



Reward and Immune Systems in Emotion (RISE) prospective longitudinal study: Protocol overview of an integrative reward-inflammation model of first onset of major depression in adolescence

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ABSTRACT

Background: Depression is associated with a reduced sensitivity to rewards and low reward-related brain function in cortico-striatal circuitry. A separate literature documents elevated peripheral inflammation in depression. Recently, integrated reward-inflammation models of depression have been proposed. These models draw on work indicating that peripheral inflammatory proteins access the brain, where they lower reward responsiveness. This blunted reward responsiveness is proposed to initiate unhealthy behaviors (substance use, poor diet), as well as sleep disruption and stress generation, which further heighten inflammation. Over time, dysregulation in reward responsiveness and immune signaling may synergize in a positive feedback loop, whereby dysregulation in each system exacerbates dysregulation in the other. Project RISE (Reward and Immune Systems in Emotion) provides a first systematic test of reward-immune dysregulation as a synergistic and dynamic vulnerability for first onset of major depressive disorder and increases in depressive symptoms during adolescence.

Methods: This NIMH-funded R01 study is a 3-year prospective, longitudinal investigation of approximately 300 community adolescents from the broader Philadelphia area, United States of America. Eligible participants must be 13–16 years old, fluent in English, and without a prior major depressive disorder. They are being selected along the entire dimension of self-reported reward responsiveness, with oversampling at the low tail of the dimension in order to increase the likelihood of major depression onsets. At Time 1 (T1), T3, and T5, each a year apart, participants complete blood draws to quantify biomarkers of low-grade inflammation, self-report and behavioral measures of reward responsiveness, and fMRI scans of reward neural activity and functional connectivity. At T1-T5 (with T2 and T4 six months between the yearly sessions), participants also complete diagnostic interviews and measures of depressive symptoms, reward-relevant life events, and behaviors that increase inflammation. Adversity history is assessed at T1 only.

Discussion: This study is an innovative integration of research on multi-organ systems involved in reward and inflammatory signaling in understanding first onset of major depression in adolescence. It has the potential to facilitate novel neuroimmune and behavioral interventions to treat, and ideally prevent, depression.

1. Background

Major depression (MD) is highly prevalent, recurrent, and a major public health concern (e.g., Whiteford et al., 2013). Even depressive symptoms in the absence of a diagnosis are associated with significant functional impairment, increased suicide risk, and can progress to MD over time (e.g., Balázs et al., 2013; van Lang et al., 2007). Moreover, adolescence is an “age of risk” marked by increases in depressive

symptoms and first onset of MD (e.g., Avenevoli et al., 2015; Beesdo et al., 2009; Hankin et al., 1998), and depressed teens often become depressed adults. However, the mechanisms responsible for adolescent vulnerability to depression are not fully understood; yet knowledge of risk mechanisms is crucial for understanding etiological pathways to MD and translating basic research to targeted interventions for depression. Thus, the overarching goal of Project RISE (Reward and Immune Systems in Emotion; R01 MH123473) is to test a novel, integrated reward-inflammation approach to increases in depressive symptoms and

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List of abbreviations (in alphabetical order):

AADIS	Adolescent Alcohol and Drug Involvement Scale	P	Participant
ACSQ	Adolescent Cognitive Style Questionnaire	PDS	Pubertal Development Scale
BDI-II	Beck Depression Inventory-II	PPI	Psychophysiological Integration
BIS/BAS	Behavioral Inhibition System/Behavioral Activation System Scales	PSQI	Pittsburgh Sleep Quality Index
CARROT	Card Arranging Reward Responsivity Objective Test	PVSS	Positive Valence Systems Scale
CLES	Children's Life Events Scale	ROI	Regions of interest
CRP	C-reactive protein	RISE	Reward and Immune Systems in Emotion
DSQ	Dietary Screening Questionnaire	RR	Reward responsiveness
fMRI	Functional Magnetic Resonance Imaging	RRS	Ruminative Responses Scale
IL	Interleukin	SCID-5	Structured Clinical Interview for DSM-5
ISS	Internal State Scale	SDS	Sheehan Disability Scale
LEI	Life Events Interview	SEQ	Social Experiences Questionnaire
LES	Life Events Scale	SIQ-Jr	Suicide Ideation Questionnaire-Junior
MD	Major Depression	SPSRQ	Sensitivity to Punishment Sensitivity to Reward Questionnaire
MID	Monetary Incentive Delay Task	T	Time
NIHTB-CB	National Institutes of Health Toolbox Cognition Battery	TNF- α	Tumor necrosis factor-alpha
OFC	Orbitofrontal Cortex	VS	Ventral Striatum
		vmPFC	Ventromedial Prefrontal Cortex

first onset of MD in adolescence.

1.1. Inflammation and risk for MD

Meta-analyses indicate that some people with MD exhibit elevated levels of inflammatory biomarkers in peripheral blood and cerebrospinal fluid (e.g., Goldsmith et al., 2016; Köhler et al., 2017) and inflammatory models of MD have emerged (e.g., A.H. Miller et al., 2009; Slavich and Irwin, 2014). In addition, a recent meta-analysis of prospective studies found that heightened inflammatory proteins predicted later depressive symptoms and vice versa (Mac Giollabhui et al., 2021). Similarly, a subset of patients treated with interferon- α to boost inflammatory response develop depression (Capuron and Miller, 2004). Much of this empirical research focused on adults, precluding the ability to determine whether inflammatory risk for MD develops during adolescence. Compared to adulthood, adolescence is characterized by the emergence of pro-inflammatory phenotypes (Brenhouse and Schwarz, 2016). Adolescents' immune system development along with maturational changes (e.g., blood brain barrier function) may set up a unique, vulnerable environment for the effect of chronic, low-grade inflammatory activity on the onset of MD.

1.2. Reward hyposensitivity and risk for MD

A separate literature also documents that depression is associated with a reduced sensitivity to rewarding stimuli and lower reward-related brain function in cortico-striatal circuitry (Alloy et al., 2016b; Nusslock and Alloy, 2017; Pizzagalli, 2014; Treadway, 2016). Moreover, low reward responsiveness (RR) is hypothesized to be a vulnerability for MD (Alloy et al., 2016b; Nusslock and Alloy, 2017; Pizzagalli, 2014; Treadway, 2016). According to reward hyposensitivity models of depression, low trait RR is proposed to lead to an excessive decrease in state approach motivation when life events that deactivate the reward system involving irreconcilable failures and losses occur, and, in turn, to depressive symptoms and episodes (Alloy et al., 2016b; Nusslock and Alloy, 2017). Considerable multimodal evidence supports blunted RR in MD (Alloy et al., 2016b; Nusslock and Alloy, 2017). To test the reward hyposensitivity theory of vulnerability for MD, a prospective, longitudinal study of first onset of MD is required. Although a few (mostly small N) prior studies found that low RR at one time predicts increases in depressive symptoms or episodes (see Alloy et al., 2016b and Nusslock and Alloy, 2017 for review), chronically low RR and attenuated

development of RR during adolescence, a developmental period when normative increases in RR and rapid maturation of neural circuitry implicated in reward processing usually occur (e.g., Galván, 2013; Olino, 2016; Somerville and Casey, 2010), may better predict first onset of MD; this has not yet been tested. In addition, work examining RR development relies on cross-sectional or longitudinal assessments with only two timepoints. However, to examine developmental trajectories of RR as predictors of depressive symptoms and first onset of MD, and to test mediators of these predictive associations, at least three timepoints are needed. Further, most research on RR in depression has focused on monetary rewards. Yet, it also is important to examine developmental trajectories of social RR as a predictor of depressive symptoms and first onset of MD in adolescence because social incentives normatively increase in importance during adolescence (Crone and Dahl, 2012; Foulkes and Blakemore, 2016; Walker et al., 2017) and interpersonal stressors are particularly likely to precipitate depression (Hamilton et al., 2013; Vrshek-Schallhorn et al., 2015).

1.3. Integrated reward-inflammation model of MD

Recently, neuroimmune network models (Eisenberger et al., 2017; Felger and Treadway, 2017; Nusslock and Miller, 2016) of depression that feature bidirectional associations between RR and the immune system have been proposed (see Fig. 1).

1.3.1. Immune to reward pathway

These models draw on research indicating that peripheral inflammatory mediators (e.g., cytokines) access the brain, where they lower RR and goal-directed behavior (Felger and Treadway, 2017; Nusslock and Miller, 2016). Although inflammatory cytokines predominately are released by immune cells in the periphery, they can access the brain via active transport, leaky regions of the blood-brain-barrier, or engaging afferent vagal fibers (Haroon et al., 2012; Irwin and Cole, 2011). Studies suggest that the cortico-striatal neural circuit subserving RR is a primary target of inflammatory proteins (Felger and Treadway, 2017; A.H. Miller et al., 2013). Inflammatory cytokines reduce animals' sensitivity to rewards and increase tolerance to the reinforcing properties of many drugs (Coller and Hutchinson, 2012; Dantzer et al., 2008). In humans, inflammatory stimuli and mediators (e.g., endotoxins, interferons) reduce ventral striatal activation to both the anticipation and receipt of monetary rewards (Brenhouse and Schwarz, 2016; Eisenberger et al., 2010; 2017), although in some contexts, inflammation is associated with

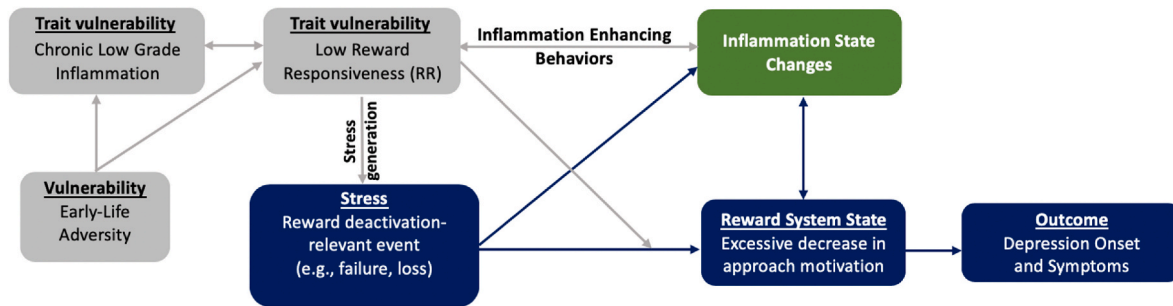


Fig. 1. Integrated reward-inflammation model of depression.

higher ventral striatal activation to rewards (Chat et al., 2021; Eisenberger et al., 2017; G.E. Miller et al., 2021). Studies suggest that inflammation can lower RR by altering the synthesis, reuptake, and release of dopamine in the ventral striatum (Capuron et al., 2012; Felger and Treadway, 2017; A.H. Miller et al., 2013). When regulated, this immune-to-reward signaling is adaptive and lowers motivation and goal-directed behavior to conserve metabolic resources for fighting infection. When dysregulated or chronic, however, it can result in sustained reductions in RR, anhedonia, and dysphoria, and risk for MD (Eisenberger et al., 2017; Felger and Treadway, 2017; Nusslock and Miller, 2016).

1.3.2. Reward-to-immune pathway

The neuroimmune network models propose that RR also can influence levels of inflammation. Individuals with blunted RR are more likely to engage in behaviors to manage their anhedonia and dysphoria that can wind up further increasing inflammation, including substance use (Bart et al., 2021; Büchel et al., 2017; Chat et al., 2021; 2023; Volkow et al., 2016), consuming a high-fat/high-sugar diet (Bastard et al., 2006; Volkow et al., 2008, 2012), neglect of normal sleep schedules leading to reduced or irregular sleep (Burani et al., 2019; Holm et al., 2009), and stress-generation of goal failures and losses (Boland et al., 2016).

Furthermore, this profile of joint reward-immune dysregulation may enhance vulnerability for increases in depressive symptoms and first onset of MD in adolescence beyond the effects of either low RR or elevated inflammation alone. Over time, dysregulation in RR and inflammation may compound each other to form a positive feedback loop, whereby dysregulation in each system exacerbates dysregulation in the other and further amplifies the vulnerability for depression. Despite a plausible joint role, most prior research examines the role of RR and inflammation in depression separately.

1.4. Influence of early adversity and recent stressors on RR and inflammation

Early and recent stress influence both RR and inflammation (Fig. 1). Adversity in childhood and adolescence (e.g., deprivation, abuse) affects development of the cortico-striatal reward circuit and is associated with later reward processing deficits (Dennison et al., 2019; McLaughlin et al., 2019). Adversity also predicts development of an enduring pro-inflammatory phenotype (Kuhlman et al., 2020; Lam et al., 2022; Slopen et al., 2013) as well as MD (Alloy et al., 2006a; Gibb et al., 2001), and enhances the link between inflammation and depression (Danese et al., 2008; G.E. Miller and Cole, 2012). Likewise, exposure to recent stressful events instigates inflammatory responses (Slavich and Irwin, 2014) and compounds the effects of earlier adversity on inflammation (Gouin et al., 2012; Kautz et al., 2023) as well as modulates reward-related brain function (Berghorst et al., 2013; Kumar et al., 2014). Early and recent stress exposure also strengthens the association between RR and inflammation (Chat et al., 2022; G.E. Miller et al., 2021; Treadway et al., 2017). Thus, childhood and adolescent adversity and recent stressors may set the foundation for heightened cross-talk

between the brain and immune system and reward-immune dysregulation in risk for depression.

1.5. The present study

Project RISE provides the first systematic test of reward-immune dysregulation as a joint vulnerability for increases in depressive symptoms and first onset of MD in the vulnerable period of adolescence. We use a biobehavioral high-risk approach involving peripheral inflammatory markers and multilevel (self-report, behavioral, neural) and multimodal (monetary, social) RR measures in a prospective longitudinal design to examine: 1) concurrent and longitudinal bidirectional associations between inflammation and RR; 2) mediators (substance use, diet, sleep, stress generation) and moderators (early adversity, recent reward system-relevant stressors) of their associations, and 3) inflammation and RR as separate and joint predictors of increases in depressive symptoms and first onset of MD during adolescence.

1.5.1. Main hypotheses

1) We predict that chronically low RR or attenuated development of RR will be associated with elevated biomarkers of inflammation. 2) We also predict that chronically high inflammation or increases in inflammation and chronically low RR or attenuated development of RR each will separately predict increases in depressive symptoms and first onset of MD. 3) We further predict that chronically high or increases in inflammation will interact with chronically low or attenuated development of RR to jointly predict increases in depressive symptoms and first onset of MD. 4) Finally, adversity in childhood and adolescence will moderate and behaviors that increase inflammation (substance use, poor diet, sleep disturbance, stress generation) will mediate RR-inflammation associations.

1.5.2. Overview and rationale

Our goal is to recruit 300, 13-16 year-old adolescents to complete a prospective, three-year longitudinal study. This age range was chosen based on several considerations. First, epidemiological studies of MD incidence suggest that the steepest rise in rates of first onset of MD occurs between ages 15-18 (e.g., Avenevoli et al., 2015; Beesdo et al., 2009; Hankin et al., 1998). Second, RR normatively increases in adolescence and may start to peak around ages 15-16 (Galvan et al., 2006; Somerville and Casey, 2010). Third, although pre-adolescence may be the most sensitive time for stress to instigate a pro-inflammatory phenotype (Lam et al., 2022), adolescence also is a sensitive period during which pro-inflammatory phenotypes may emerge and consolidate (Brenhouse and Schwarz, 2016), and substance use, a hypothesized mediator of the RR-inflammation association, begins to increase in mid-adolescence. Thus, this age range should provide the best opportunity to observe trajectories of RR-inflammation associations and prediction of first onset of MD.

Participants with no prior history of MD diagnosis are being selected along the entire dimension of self-reported trait RR, with oversampling at the low tail of the dimension to increase the likelihood of MD onsets.

At Time 1 (T1), T3, and T5, each a year apart, participants complete blood draws to quantify inflammatory proteins, self-report and behavioral measures of RR, fMRI scans of reward neural activity and functional connectivity during monetary and social reward tasks, self-report measures of cognitive styles, and behavioral measures of executive function. At T1-T5 (with T2 and T4 occurring six months between the yearly sessions), participants also complete psychiatric diagnostic interviews and self-report measures of depressive symptoms, recent life events coded for reward-relevance and stress-generation, and behaviors that increase inflammation (sleep [self-report and actigraphy], diet, and substance use). At T1 only, mothers provide information on their own psychiatric history, family psychiatric history, socioeconomic status, and adolescents' adversity history from birth to T1 (see Fig. 2).

2. Methods

2.1. Participant recruitment, eligibility, and characteristics

Adolescents are recruited from the community via a two-phase screening process. In Phase I, they complete an online screening questionnaire that includes the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS; Carver and White, 1994) Scales, demographics questions, and contact information for themselves and a parent. The BAS total score from the BIS/BAS is a reliable and valid measure of trait reward sensitivity (Alloy et al., 2012a; Alloy et al., 2012c; Colder and O'Connor, 2004) that has been used previously to select participants with different levels of RR (Alloy et al., 2012a; Alloy et al., 2012c). Based on their scores on the BAS, we plan to recruit 200 adolescents from the low (0–20th %) quintile of the RR dimension, and 100 adolescents from the rest of the dimension, distributed so that 25 each come from the 21–40th %, the 41–60th %, 61–80th %, and the 81–100th %. Adolescents must be ages 13–16 to be eligible. We plan to recruit equal numbers of males and females within each BAS quintile to allow exploration of sex differences and adolescents from all races and ethnicities are eligible. This design, with oversampling at the low tail of the RR dimension, insures both that we will have the full dimension of RR represented in the sample and enough participants at increased risk for depressive symptoms and MD.

Adolescents who are potentially eligible based on the online screener and their parents are then contacted to schedule a Phase II phone

screening interview. The phone screening interview is used to describe the project to adolescents and their parents in detail and, if they are interested, to more fully determine whether the adolescent is fully eligible. The interview contains an MRI safety screening questionnaire, questions about eligibility for the immune component of the study, and the current and past MD sections of the Structured Clinical Interview for DSM-5 (SCID-5) (First et al., 2015). Adolescents who are fully eligible and wish to participate in the longitudinal project provide written assent and their parent provides written consent. Project RISE is approved by the Temple University IRB (#27918).

We exclude adolescents with a history of a MD episode because one of the aims of the project is to predict first onset of MD in adolescence. We also exclude participants with current psychotic symptoms (hallucinations, delusions) to insure validity of project assessments. In addition, we exclude adolescents with a history of cancer, heart disease, surgery, an ongoing autoimmune disease or disorder involving chronic inflammation (e.g., Crohn's disease, type 1 diabetes, lupus, asthma), and anyone who is HIV positive. We also exclude anyone taking immunosuppressant medications (e.g., an inhaler, systemic steroids, prescription nonsteroidal anti-inflammatory drugs in the past three months). This approach strikes a balance between enrolling a sample that is generalizable to the broader population, while excluding adolescents whose inflammatory profile is likely to be affected by disease or treatment. Adolescents also are excluded according to standard MRI exclusion criteria (e.g., metal in the body, traumatic brain injury, pregnancy, severe claustrophobia). We do not exclude on the basis of psychotropic medications, but instead will control for psychotropic medication use in analyses. Given elevated rates of psychotropic medication use in individuals with, and at risk for, mood symptoms (Hafeman et al., 2012), excluding such participants would reduce the representativeness of our sample and limit generalizability of findings.

2.2. Measures

Study assessments and their timing are summarized in Table 1. Baseline T1 and yearly T3 and T5 involve two in-person sessions designed to occur a week apart and T2 and T4, which occur 6 months in between, involve one remote session via videoconferencing (see Fig. 2).

STUDY TIMELINE

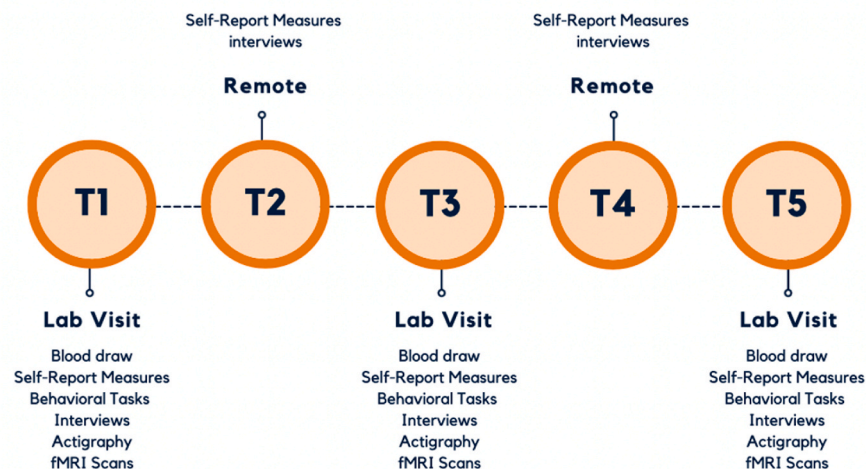


Fig. 2. Study timeline.

Table 1
Summary and timing of assessments.

Construct	T1 S1	T1 S2	T2	T3 S1	T3 S2	T4	T5 S1	T5 S2
Reward Responsiveness (RR)								
Behavioral Inhibition Scale/ Behavioral Activation Scale (BIS/BAS)	✓			✓			✓	
Sensitivity to Punishment/ Sensitivity to Reward Quest. (SPSRQ)	✓			✓			✓	
Positive Valence Systems Scale (PVSS)		✓	✓		✓	✓		✓
Card Arranging Reward Responsivity Objective Test (CARROT)	✓			✓			✓	
Delay Discounting Task (DD)	✓			✓			✓	
fMRI Monetary Incentive Delay Task (MID)		✓			✓			✓
fMRI Chatroom Interact Task (CHAT)		✓			✓			✓
Mock Scanner		✓			✓			✓
Immune System								
Blood Draw for Inflammatory Protein Assays (Fasting)	✓			✓			✓	
Breakfast after Blood Draw	✓			✓			✓	
Childhood/Adolescent Adversity								
Childhood Life Events Scale (CLES) (Ps & Mothers)	✓							
Current and Prospective Life Events								
Life Events Scale (LES) & Life Events Interview (LEI)	✓		✓	✓		✓	✓	
Social Experiences Questionnaire (SEQ)	✓		✓	✓		✓	✓	
Inflammation-Enhancing Behaviors								
Adolescent Alcohol and Drug Involvement Scale (AADIS)	✓		✓	✓		✓	✓	
Diet Screening Questionnaire (DSQ)	✓		✓	✓		✓	✓	
Actigraphy w/Sleep Diary		✓			✓			✓
Pittsburgh Sleep Quality Index (PSQI)	✓		✓	✓		✓	✓	
Diagnoses/Symptoms/ Pubertal Maturation								
Expanded SCID-5 Diagnostic Interview	✓		✓	✓		✓	✓	
Maternal Expanded SCID-5 and Family History Interview (Mothers)	✓							
Beck Depression Inventory - II (BDI-II)		✓	✓		✓	✓		✓
Internal State Scale (ISS) – done on day of fMRI scan		✓			✓			✓
Sheehan Disability Scale (SDS)		✓	✓		✓	✓		✓
Suicidal Ideation Questionnaire Jr. (SIQ-Jr)		✓	✓		✓	✓		✓
Pubertal Development Scale (PDS)	✓		✓	✓		✓	✓	
Cognitive Vulnerability/ Executive Function								
Adolescent Cognitive Style Questionnaire (ACSQ)		✓			✓			✓
Ruminative Responses Scale (RRS)		✓			✓			✓
NIH Cognitive Toolbox (Working Memory, Inhibition, Switching)		✓			✓			✓
Other								
Child SES Interview – Parent Version (Mothers)	✓							
MacArthur Scale of Subjective Social Status (Ps and Mothers)	✓							
Chapman Handedness Scale (CHS)	✓							

2.2.1. Inflammatory indices

Blood is sampled via antecubital venipuncture by certified phlebotomists in the morning after an overnight fast to control for diurnal variation and food intake. To assess factors associated with inflammatory activity that will be used as covariates as needed, anthropometric measures are taken at the beginning of the blood draw, including time of blood draw, time of last meal, body fat, weight and height to calculate body mass index, waist and hip circumference, body temperature, past-month prescription psychotropic and anti-inflammatory medications, physician-diagnosed physical health conditions, and recent infections, sickness, and physical injury. The blood draw is followed by breakfast before participants complete other study assessments. Blood is drawn into a Serum Separator Tube (8.5 mL) for quantification of circulating cytokines and C-reactive protein (CRP). The Serum Separator Tube is centrifuged between 30 minutes–2 hours after blood sampling for 10 minutes at 1300 RPMs. Harvested sera then are divided into 200 µL aliquots and frozen for long term storage in a –80 °C freezer until assays are performed by Dr. Gregory Miller and his team at the Foundations of Health Research Center at Northwestern University at yearly intervals. Interleukin (IL)-6, IL-8, IL-10, and tumor necrosis factor-alpha (TNF-α) will be quantified by multi-cytokine array, and high-sensitivity CRP will be determined in a singleplex assay, both using an automated microfluidic platform (Simple Plex, Protein Simple; Aldo et al., 2016). Each specimen will be assayed in triplicate, and the intra- and inter-assay coefficients of variation and lower limits of detection for the inflammatory proteins of interest will be assessed. An aggregate of inflammatory biomarkers will be used in the primary analyses.

2.2.2. Reward measures

2.2.2.1. Behavioral reward measures. The Card Arranging Reward Responsivity Objective Test (CARROT; al-Adawi et al., 1998; Powell et al., 1996) is a brief three-trial task measuring the extent to which participants increase their card-sorting speed when offered small financial incentives compared to a no-reward condition. Participants sort 60 cards into three numbered trays corresponding to whether the digits printed on the card include a 1, 2, or 3. Trial 1 is used to establish sorting speed at baseline. In Trial 2, the participant is given 75% of their baseline sorting time to sort another deck of cards. In Trial 3, the participants are given the same time limit, but the experimenter places a quarter in front of the participant after every 5 cards sorted. The number of cards sorted in Trial 3 minus Trial 2 is the RR measure. The CARROT correlates with self-reported RR (Alloy et al., 2012a; Kambouropoulos and Staiger, 2004), and relates to the DRD2 gene (White et al., 2008).

The Delay Discounting Task (Ahn et al., 2011; Rachlin et al., 1991) is administered to assess temporal discounting of reward value. Participants select between immediate and delayed hypothetical rewards (e.g., \$400 today or \$1000 in a week) considered roughly equal over 4 delay intervals (1 week, 1 month, 6 months, 1 year). Each participant's subjective value of \$1000 at each delay period will be fitted into a hyperbolic model. The steepness of the slope in this model (k) reflects the preference for smaller-but-immediate (as compared to larger-but-delayed) rewards. The larger the k, the greater the extent to which delay affects reward value.

2.2.2.2. Self-report reward measures. In addition to the BAS subscale of the BIS/BAS (Carver and White, 1994), the Sensitivity to Reward (SR) subscale of the Sensitivity to Punishment (SP)/Sensitivity to Reward (SR) Questionnaire (SPSRQ; Torrubia et al., 2001) is a commonly used measure of individual differences in trait sensitivity to social and non-social rewards (Alloy et al., 2012a). The SPSRQ contains 48 yes-no items divided into SP and SR subscales. Subscale scores are derived by summing the number of “yes” responses on each scale. The SR subscale has strong retest reliability (Torrubia et al., 2001) and validity as a measure of trait reward sensitivity among adolescent samples (Alloy

et al., 2012a).

The Positive Valence Systems Scale (PVSS; [Khazanov et al., 2020](#)) is a 21-item self-report measure assessing core constructs within the RDoC Positive Valence Systems domain (e.g., reward expectancy, reward anticipation, etc.) using seven reward types (i.e., food, physical touch, outdoors, positive feedback, hobbies, social interactions, and goals). Participants are asked to rate the extent to which the items describe their responses over the past two weeks on a 9-point Likert scale, ranging from 1 (*Extremely untrue of me*) to 9 (*Extremely true of me*). In adult samples, the PVSS demonstrated good retest reliability and internal consistency ([Khazanov et al., 2020](#)).

2.2.2.3. Neural reward measures. The Monetary Incentive Delay task (MID; [Knutson et al., 2001](#); [Samanez-Larkin et al., 2007](#)) a fMRI behavioral paradigm, was administered to examine neural activity to anticipation and receipt of monetary reward and loss. On each trial, a circle cue is presented for 200ms either indicating that participants can win or avoid losing money if they respond to a target stimulus in time, that is, make a button response before a solid white triangle disappears. The MID Task consists of two runs, with each of the six types of trials presented eight times in random order. Each Win trial entailed the opportunity to win \$.00, \$1.50, or \$5.00, and each Loss trial involved the opportunity to avoid losing \$.00, \$1.50, and \$5.00. On the Win trials, participants win money if they hit the white triangle in time and do not win money if they miss the target. On the Loss trials, they avoid losing money if they hit the white triangle in time and lose money if they miss it. Feedback about the amount of money won or lost then is displayed for 200ms. The initial target duration is determined based on each participant's mean hit reaction time (ms) to the white triangle in a pre-scan task. As the task progresses, the target duration adapts in response to the previous trials to maintain task difficulty, such that each participant maintains an approximate 66% success rate. The analyses will focus on the reward anticipation phase, as defined by the time window between the offset of a circle cue and onset of a white triangle (target stimulus; 200ms–250ms), and the reward outcome phase, as defined by the time window between the onset and offset of the feedback (200ms).

The Chatroom Interact Task ([Kumar et al., 2019](#); [Olino et al., 2015](#); [Silk et al., 2014](#)), a fMRI behavioral paradigm, is administered to assess reactions to social acceptance (i.e., reward) and rejection (i.e., loss) from virtual peers in an online setting. Participants are told that they are able to interact online with peers while in the scanner. Prior to engaging in the task in the scanner, participants are asked to provide their own biographical profile and their photograph is taken. They also are shown fictitious biographical profiles and photographs of potential virtual peers they can select to chat with. They are asked to select five same-sex peers that they would like to interact with during the task. Once in the scanner, the participant is told that they were matched with two same-sex peers who also are participating in the same study at different research sites. Participants review the photograph and biographical profile of the matched peers prior to the task. During neuroimaging, pictures of the participant and the two virtual peers are projected onto the screen two at a time, and the participant and peers each take turns selecting who they would rather chat with about a series of interests (e.g., school, music, sports). The task includes three experimental blocks, each with 15 trials and a fourth control block (total run time 13 minutes, 30 seconds). In each experimental block, the participant or the peers are either chosen or not chosen to discuss a given topic. Stimuli are presented using Matlab (Version 9.10.0 [R2021a]; Mathworks). Each block begins with instruction about who will be making a selection in that block (i.e., agent). The photograph of the agent is displayed in the bottom left corner of the screen and the photographs of the other two players are displayed in the middle of the screen. At the beginning of each trial, the question 'who would you rather talk to about ...' with a selected topic for that trial (e.g., ... 'music?') appears on the screen for 3.34 seconds (task component durations are chosen to be multiples of

the 1.67 TR). Feedback then is provided about the person who was chosen, indicated with a highlighted grey border around their photograph, and the person who was not chosen, indicated with a superimposed grey 'X' on their photograph. This feedback is presented for 10.02 seconds (i.e. 6 TR). The participant is instructed to press their index finger or middle finger to indicate whether the person on the left or right was chosen. Trials are arranged in blocks so the participant experiences an 'accept' block, where they are chosen two thirds of the time, and a 'reject' block, where they are rejected two thirds of the time. Each block consists of the same topics (presented randomly), but with a different "agent". The participant is the "agent" in block 1 and makes selections between the two same-gender peers. Blocks two and three consist of the participant being either chosen or not chosen by their virtual peers. Analyses are derived from these two blocks of 'acceptance' or 'rejection'. The order of accept versus reject trials are randomized for each gender grouping. The fourth block consists of a perceptual and motor control task, where the picture of the participant and one virtual peer are displayed on the screen and a small grey dot appears on one of the faces. The participant is instructed to press their index finger or middle finger to indicate whether the person on the left or right has the dot. This block is designed to control for viewing faces (self and other) and pressing a button to identify a stimulus appearing on one of the faces.

Participants complete a debriefing questionnaire at the conclusion of the task and are asked to rate how they felt along six dimensions (i.e., happy, sad, angry, nervous, included, excluded) when they were chosen and not chosen. They also are asked to rate their level of interest in the task and about their level of experience chatting online.

2.2.2.4. fMRI data acquisition, preprocessing, and analysis. A Prisma 3.0 T Siemens MAGNETOM MRI scanner with a 64-channel gradient head coil is used to acquire fMRI data at Temple University. Prior to the scans, participants are trained on the fMRI procedures via mock scans. Functional runs use a slice-accelerated multiband EPI sequence (multiband acceleration factor: 2. GRAPPA acceleration factor: 2) covering 64 axial slices (voxel size = 2.0 × 2.0 × 2.0mm; TR = 2050ms; TE = 25ms; FOV = 208 × 208mm; Matrix = 104 × 104; Flip Angle 76°). Structural images are acquired using an MPRAGE sequence to obtain 208 axial slices (voxel size = 0.8 × 0.8 × 0.8mm; TR = 2300ms; TE = 2.99ms; FOV = 256 × 256; Matrix = 320 × 320; Flip Angle = 7°). We use FIRMM software to generate real-time metrics of head motion, so we can give youth in-scanner feedback ([Dosenbach et al., 2017](#)). Data are processed using fMRIPrep ([Esteban et al., 2018](#); [Esteban et al., 2019](#)).

For the MID Task, hemodynamic signal is deconvolved using a generalized linear model identifying six trial types (Win or Lose \$0.00, \$1.50, \$5.00) during the anticipation and outcome phases. First-level voxel-wise t-statistics are computed for each participant contrasting reward (i.e., Win \$1.50 and \$5.00) vs. non-reward (i.e., Win \$0.00) trials to calculate reward anticipation and outcome, and loss (i.e., Lose \$1.50 and \$5.00) vs. non-loss (i.e., Lose \$0.00) trials to calculate loss anticipation and outcome ([Samanez-Larkin et al., 2007](#); [Young and Nusslock, 2016](#)). The analyses will include a nuisance regressor for high motion volumes (>.2mm) and 6 motion parameters.

For the Chatroom Interact Task, a first-level fixed-effect model is constructed for each participant and predetermined conditioned effects at each voxel are calculated using a t-statistic. Analyses will focus on reward trials (i.e., peer acceptance) versus the motor control task. Secondary analyses will examine loss trials (i.e., peer rejection) versus the motor control task to examine specificity of results to reward processing. Exploratory analyses will examine anticipation of reward.

The a priori regions of interest (ROIs), including the orbitofrontal cortex (OFC), ventral striatum (VS), and other reward-relevant brain regions are defined using anatomical atlases and/or prior meta-analytic research to insure independence from the present study. Psychophysiological interaction (PPI) models will be used to examine functional

connectivity between the VS, OFC, and/or other reward-relevant brain regions. After generating the parameter estimates (beta-weights) of activation in the ROIs, as well as PPI functional connectivity within the cortico-striatal circuit, the extracted parameter estimates will be imported into R statistical software for ROI activation and connectivity analyses.

2.2.3. Life events, adversity, and SES measures

Participants complete a modified version of the Life Events Scale (LES; Francis-Raniere et al., 2006) at T1-T5 to assess occurrence of major and minor, negative and positive life events spanning the past six months. The original 193-item LES was shortened for Project RISE so that it contains 156 events in multiple domains (e.g., school, peers, romantic interests, family, financial) relevant to adolescents, including items to cover events relevant to adolescents today (e.g., “Received a lot more positive attention in-person or on social media (e.g., more “likes” than usual)”, “Tested positive for COVID-19”). Events were coded a priori as reward-relevant or not and into specific reward-relevant categories with inter-rater reliabilities of α 's = 0.79-0.94: Goal-Striving, Goal Attainment/Reward, Goal Obstacle, and Goal Failure/Loss (Urošević et al., 2010).

Following completion of the LES, adolescents complete a Life Events Interview (LEI; Francis-Raniere et al., 2006; Safford et al., 2007) about the endorsed events, to obtain further information about them and date when they occurred. Trained post-baccalaureate and clinical psychology doctoral students, blind to all study measures, conduct the interviews with adolescents. The LEI uses manualized, event-specific definitional criteria and probes to maintain consistency, avoid double-counting of events, and reduce dating errors. Events not meeting definitional criteria are disqualified to reduce subjective reporting biases. The LEI also employs the “gold-standard” contextual threat method (Safford et al., 2007) to rate the events’ objective impact on a scale from 1 (*Mild*) to 4 (*Extreme*) and independence (e.g., death of a family member) vs. dependence (e.g., fight with a friend) on the participant’s behavior. Events rated as dependent on participants’ behavior are used to assess stress generation. These procedures have yielded excellent reliability and validity of event dating and ratings (κ = 0.76 – 0.89) in our previous studies (Francis-Raniere et al., 2006; Safford et al., 2007).

The Social Experiences Questionnaire-Self-Report (SEQ; Crick and Grotpeter, 1996) is a self-report measure of frequency of victimization and pro-social behaviors experienced from peers over the past six months. This 15-item measure has three subscales (5-items each): relational victimization, overt victimization, and receipt of prosocial acts and is completed at T1-T5. Specifically, adolescents are asked if they have experienced each event and how often it occurred, on a scale from 1 (“Never”) to 5 (“All the Time”). The SEQ has shown sufficient internal consistency, reliability, and validity among child and adolescent samples (Crick and Bigbee, 1998; Crick and Grotpeter, 1996; Shapero et al., 2013).

The Childhood Life Events Scale (CLES) is a 50 life events checklist that is completed by the adolescent and their mother at T1 only (Crossfield et al., 2002). Given that adolescents may have been too young to remember some events, the adolescent and their mother separately identify moderate to severe stressful life events that happened in the child’s life and provide the age from birth to present at which the events happened. Domains of the CLES include achievement-related events (e.g., “academic failure”), peer difficulties (e.g., “break up of serious romantic relationship”), family difficulties (e.g., “divorce of parents”, “serious financial difficulties of family”) and assorted other categories (e.g., “death of a pet”, “unwanted pregnancy”). The events also range in severity from less severe events, such as “beginning school”, to “death of a parent” or “experienced sexual abuse, including rape”. For the current study, a score for the CLES is derived from the total number of events reported. Additional subset scores are derived from the total number of events reported within each subset category. These event subsets represent negative emotional feedback (i.e., “frequent teasing by

peers”, “decrease in acceptance by peers”), family deaths (e.g., “death of a grandparent”, “death of a parent”), achievement failures (e.g., “academic failure”, “nonacademic failure”), events suggesting inadequacy (e.g., “acquired a physical deformity”, “needed special education services”), and dependent events and independent events. Total scores ranging between 0 and 50 serve as a measure of adversity exposure. The CLES has shown predictive validity and good internal consistency (α = 0.75; Crossfield et al., 2002; Grandin et al., 2007; Shapero et al., 2015).

At T1 only, each teen’s mother also completes an interview assessing the teen’s family socioeconomic conditions throughout their lives and during the teen’s first year of life, based on: family structure, parent/legal guardian’s marital status, years of education, employment status, home living conditions (i.e., house and automobile ownership, and number of bedrooms), family income and savings, and immigration status. Family socioeconomic disadvantage during the teen’s first five years of life vs. throughout their life will be scored as a sum of these indicators (1 = present vs. 0 = absence): family poverty (i.e., income-to-poverty ratio <1.00 (Shrider et al., 2021), single-parent family structure, parent non-completion of high school degree or equivalent, unemployment, and immigration status. Family social class is assessed by reports of ownership of residence and automobile via the aforementioned interview. Perceived social standing is measured by the MacArthur Scale of Subjective Social Status (Adler et al., 1994; Goodman et al., 2001). Teen and parent complete the Youth and Adult versions respectively, where they each mark the rung on a 10-step ladder that represents their family’s social standing in the society.

2.2.4. Inflammation-enhancing behaviors measures

2.2.4.1. Substance use measure. The Adolescent Alcohol and Drug Involvement Scale (AADIS; Moberg, 2003) is a two-part (drug and alcohol) self-report measure assessing the frequency of use of alcohol, nicotine, and 10 other drug types (Moberg, 2000). Patterns of drug use are assessed for the past month on a 6-point scale at T1-T5. For each substance type, the questionnaire asks whether the participants “Never Used”, “Tried it once Or Twice”, “Several Times a Month”, “Weekends Only”, “Several Times a Week”, “Daily”, or “Several Times a Day”. The AADIS is a reliable and consistent measure (Mason et al., 2010; Moberg, 2000; Moberg and Hahn, 1991), with α = 0.71 in Bart et al. (2021).

2.2.4.2. Dietary measure. At T1-T5, participants also complete the Dietary Screening Questionnaire (DSQ), a 25-question self-report questionnaire assessing dietary intake over the past month (National Cancer Institute, 2023). Participants rate their intake frequency of different food groups on questions such as “During the past month, how often did you eat hot or cold cereals?”. Answer options include “Never”, “1-time last month”, “2–3 times last month”, “1 time per week”, “2 times per week”, “3–4 times per week”, “5–6 times per week”, “1 time per day”, to “2 or more times per day”. Then, an algorithm is used to score responses by estimating individuals’ dietary intake for fruits and vegetables (cup equivalents), added sugars (teaspoon equivalents), whole grains (ounce equivalents), fiber (g), and calcium (mg) (National Cancer Institute, 2023).

2.2.4.3. Sleep measures. To objectively assess participants’ sleep and activity patterns, at T1 and yearly (T3, T5), adolescents wear an actiwatch (Philips Healthcare) on their non-dominant wrist continuously for 7 days. Actigraphy provides an objective, reliable, and valid method for assessing sleep and activity patterns in participants’ natural environment with minimal restriction on normal routines (e.g., Ancoli-Israel et al., 2003, 2015). It corresponds highly with polysomnography, including in adolescents (Kaplan et al., 2012; Marino et al., 2013). Participants are instructed to keep the watch on at all times, except when daily activities require its removal or when the watch may get wet (e.g., during showers, baths, swimming), thus minimally interfering with their daily routine. Data are sampled in 1-min epochs and stored

digitally. Given that both inflammation and RR are associated most consistently with sleep duration (Acheson et al., 2007; Burani et al., 2021; Holm et al., 2009), the sleep variables collected with the actiwatch will include the mean and standard deviation (SD) of sleep duration across the 7 days and weekday/weekend duration ratios (Jones et al., 2005). To assist with interpretation of actigraphy data, participants also are asked to complete a 7-day sleep diary (Monk et al., 1994) during the same period they wear the actiwatch. Each morning, participants receive a notification via text or email alerting them to complete the survey. The surveys assess bedtime, waketime, naps, medications, caffeine use, and daily exercise. If a survey is missed, reminders are sent to the participant's phone.

The Pittsburgh Sleep Quality Index (PSQI) is an 18-item self-administered questionnaire assessing sleep quality and disturbances over the past month (Buysse et al., 1989) completed at T1-T5. The questionnaire consists of 7 components: subjective sleep quality, sleep latency, duration of sleep, sleep efficiency, sleep disturbances, sleeping medication use, and daytime dysfunction. Items 1–4 ask participants to include their bedtime and wake-time, to specify how long it typically takes them to fall asleep and the number of hours they sleep per night. Items 5–17 ask them to rate the frequency of specific sleeping problems on a 4-point Likert scale: “Not during the past month”, “Less than once a week”, “Once or twice”, and “Three or more times a week”. Items 14 and 15 ask for a general rating of overall sleep quality and sleep problems. Item 19 has a 4-point Likert response scale relating to the participants’ “enthusiasm to get things done”. A global PSQI score >5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% ($\kappa = 0.75$, $p < 0.001$) in differentiating good (lower scores) from poorer sleep quality (higher scores).

2.2.5. Diagnostic and symptom measures

2.2.5.1. Diagnostic interview measure.

At T1, lifetime history of mood and other disorders based on DSM-5 criteria (American Psychiatric Association, 2013) are assessed using the Structured Clinical Interview for DSM-5 (SCID-5; First et al., 2015). The current study utilizes the Non-patient Version Overview and Modules A (Mood Episodes), B/C (Psychotic Symptom Screen), D (Differential Diagnosis of Mood Disorders), E (Substance Use Disorders), F (Anxiety Disorders), G (Obsessive-Compulsive and Related Disorders), I (Feeding and Eating Disorders), K (Externalizing Disorders), and L (Trauma- and Stressor-Related Disorders) of the SCID-5 (First et al., 2015), as well as the expanded SADS-L (exp-SADS-L) diagnostic interview (Alloy et al., 2006b; Endicott and Spitzer, 1978) for current and past mood episodes and symptoms. These mood modules were combined to include DSM-5 criteria and avoid skip outs in the mood disorder sections, ensuring that we obtain all mood symptom ratings, even if a participant endorses a period of mood symptoms for a duration shorter than required by DSM-5 criteria.

Every 6-months (T2-T5) after T1, interviewer-rated symptoms, functioning, and onsets of DSM-5 mood and other disorders since the previous interview are assessed using this modified version of the SCID-5 with expanded mood modules. In addition, at T1, adolescents’ primary caregiver also completes this version of the SCID-5 and Family History Interview (Andreasen et al., 1977) to assess history of mood disorders for themselves and other 1st and 2nd degree relatives.

The expanded SCID-5 is administered to both adolescents and primary caregivers by trained post-baccalaureate and clinical psychology doctoral student interviewers, blind to participants’ RR quintile. Diagnostic training includes didactic instruction, observation, and interview practice before being observed and evaluated for clearance by senior study members. The clinician version of the SCID-5 ($\kappa > 0.70$; Osório et al., 2019) and the exp-SADS-L ($\kappa > 0.90$ for MDD; Alloy et al., 2006b, 2008; 2012b) have shown good to excellent inter-rater reliability for both mood and other diagnoses.

2.2.5.2. Self-report depressive symptom and suicide measures.

All self-report symptom and suicide measures are completed at T1-T5. The Beck Depression Inventory-II (BDI-II (Beck et al., 1996)); is a widely used self-report measure of anhedonia and general depressive symptom severity. This 21-item questionnaire asks participants to use a 0 to 3 scale to indicate which statement best describes their feelings over the past two weeks. The BDI-II has demonstrated strong reliability and validity in community and adolescent samples (Osman et al., 2008; Wang and Gorenstein, 2013).

The Sheehan Disability Scale (SDS; Sheehan, 1983) is a commonly used measure of symptom-related impairment. This measure asks adolescents to rate on a 10-point Likert scale the degree of disruption their mental health has had on their school/work, social, and family lives. With higher scores representing greater impairment, the SDS is considered a change-sensitive and valid measure of global impairment, especially among populations experiencing depression (Sheehan et al., 1996, 2017).

The Suicide Ideation Questionnaire-Junior (SIQ-Jr; Reynolds, 1987) is a 15-item, self-report measure of suicidal ideation. Adolescents rate the frequency of suicidal ideation within the past month on a 7-point Likert scale (0 = “I have never had this thought” to 6 = “Almost every day”). Total scores on the SIQ-Jr have demonstrated strong internal consistency, retest reliability, and validity among adolescent samples (Reynolds, 1987; Reynolds and Mazza, 1999).

If an adolescent endorses suicidal ideation on the SIQ-Jr, BDI-II, or the SCID interview, the interviewer administers a comprehensive suicide risk assessment interview. Depending on the level of risk and whether the teen already is in treatment with a mental health professional, follow-up ranges from providing treatment referrals to transporting the teen to an emergency room if the threat of a suicide attempt is imminent. In addition, when teens are determined to be at higher risk, their parent is informed of the risk for suicide (as explained in advance in the written teen assent and parent consent forms).

On the day of each fMRI scan, participants complete the 15-item Internal State Scale (ISS; Bauer et al., 1991) to assess current affect and discriminate between manic and depressive mood states (Bauer et al., 2000). The scale contains activation, well-being, perceived conflict, and depression subscales. Participants indicate the extent to which each statement applies to them today on 5-point Likert scales (*Very Slightly or Not at All to Extremely*). The ISS has previously shown good convergent and discriminant validity (Bauer et al., 1991; Cooke et al., 1996), and has been used with several clinical and non-clinical samples (Boland et al., 2016; Nusslock et al., 2012).

2.2.6. Cognitive measures

2.2.6.1. Self-report cognitive style measures.

Additional measures of cognitive styles are included both because they have been shown to be important predictors of MD onset in their own right (Alloy et al., 2006b; Robinson and Alloy, 2003) and because they reflect a shared vulnerability to MD with blunted RR (Nusslock et al., 2011). Modified from the Adolescent Cognitive Style Questionnaire (ACSQ; Hankin and Abramson, 2002), the Adolescent Cognitive Style Questionnaire-Modified (ACSQ-M; Alloy, Black, et al., 2012) is a self-report measure of adolescents’ inferential style based on interpretations of the causes and consequences of 12 hypothetical negative events. In the ACSQ-M, the negative events consist of three domains (achievement, interpersonal, and appearance) with four scenarios per domain. After reading the hypothetical situation, adolescents are asked to make inferences about the stability and globality of causes, the consequences, and implications for the adolescents’ self-worth. Each dimension is rated on a 1 to 7-point scale, with higher values representing greater negative inferential style. The ACSQ-M is completed at T1 and yearly (T3, T5). Good to excellent internal consistency and reliability were found for the ACSQ-M among adolescents (Alloy, Black, et al., 2012).

Participants also complete the Ruminative Responses Scale (RRS; [Treyner et al., 2003](#)) at T1 and yearly (T3, T5). The RRS is a 10-item self-report measure of one's tendency to ruminate in response to negative affect. This scale includes a ruminative reflection and a ruminative brooding subscale. Each subscale contains five items scored on 4-point Likert scales (1 = "Almost never", 4 = "Almost always"), previously demonstrating good retest reliability and positive associations with other measures of trait rumination ([Siegle et al., 2004](#); [Treyner et al., 2003](#)).

2.2.6.2. Behavioral executive function measure. At T1 and yearly (T3, T5), participants complete parts of the National Institutes of Health Toolbox Cognition Battery (NIHTB-CB) to objectively assess neurocognitive function. The NIHTB-CB is a standardized battery of cognitive tests created by NIH to unify neuropsychological research ([Weintraub et al., 2013](#)). Of the 7 tests in the NIHTB-CB, we administer 3 tests assessing working memory, executive functioning, and attention. Scores are demographically adjusted with a mean (SD) of 50 (10), comparing participants' scores with a normative sample (HealthMeasures, 2023).

We administer the List Sorting Working Memory Test, which is a sequencing task assessing working memory. Participants sort visual and auditory information and sequence it. They are visually presented with a series of illustrated pictures depicting an item (e.g., a fruit), along with their auditory names. Then, they are instructed to remember each item and to repeat the list of items verbally in order of size from smallest to largest. The list of items increases as the participant remembers the item order correctly. If the participant fails to remember correctly during two consecutive trials, the test is discontinued. Two rounds of this test are administered. During the first round, all the items come from one object category. During the second round, items are presented from two object categories, and the participant must first report all the objects from one category, then from the other, in order of size. The task takes approximately 7 minutes to complete, and test scores consist of the total correct answers.

The Flanker Inhibitory Control and Attention Test derives from the Eriksen flanker Attention Network Test ([Rueda et al., 2004](#)). This task measures executive functions by testing the ability to inhibit irrelevant visual stimuli. During this task, participants are presented with a set of five arrows horizontally aligned in the middle of the screen either oriented to the left or right. They are asked to indicate the orientation of the middle arrow, which can sometimes be oriented differently than the rest of the arrows. By having to visually inhibit the orientation of the non-target arrows and having to indicate the orientation of the target, the participant's ability to inhibit irrelevant stimuli is tested. Scoring (0–10) uses an algorithm that is weighted based on reaction time (for individuals older than 8 years old). The task takes about 4 minutes to complete and consists of 40 trials.

The Dimensional Change Card Sort Test assesses the set-shifting component of executive functioning ([Zelazo, 2006](#)). During this task, a target visual stimulus must be matched to one of two other visual stimuli based on shape or color. Before the start of each trial, the word "color" or "shape" appears on the screen to cue the participant about whether the stimulus must be matched based on shape or color. Similar to the flanker task, scoring uses a weighted algorithm based on reaction time. This task takes about 4 minutes to complete a total of 40 trials.

2.2.7. Potential covariates

Pubertal maturation is associated with both RR (e.g., [Forbes et al., 2010](#); [Icenogle et al., 2017](#); [Urošević et al., 2014](#)) and inflammation (e.g., [Stumper et al., 2020](#)). Thus, we plan to control for pubertal maturation as needed. At T1–T5, pubertal maturation is assessed with the Pubertal Development Scale (PDS) ([Petersen et al., 1988](#)). The PDS consists of 5 items asking participants about their growth in height, body hair, skin change, breast or menstruation for females, or voice change and facial hair for males. Item scores are averaged, yielding a final score

of 1–4 (less to more mature). This questionnaire shows good reliability (average $\alpha = 0.77$) and convergent validity (r 's of 0.61–0.67 with physician ratings; $r = 0.84$ with mothers' ratings) (e.g., [Alloy et al., 2016a](#); [Petersen et al., 1988](#); [Stumper et al., 2020](#)).

Given that we are excluding adolescents with past MD, we do not expect high rates of medication use at T1. However, we will not exclude participants taking psychotropic medications since this would reduce representativeness and limit generalizability. We will statistically control for medication status (on vs. off) in analyses. Further, we will re-run analyses after removing participants taking medications affecting cortico-striatal signaling. We also will control other psychiatric disorders and family history of mood disorders as needed, as well as the potential confounders of the inflammatory markers (time of blood draw, time of last meal, body fat, body mass index, waist and hip circumference, past-month anti-inflammatory medications, physician-diagnosed physical health conditions, and recent infections, sickness, and physical injury).

3. Discussion

Results from this study should be considered in the context of several limitations. First, although peripheral inflammatory proteins (e.g., cytokines) access the brain, our assessments of inflammation are limited to the periphery and do not directly assess neural inflammation. Second, we assess inflammatory activity in the context of naturally occurring early adversity and recent stressful life events, but do not measure inflammatory reactivity to an immune system challenge (e.g., endotoxin or a laboratory stress test). Third, although the Positive Valence Systems Scale (PVSS) included in this study assesses multiple domains of reward processing, our measures of RR primarily focus on reward anticipation and consumption and do not comprehensively assess other components of reward function, such as effort expenditure for reward or reward learning. Unfortunately, these additional assessments were not possible within the scope of budget limitations but would be important directions for future work on reward-inflammation mechanisms involved in depression.

These limitations notwithstanding, the findings from Project RISE hold promise for advancing understanding of vulnerabilities and mechanisms involved in the emergence of depression in adolescence. Although research has separately examined the relationship between RR and depression and inflammation and depression, no studies have taken the integrative, multi-organ, perspective that we take in this study. Drawing on research highlighting bidirectional signaling between the brain and the immune system (e.g., [Eisenberger et al., 2017](#); [Felger and Treadway, 2017](#); [Nusslock and Miller, 2016](#)), we propose a novel neuroimmune network model, which predicts that dysregulated signaling between reward neural circuitry and inflammation is a joint vulnerability for depression ([Nusslock and Miller, 2016](#)). In line with the Research Domain Criteria and Goals 1 and 2 of the NIMH Strategic Plan, this project is the first test of the relationship between RR in both monetary and social domains, inflammation, and first onset of MD and increases in depressive symptoms during adolescence, an "age of risk" for development of MD. Our high-risk, longitudinal design with multiple time points allows us to assess whether abnormalities in reward-immune signaling predate the onset of first MD, reflecting a preexisting vulnerability, or emerge as a consequence of the illness. This is important for understanding etiological pathways to depression and identifying bi-behavioral markers of risk. Identifying reward-immune pathways in the emergence of MD and depressive symptoms also could facilitate "a next generation" of behavioral and biological interventions that target brain-to-immune and immune-to-brain signaling to treat, and ideally prevent, depression.

Moreover, our test of the behaviors (substance use, diet, sleep disturbance, stress-generation) that may mediate RR-inflammation associations is innovative, and, in particular, the test of the role of sleep disturbance and stress generation as mediators is completely novel. This

will provide better understanding of potential mechanisms that may contribute to reward–inflammation associations and prediction of MD and depressive symptoms, and also will suggest potential targets for novel interventions.

Ethics approval and consent to participate

Ethics approval was granted by the Temple University IRB (IRB #27918) for this study.

Consent for publication

Not applicable.

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Authors' contributions

LBA and RN generated the research questions and methodology for the study, wrote the R01 grant that is funding its execution with help from TO, LE, and GM, managed all parts of the project execution, recruited and trained all project personnel and research assistants, and provided lab space and resources. LBA also drafted many parts of this manuscript. IC, MG, AS, and ZA helped to develop the project protocol and assessments, ran participants, and drafted parts of this manuscript. RN, TO, LE, and GM also provided feedback on drafts of this manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

Data from this study will be available on the NIMH National Data Archive (Collection #C3835).

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