0.05 | -0.65 | $p = 3.98$ | $3.0e^{-3}$ | [-2.09, 1.34] |
| Sex (male) | -0.04 | -0.33 | $p = 4.51$ | $2.1e^{-3}$ | [-5.55, 4.03] |
| Baseline CDI | 0.21 | 1.75 | $p = 0.59$ | 0.04 | [-0.05, 0.57] |
| **VS-mOFC** | 0.15 | 0.98 | $p = 1.44$ | 0.02 | [-3.81, 14.90] |
| Scan Age | -0.04 | -0.38 | $p = 4.71$ | 0.001 | [-2.04, 1.55] |
| Sex (male) | -0.09 | -0.70 | $p = 2.82$ | $9.3e^{-3}$ | [-6.84, 3.19] |
| Baseline CDI | 0.18 | 1.42 | $p = 1.08$ | 0.03 | [-0.11, 0.55] |
| **VS-VTA** | 0.15 | 1.27 | $p = 1.38$ | 0.02 | [-4.9, 20.07] |
| Scan Age | -0.02 | -0.17 | $p = 5.37$ | $3.3e^{-4}$ | [-1.92, 1.68] |
| Sex (male) | -0.10 | -0.95 | $p = 2.51$ | 0.01 | [-7.12, 3.00] |
| Baseline CDI | 0.21 | 1.75 | $p = 0.72$ | 0.04 | [-0.07, 0.59] |
| **VTA-rACC** | 0.03 | 0.28 | $p = 4.82$ | $1.4e^{-3}$ | [-10.23, 13.145] |
| Scan Age | -0.04 | -0.35 | $p = 4.74$ | $1.4e^{-3}$ | [-2.09, 1.59] |
| Sex (male) | -0.08 | -0.66 | $p = 3.20$ | $6.2e^{-3}$ | [-6.64, 3.47] |
| Baseline CDI | 0.19 | 1.56 | $p = 0.97$ | 0.03 | [-0.10, 0.57] |
| **VTA-mOFC** | 0.02 | 0.14 | $p = 5.30$ | $4.1e^{-4}$ | [-13.84, 16.05] |
| Scan Age | -0.03 | -0.31 | $p = 4.90$ | $9.2e^{-4}$ | [-2.03, 1.61] |
| Sex (male) | -0.07 | -0.67 | $p = 3.45$ | $5.0e^{-3}$ | [-6.76, 3.79] |
| Baseline CDI | 0.19 | 1.62 | $p = 0.97$ | 0.03 | [-0.10, 0.57] |
| **rACC-mOFC** | 0.01 | 0.11 | $p = 5.53$ | $2.6e^{-4}$ | [-11.45, 12.62] |
| Scan Age | -0.03 | -0.32 | $p = 4.86$ | $1.4e^{-3}$ | [-2.06, 1.61] |
| Sex (male) | -0.08 | -0.70 | $p = 3.31$ | $6.3e^{-3}$ | [-6.72, 3.62] |
| Baseline CDI | 0.19 | 1.46 | $p = 1.04$ | 0.03 | [-0.10, 0.57] |

**Table 3.3.1 Linear regression model results for childhood trauma predicting adolescent WOF reward response.**

| | Std. Beta | *t*-value | *p*-value (corrected) | Partial $R^2$ | 95% Confidence Interval |
|---|---|---|---|---|---|
| **rACC WOF** | | | | | |
| CTQ total | 0.33 | 2.75 | $p = 0.04$ | $9.48e^{-2}$ | [0.001, 0.004] |
| Scan Age | -0.0001 | -0.01 | $p = 5.96$ | $8.60e^{-7}$ | [-0.02, 0.02] |
| Sex (male) | 0.07 | 0.63 | $p = 3.20$ | $5.45e^{-3}$ | [-0.04, 0.08] |
| Baseline CDI | -0.10 | -0.78 | $p = 2.64$ | $8.32e^{-3}$ | [-0.005,0.002] |
| **mOFC WOF** | | | | | |
| CTQ total | 0.14 | 1.12 | $p = 1.60$ | 0.02 | [-0.01,0.02] |
| Scan Age | 0.04 | 0.35 | $p = 4.39$ | $2.0e^{-3}$ | [-0.15, 0.21] |
| Sex (male) | 0.18 | 1.55 | $p = 0.75$ | 0.03 | [-0.11, 0.88] |
| Baseline CDI | -0.09 | -0.72 | $p = 2.84$ | $7.0e^{-3}$ | [-0.04, 0.02] |
| **VS WOF** | | | | | |
| CTQ total | 0.10 | 0.80 | $p = 2.56$ | $8.83e^{-3}$ | [-0.002, 0.004] |
| Scan Age | -0.01 | -0.10 | $p = 5.55$ | $1.24e^{-4}$ | [-0.04, 0.03] |
| Sex (male) | -0.02 | -0.16 | $p = 5.26$ | $3.34e^{-4}$ | [-0.10, 0.09] |
| Baseline CDI | -0.01 | -0.08 | $p = 5.61$ | $9.13e^{-5}$ | [-0.006, 0.006] |
| **VTA WOF** | | | | | |
| CTQ total | 0.30 | 2.45 | $p = 0.10$ | 0.08 | [0.00, 0.004] |
| Scan Age | 0.19 | 0.16 | $p = 5.24$ | $3.5e^{-4}$ | [-0.02, 0.02] |
| Sex (male) | 0.03 | 0.29 | $p = 4.78$ | $9.2e^{-4}$ | [-0.06, 0.07] |
| Baseline CDI | -0.15 | -1.17 | $p = 1.48$ | 0.02 | [-0.007, 0.002] |

**Table 3.3.2 Linear regression model results for childhood trauma predicting adolescent mesocorticolimbic rsFC.**

| | Std. Beta | *t*-value | *p*-value (corrected) | Partial $R^2$ | 95% Confidence Interval |
|---|---|---|---|---|---|
| **VS-rACC** | | | | | |
| CTQ total | 0.47 | 3.94 | $p = 0.001$ | 0.20 | [0.003, 0.009] |
| Scan Age | 0.12 | 1.00 | $p = 1.94$ | 0.02 | [-0.02, 0.05] |
| Sex (male) | -0.08 | -0.72 | $p = 2.82$ | $8.6e^{-3}$ | [-0.13, 0.06] |
| Baseline CDI | -0.19 | -1.54 | $p = 0.77$ | 0.04 | [-0.01, 0.002] |
| **VS-mOFC** | | | | | |
| CTQ total | 0.18 | 1.35 | $p = 1.09$ | 0.03 | [-0.001, 0.001] |
| Scan Age | 0.05 | 0.40 | $p = 4.13$ | 0.003 | [-0.04, 0.06] |
| Sex (male) | 0.09 | 0.72 | $p = 2.83$ | 0.009 | [-0.09, 0.18] |
| Baseline CDI | 0.01 | 0.10 | $p = 5.51$ | $1.7e^{-4}$ | [-0.009, 0.01] |
| **VS-VTA** | | | | | |
| CTQ total | 0.03 | 0.22 | $p = 4.93$ | $8.4e^{-4}$ | [-0.003, 0.003] |
| Scan Age | -0.08 | -0.62 | $p = 3.23$ | $6.2e^{-3}$ | [-0.04, 0.16] |
| Sex (male) | 0.15 | 1.2 | $p = 1.41$ | 0.02 | [-0.05, 0.03] |
| Baseline CDI | -0.14 | -1.1 | $p = 1.77$ | 0.02 | [-0.01, 0.003] |
| **VTA-rACC** | | | | | |
| CTQ total | 0.03 | 0.19 | $p = 5.09$ | $6.0e^{-4}$ | [-0.003, 0.004] |
| Scan Age | 0.17 | 1.2 | $p = 1.33$ | 0.02 | [-0.02, 0.06] |
| Sex (male) | -0.02 | -0.14 | $p = 5.35$ | $3.1e^{-4}$ | [-0.12, 0.10] |
| Baseline CDI | -0.04 | -0.26 | $p = 4.80$ | $1.1e^{-3}$ | [-0.01, 0.007] |
| **VTA-mOFC** | | | | | |
| CTQ total | 0.18 | 0.93 | $p = 2.14$ | 0.01 | [-0.002, 0.004] |
| Scan Age | 0.02 | 0.17 | $p = 5.18$ | $4.9e^{-4}$ | [-0.03, 0.03] |
| Sex (male) | -0.28 | -2.24 | $p = 0.17$ | 0.08 | [-0.18, -0.01] |
| Baseline CDI | -0.11 | -0.86 | $p = 2.37$ | 0.01 | [-0.008, 0.003] |
| **rACC-mOFC** | | | | | |
| CTQ total | -0.22 | -1.80 | $p = 0.47$ | 0.05 | [-0.007, 0.0004] |
| Scan Age | 0.11 | 0.87 | $p = 2.21$ | 0.01 | [-0.02, 0.05] |
| Sex (male) | -0.22 | -1.82 | $p = 0.44$ | 0.05 | [-0.20, 0.01] |
| Baseline CDI | 0.21 | 1.63 | $p = 0.65$ | 0.04 | [-0.001, 0.01] |

**Table 3.4.1 Heightened rACC WOF response strengthens the emotional neglect to adult depression relationship.**

| | Std. Beta | *t*-value | *p*-value (uncorrected) | Partial $R^2$ | 95% Confidence Interval |
|---|---|---|---|---|---|
| rACC WOF | -0.53 | -1.95 | $p = 0.06$ | 0.05 | [-80.56, 0.96] |
| CTQ emotional neglect | 0.39 | 3.12 | $p = 0.003$ | 0.12 | [0.28, 1.29] |
| Sex (male) | -0.09 | -0.91 | $p = 0.36$ | 0.01 | [-5.63, 2.09] |
| Baseline CDI | 0.13 | 1.21 | $p = 0.23$ | 0.02 | [-0.10, 0.40] |
| Scan Age | 0.02 | 0.17 | $p = 0.89$ | $4.0e^{-4}$ | [-1.26, 1.49] |
| rACC * CTQ | 0.60 | 1.99 | $p = 0.05$ | 0.05 | [-0.005, 6.86] |

*Note: * p<0.05, **p<0.01, ***p<0.001*

**Table 3.5.1 Adolescent VS-rACC rsFC partially explains the CTQ to adult BDI-2 score association in assigned females at birth.**

| | ***Indirect*** **CTQ→ VS-rACC→ BDI** | **C' *Direct*** **CTQ → BDI + Brain** | **C *Total*** |
|---|---|---|---|
| **CTQ total** | | | |
| **Model 2a** Constrained | $\beta = 0.07,\ p = 0.22$ | $\beta = 0.43,\ p < 0.01^{*}$ | $\beta = 0.50,\ p < 0.01$ |
| **Model 2b** Moderated Mediation Unconstrained | | | |
| *Females* | $\beta = 0.17,\ p = 0.07^{\dagger}$ | $\beta = 0.26,\ p = 0.08^{\dagger}$ | $\beta = 0.43,\ p = 0.07^{\dagger}$ |
| *Males* | $\beta = 0.004,\ p = 0.82$ | $\beta = 0.66,\ p < 0.01^{*}$ | $\beta = 0.66,\ p = 0.82$ |
| **CTQ Emotional Neglect** | | | |
| **Model 2c** Constrained | $\beta = 0.06, p = 0.17$ | $\beta = 0.50,\ p < 0.01^{*}$ | $\beta = 0.56,\ p < 0.01$ |
| **Model 2d** Moderated Mediation Unconstrained | | | |
| *Females* | $\beta = 0.14,\ p = 0.06^{\dagger}$ | $\beta = 0.29,\ p = 0.04^{*}$ | $\beta = 0.42,\ p = 0.06^{\dagger}$ |
| *Males* | $\beta = 0.01,\ p = 0.69$ | $\beta = 0.60,\ p < 0.01^{*}$ | $\beta = 0.61,\ p = 0.66$ |

[a] *All models had the same covariates: Scan Age, Sex, and baseline CDI*
[b] *In models 2b and 2d Sex was used as a moderating variable*
† *Indicated a marginally significant effect*

**Table 3.5.2 Model comparisons and fit statistics of mediation models for resting-state sample**

| | AIC | df | BIC | CFI | SRMR | Chi-sq | RMSEA | p-value |
|---|---|---|---|---|---|---|---|---|
| **Test 2a vs 2b (CTQ total)** | | | | | | | | |
| **Model 2a** CTQ total constrained | 1006.4 | 11 | 1030.5 | 0.79 | 0.12 | 19.5 | 0.15 | |
| **Model 2b** Moderated mediation CTQ total unconstrained | 1003.2 | 8 | 1033.8 | 0.94 | 0.07 | 10.3 | 0.09 | $p = 0.03^{*}$ |
| **Test 2c vs 2d (CTQ emotional neglect)** | | | | | | | | |
| **Model 2c** Constrained | 848.8 | 11 | 872.8 | 0.83 | 0.09 | 19.0 | 0.15 | |
| **Model 2d** Unconstrained | 849.5 | 8 | 880.2 | 0.88 | 0.07 | 13.8 | 0.15 | $p > 0.05$ |

[a]*Model 2b is the better fitting model, however, it should be noted that neither model are well fitting and caution should be taken with interpretation. There is no significant difference between the fit of model 2c and 2d.*

**Table A1. PRT participant characteristics.**

| | Depressed | Non-Depressed | test-statistic | p-value |
|---|---|---|---|---|
| Sample (N's) | Female N=13 | Female N=33 | | |
| | Male N=4 | Male N=18 | $\chi^2 = 25.41$ | $p = 0.04^*$ |
| Age in years, Mean (SD) | 23.7 (1.9) | 24.8 (1.6) | $t = -2.77$ | $p = 0.04^*$ |
| BDI-2 scores, Mean (SD) | 22.8 (7.0) | 5.7 (3.9) | $t = 16.50$ | $p = 2.2e\text{-}16^*$ |

**Table A2. Data cleaning.**

| | Depressed | Non-Depressed | test-statistic | p-value |
|---|---|---|---|---|
| *Collapsed across blocks* | | | | |
| Outlier trials, Mean (SD) | 3.8 (1.7) | 3.9 (1.6) | $t = -0.30$ | $p = 0.37$ |
| Mean Accuracy (%) | 86.5% | 87.5% | $t = -0.76$ | $p = 0.44$ |
| Response Bias, Mean (SD) | 0.03 (0.2) | 0.05 (0.3) | $F = 0.06$ | $p = 0.69$ |
| Discriminability, Mean (SD) | 0.89 (0.3) | 0.97 (0.4) | $F = 0.82$ | $p = 0.13$ |
| RT (all), Mean (SD) | 551.9 (209.5) | 552.0 (209.5) | $t = -0.08$ | $p = 0.09$ |
| RT (rich correct), Mean (SD) | 549.7 (126.7) | 540.3 (90.2) | $F = 0.13$ | $p = 0.58$ |
| RT (lean correct), Mean (SD) | 559.1 (108.0) | 566.6 (121.4) | $F = 0.06$ | $p = 0.72$ |

**Table A3. Block Effects.**

| | Block 1 | Block 2 | Block 3 | test-statistic | p-value |
|---|---|---|---|---|---|
| *Separated by blocks* | | | | | |
| Outlier trials, Mean (SD) | 95 | 77 | 87 | $\chi^2 = 6.0$ | $p = 0.20$ |
| Mean Accuracy (%) | 86% | 88% | 88% | $F = 0.72$ | $p = 0.13$ |
| Response Bias, Mean (SD) | 0.07 (0.3) | 0.05 (0.3) | 0.02 (0.3) | $F = 0.96$ | $p = 0.32$ |
| Discriminability, Mean (SD) | 0.91 (0.3) | 0.98 (0.4) | 0.96 (0.3) | $F = 3.30$ | $p = 0.04^*$ |
| RT (all), Mean (SD) | 560.1 (214.4) | 547.0 (205.6) | 543.8 (204.5) | $F = 14.53$ | $p < 0.0001^*$ |
| RT (rich correct), Mean (SD) | 550.2 (101.3) | 541.5 (101.7) | 536.2 (98.9) | $F = 1.45$ | $p = 0.22$ |
| RT (lean correct), Mean (SD) | 570.8 (119.6) | 562.3 (112.0) | 561.0 (123.5) | $F = 0.47$ | $p = 0.56$ |

*BDI-2 = Beck Depression Inventory; Rich = more frequently rewarded stimuli condition; Lean = less frequently rewarded stimuli condition; RT = reaction time in milliseconds*

[a] *Reaction time measures only included correct trials to reduce outliers' reaction times on incorrect trials*

[b] *Depression category was identified to include depressive symptoms spanning mild-severe (BDI $\geq$ 13) to maximize power*

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