Identifying Psychobiological Mechanisms that Predict Depression in High-Risk Adolescents

An honors thesis for the Department of Psychology

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Abstract

Major depressive disorder (MDD) is a debilitating psychiatric disorder with a peak age of onset in adolescence, and epidemiological studies find that it occurs more frequently in female adolescents. Several studies have examined putative mechanisms that underlie risk for depression by investigating behavioral or biological deficits that exist prior to symptom and disorder onset in order to tease apart whether these deficits are a cause or effect of depression. The thesis utilized a high-risk design to probe behavioral and neural differences in one such mechanism, reward responsivity, in low- and high-risk adolescents. Participants included healthy, female adolescents (n = 33) ages 12-14 years classified as high-risk (HR = 9) or low-risk (LR = 24) based on the presence or absence of maternal history of depression. Participants were administered clinical interviews and completed self-report symptom measures. Additionally, adolescents completed a behavioral task that probed initial reward responsiveness, and functional magnetic resonance (fMRI) imaging data were acquired during a monetary reward task (i.e., wins vs. losses). Results indicated that the LR group demonstrated an increase in response bias over time, while the HR group exhibited an attenuated response bias. Additionally, although no group differences emerged when examining differential activation to wins versus losses in mesolimbic regions (nucleus accumbens, putamen, caudate), there was a significant negative association between activation in the right putamen (i.e., contrast of wins versus losses) and levels of depressive symptoms. Taken together, these results indicate a blunted reward response in HR participants may precede the onset of depressive symptoms, which may have important implications for early identification and treatment.

Introduction

Adolescence is the peak period for the onset of major depressive disorder (MDD) with a lifetime prevalence rate of 11.7% (Merikangas et al., 2010). During this period, gender differences arise whereby females are twice as likely as males to develop depression – a gender disparity that persists throughout adulthood (Cyranowski, Frank, Young, & Shear, 2000). Importantly, there are a number of neurocognitive (e.g., cortical growth), developmental (e.g., pubertal onset), and psychosocial (e.g., greater reliance on peer relationships) changes that arise during adolescence, and research posits that these profound transitions contribute to the manifestation of depressive symptoms (Nolen-Hoeksema & Hilt, 2009). The occurrence of MDD in adolescents is marked by a cascade of negative short- and long-term consequences. Specifically, in the short-term, MDD is associated with relationship problems, low academic functioning, and increased suicidality. These short-term negative consequences have a deleterious impact on psychosocial functioning and the course of this debilitating disorder, and often, these problems progress into adulthood (Hammen & Rudolph, 2003). In the long-term, depression in adolescence is predictive of recurrent depressive episodes, increased comorbidity (especially with substance use and anxiety disorders), unemployment status, and educational underachievement (Fergusson & Woodward, 2001). While adolescent-onset depression does not directly predict later health outcomes such as cardiac disease, it is related to impaired physical functioning (chronic pain, sleep disturbances) that may contribute to a poor health prognosis (Keenan-Miller, Hammen, & Brennan, 2007). Given these alarming epidemiological data and associated negative consequences, it is critical to identify factors that contribute to the onset and maintenance of depressive symptoms during this critical developmental period.

Major Depressive Disorder: Symptoms and Gender Differences

Similar to depression among adults, depression during adolescence may result in marked impairment (Wight, Sepúlveda, & Aneshensel, 2004). According to the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*), MDD is characterized by a variety of symptoms – the core symptoms include sad mood and inability to experience pleasure (i.e., anhedonia). Other symptoms include weight loss/gain, sleep disturbances (e.g., insomnia, hypersomnia), fatigue, psychomotor agitation/retardation, feelings of worthlessness, inattention, and suicidal ideation (American Psychiatric Association [APA], 2013). In order to receive a *DSM-5* diagnosis of MDD, an individual must experience a minimum of five of the nine symptoms for at least two weeks. As several of the symptoms (e.g. anhedonia, weight loss/gain, sleep disturbances) are also common in other disorders (APA, 2013), discovering more objective (e.g., biological) markers may, ultimately, help clinicians obtain more accurate diagnoses and critically, identify risk factors that lead to this debilitating disorder.

Gender differences have been reported across adolescents (Nolen-Hoeksema & Girgus, 1997) and adults (Kessler et al., 1993). Specifically, female adolescents report twice as many depressive episodes relative to male adolescents – a difference that emerges at the age of 14 and persists throughout adulthood (Hankin, Mermelstein, & Roesch, 2007). Several related factors that arise during adolescence may contribute to the onset of depressive symptoms, including: (1) greater reliance on peers (interpersonal stress; Shih, Eberhart, Hammen, & Brennan, 2006), (2) greater exposure to stress (increased stress generation; Hammen, 2006), and (3) co-rumination (the repeated discussion of distressing events with close friends; Rose, 2002). These factors are particularly salient when considering depression in female adolescents, who have a heightened vulnerability to stress stemming from peer relations (Cyranowski et al., 2000). Therefore, it is

important to investigate changes during adolescence that may stem from underlying deficits and potentially influence the development of depressive symptoms.

First, research suggests that interpersonal stress is a robust predictor of adolescent MDD in both males and females (Hankin et al., 2007). However, it is believed that peer relations may be more central for female adolescents during this developmental period, especially in providing examples of prosocial behavior, encouraging intimacy, and supporting self-disclosure (Rose & Rudolph, 2006). Adolescent females prefer dyadic relationships, which influences the nature of interpersonal stress that can lead to depression during adolescence; namely, there is more close friend stress, as opposed to stress stemming from the larger social circles preferred by male adolescents (Rudolph, 2002). Additionally, increased reliance on peer relationships generates more stressful life events in females and increases the likelihood of reacting to stress in a depressive manner (Shih et al., 2006). This leads to a heightened sensitivity to the occurrence of depressive symptoms as a result of peer-related stress (Cyranowski et al., 2000; Hampel & Petermann, 2006), demonstrating that while interpersonal relationships become increasingly important during adolescence, they also contribute to increased stress and vulnerability to depression.

Second, female adolescents also may generate more interpersonal stress across relationships, and Shih and colleagues (2006) posit that this stress increases risk for depression. Hammen (1991) coined the term stress generation to describe this phenomenon. Stress generation theory suggests that individuals exhibit certain characteristics or behaviors that increase the likelihood that stressors occur – partly due to their own actions, which then contributes to depression onset (Hammen, 2005). This theory has been studied in adolescent samples (Rudolph et al., 2000), demonstrating that adolescents also play a role in generating

interpersonal stress, which contributes depression in adolescents (Auerbach et al., 2011; Auerbach et al., 2014).

Last, co-rumination is more common in females, which may help account for gender differences in emotional adjustment (Rose, 2002). Co-rumination is the tendency for individuals to utilize close peer relationships to dwell on negative events, which increases the severity and duration of their depressive symptoms. In doing so, adolescents tend to overthink and perseverate on depressive symptoms as opposed to actively problem solving or applying more adaptive coping strategies. Past research has demonstrated that higher levels of co-rumination, particularly among female adolescents, prospectively predict depressive symptoms (Stone, Hankin, Gibb, & Abela, 2011) and episodes (Hankin, Stone, & Wright, 2010).

Taken together, these factors contribute to greater vulnerability in female adolescents in that they: (a) exhibit a greater reliance on peers (Cyranowski et al., 2000), (b) are more susceptible to stress generation (Rudolph et al., 2000), and (c) engage in co-rumination (Rose, 2002). Critically, these findings underscore the importance of identifying behavioral indicators and biological markers that underlie vulnerability factors, particularly as this may relate to understanding depression onset among female adolescents.

Examining Putative Mechanisms Underlying Depression

The field of depression research has begun investigating putative mechanisms that may underlie depression (Austin, Mitchell & Goodwin, 2001) in order better understand concurrent cognitive deficits, namely, impairment in response to feedback (Beats et al., 1996; Elliot et al., 1996). In particular, depression is related to a heightened risk of committing an error after previously committing one, which indicates a possible failure to learn based on reinforcing feedback (Steffens et al., 2001; Beats et al., 1996). Reduced reinforcement from positive stimuli

(Lewinsohn et al., 1979) and weakened response to positive stimuli (Berenbaum & Ottmanns, 1992) are hallmark features in depressed individuals, and such traits are related to anhedonia—a core feature of MDD that connotes a diminished ability to experience pleasure (Pizzagalli et al., 2005). As depression is categorized by a disruption in hedonic capacity, Pizzagalli and colleagues (2005) modified a signal detection task (see Tripp & Alsop, 1999) to obtain an objective measure of anhedonia. In the task, participants are differentially reinforced for correct responses, which results in a response bias (Pizzagalli et al., 2005; McCarthy, 1991). In comparison to individuals with high levels of depressive symptoms, adults with low levels of depressive symptoms developed a greater response bias toward the more frequently rewarded condition. Critically, response bias was negatively associated with a self-report measure of anhedonia (Pizzagalli et al., 2005; Bogdan & Pizzagalli, 2006). Building on these promising findings, results also have indicated that relative to healthy adults, depressed adults exhibited a blunted response bias (Pizzagalli et al., 2008). Further, stress-induced hedonic dysfunction – manipulated to increase anhedonic symptoms – resulted in reduced reward responsiveness by blunting the development of a response bias in healthy individuals suggesting a potential connection between stress and depression onset (Bogdan & Pizzagalli, 2006).

Reward-related research also has extended to depressed adolescents. Specifically, Forbes and colleagues (2007) found that depressed boys are unable to differentiate between small and large rewards when the probability of receiving rewards was high. In the task, participants were given two options—one, a constant 50% probability of winning 10 points, and another *risky* option, which varied in the probability of winning (33% and 66%) a smaller or larger value (20 or 80 points). Depressed participants failed to choose the higher-magnitude rewards when presented with a high probability of winning. In another study focusing on depressed male and

female adolescents, Boger and colleagues (2014) used a probabilistic reward task (Pizzagalli et al., 2005) to demonstrate reduced levels of anhedonia and a subsequent increase in reward responsiveness in depressed individuals from pre- to post-treatment. As levels of self-reported anhedonia decreased following treatment (comprised of motivational interviewing, cognitive-behavioral therapy, and dialectal behavioral therapy), adolescents were better able to moderate behavior based on reward reinforcement history. Taken together, these results suggest that hedonic capacity can be assessed using an objective measure, differentiate healthy and depressed individuals, and examine treatment progress (i.e., outcomes). However, less is known about the neural correlates that may underlie reward dysfunction in depressed adolescents.

Biological Markers of Depression

Behavioral investigations of hedonic capacity have led to neuroimaging research that focuses on the learning and reinforcement of reward (Treadway & Zald, 2012). Specifically, research has investigated the neural pathways that mediate how individuals process and respond to reward (Schultz, 2000). Using functional magnetic resonance imaging (fMRI) allows researchers to examine specific brain regions related to reward-related pathways in the brain (Treadway & Zald, 2012). Consistent with animal research (Apicella et al., 1992; Apicella et al., 1991), neuroimaging research has implicated mesolimbic regions, which mediate goal-directed behaviors and reward learning (Delgado et al., 2000; O'Doherty, 2004).

Due to the importance of anhedonia in both the onset and maintenance of depressive symptoms, neuroimaging research has begun examining reward-related pathways that may underpin depression (Steele et al., 2007). In studies of depressed adults, MDD was related to a blunted response to reward feedback in the anterior cingulate (Steele et al., 2007) and striatum (Pizzagalli et al., 2009). In particular, Pizzagalli and colleagues (2009) explored the differential

neural responses to both anticipatory and consummatory phases of reward processing, and implicated left nucleus accumbens and bilateral caudate dysfunction in the consummatory phase, especially to "winning" feedback. Furthermore, Steele and colleagues (2007) found a direct correlation between anhedonia and abnormalities in ventral striatum and anterior cingulate activation to wins and losses, respectively.

Given important developmental differences, recent research also has begun examining these models in adolescents. For example, relative to healthy adolescents, depressed youth demonstrated a decreased neural response in reward-related brain regions during both reward anticipation and outcomes (Forbes et al., 2006). Specifically, among depressed participants, a blunted response to a rewarding outcome was seen in the anterior cingulate cortex (ACC; sub-region not specified), left caudate, and orbitofrontal cortex (OFC). In another study that focused on social rewards, compared to healthy participants, depressed youth showed increased activation to a peer rejection paradigm (Silk et al., 2012) relative to controls in the bilateral amygdala, subgenual anterior cingulate, left anterior insula and left nucleus accumbens (Silk et al., 2013). These results demonstrate the similarity between depressed adults and adolescents with regards to abnormal neural reactivity in mesolimbic brain regions.

Although these studies highlight the importance of examining reward-related pathways in adolescents, they do not address whether differential activation between depressed and healthy youth is a cause or effect of depression. Thus, several research groups have employed high-risk designs, using healthy adolescents with differential familial risk (e.g., maternal history of depression). This design is critical, as offspring of depressed mothers are at significantly greater risk to develop depression during adolescence (Hammen, 2009; Weissman et al., 2006). Therefore, it provides a means of testing whether reward-processing deficits are present prior to

depression onset among at-risk youth. For example, when comparing low- and high-risk healthy adolescents, Gotlib and colleagues (2010) utilized a monetary incentive delay task and found that compared to low-risk youth, high-risk adolescents exhibited: (a) attenuated responses in the putamen and left insula while anticipating gains and (b) greater activation in the dorsal anterior cingulate gyrus following punishment. Similarly, Olino and colleagues (2014) found that high-risk youth exhibited a lower striatal response during the anticipatory phase of reward processing, suggesting that blunted reward responsiveness in the ventral striatum may be an endophenotype for MDD onset. Building on the high-risk design, Sharp and colleagues examined low-risk (healthy youth with no maternal history of MDD), high-risk (healthy youth with a maternal history of MDD), and currently depressed female adolescents (with a maternal history of MDD) aged 10-16 years. Results indicated that both the high-risk and currently depressed youth exhibited blunted activation in the ventral striatum following reward. This effect was not present in the healthy, low-risk group, suggesting that blunted reward responsiveness may be an neural phenotype that contributes to depression onset. As a whole, these findings strongly suggest that blunted reward response in the ventral striatum may play a key role in depression onset among adolescents.

Overall, these high-risk studies have begun to converge with evidence for neural abnormalities in reward processing that exist before the onset of psychopathology or clinical symptoms in adolescents. Risk profiling has begun to indicate neural characteristics of individuals at risk for developing depression by identifying abnormalities – known to be present in currently depressed populations – in otherwise healthy adolescents (Gotlib et al., 2010). However, while differences have been seen in high-risk populations, it is important to follow adolescents over time in order to investigate if these neural differences prospectively predict

MDD in adolescents by implementing a longitudinal design. The course of these abnormalities and the impact they have are still largely unknown.

Goals of the Current Study

Toward the goal of better understanding the putative mechanisms that underlie reward dysfunction and depression generation, the current study will examine low- and high-risk (by virtue of a maternal history of MDD) healthy female adolescents aged 12-14 years to determine whether putative mechanisms underlying reward processing prospectively predict depression. Participants completed a probabilistic reward task (Pizzagalli et al., 2005) to examine behavioral differences in reward responsiveness. Participants also completed a monetary reward task while fMRI data were collected to examine neurobiological activation following wins and losses. Following completion of the baseline behavioral and neuroimaging assessments, follow-up assessments of depressive symptoms were completed every 3 months for 2 years, though follow-up data is not covered in this thesis. We hypothesize that (1) the high-risk youth will demonstrate an attenuated response bias to rewarding stimuli during the behavioral task. During the fMRI reward task, (2) adolescents in the high-risk group are expected to demonstrate blunted striatal activation to rewarding feedback, which has emerged as a robust correlate of depression. Overall, better understanding of the putative mechanisms will improve identification, prevention, and treatment of depression in adolescence. This thesis draws data from an ongoing study in the Child and Adolescent Mood Disorders Laboratory at McLean Hospital (described in Auerbach et al., 2015). The larger study includes several behavioral, neural, and genetic components in order to examine vulnerabilities that precede depression onset in female adolescents.

Methods

Participants

Healthy female adolescents (N = 33) between the ages of 12 and 14 were recruited from the greater Boston area through flyers, Internet advertisements, and postcards targeting specific demographics. The study included healthy low-risk (LR; n = 24) and high-risk (HR; n = 9) female adolescents, and certain youth were high-risk by virtue of a maternal history of MDD. Inclusion criteria for the adolescents included: female, between 12-14 years of age, English fluency, and right-handedness. Exclusion criteria included: history of any Axis I disorder, use of psychotropic medication, presence of medical or neurological illness (e.g. head injury, loss of consciousness greater than 5 minutes, seizures), and any contraindication for MRI (e.g., metal implants, history of seizures, certain transdermal patches). Inclusion criteria for high-risk youth also included a current or past maternal history of maternal MDD. Groups (LR = 24, HR = 9) did not differ in terms of age ($t(31) = 0.374$, $p = 0.711$), race (χ^2 (2, 33) = 0.836, $p = 0.658$), or family income (χ^2 (2, 33) = 5.182, $p = 0.268$).

Procedure

Approval for this study protocol was obtained through the McLean Institutional Review Board. Prior to data collection, female adolescents provided assent and mothers signed consent forms for both their own participation and that of their daughter. The study included a 2-day baseline assessment. During Day 1, adolescents completed a diagnostic interview assessing current and past psychopathology and self-report instruments regarding current symptoms (e.g., depressive, anxious). Additionally, adolescents completed a performance-based computer task, the Probabilistic Reward Task (PRT), which probed initial reward responsiveness. Similar to the adolescents, mothers were administered a diagnostic interview to assess lifetime history of mental illness. Additionally, they completed self-report measures of their own symptoms. On Day 2 of the baseline assessment, which occurred 1-2 weeks later, adolescents completed a

gambling task, the Doors Task, while fMRI data were collected. For their participation, adolescents were remunerated $80, and mothers received $20.

Adolescent Instruments

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1996). The K-SADS-PL is a semi-structured diagnostic interview that assesses the presence of current and past psychopathology in children and adolescents according to DSM-IV criteria (APA, 2000). The K-SADS is a reliable and valid measure of Axis I disorders (Kaufman et al., 1997), particularly as this relates to diagnosing MDD (Chambers et al., 1985). Graduate students and BA-level research assistants administered clinical interviews after receiving 40 hours of training. All interviews were digitally recorded, and the principal investigator (RPA) randomly selected 25% of the interviews to assess inter-rater reliability. The Cohen's kappa coefficients were excellent ($\kappa = 1.00$).

Mood and Feelings Questionnaire (MAFQ; Angold & Costello, 1987). The MAFQ is a 30-item self-report instrument that assesses current depressive symptoms. Item responses are scored from 0 to 2 (0=*never true*; 1=*sometimes true*; 2=*always true*), and greater scores indicate higher levels of depressive symptoms over the preceding 2-week period. A score of 12 or higher indicates individuals at risk for depression. Exemplar items include, "I didn't enjoy anything at all" and "I was very restless." Past research has shown that the MAFQ has moderate to high criterion validity in distinguishing non-depressed from depressed youth experiencing a major depressive episode (Daviss et al., 2006). It also has acceptable reliability in detecting major depression in children (ages 10-19; Wood et al., 1995). The Cronbach's alpha for the MAFQ ranged from .81 to .94, indicating good to excellent internal consistency.

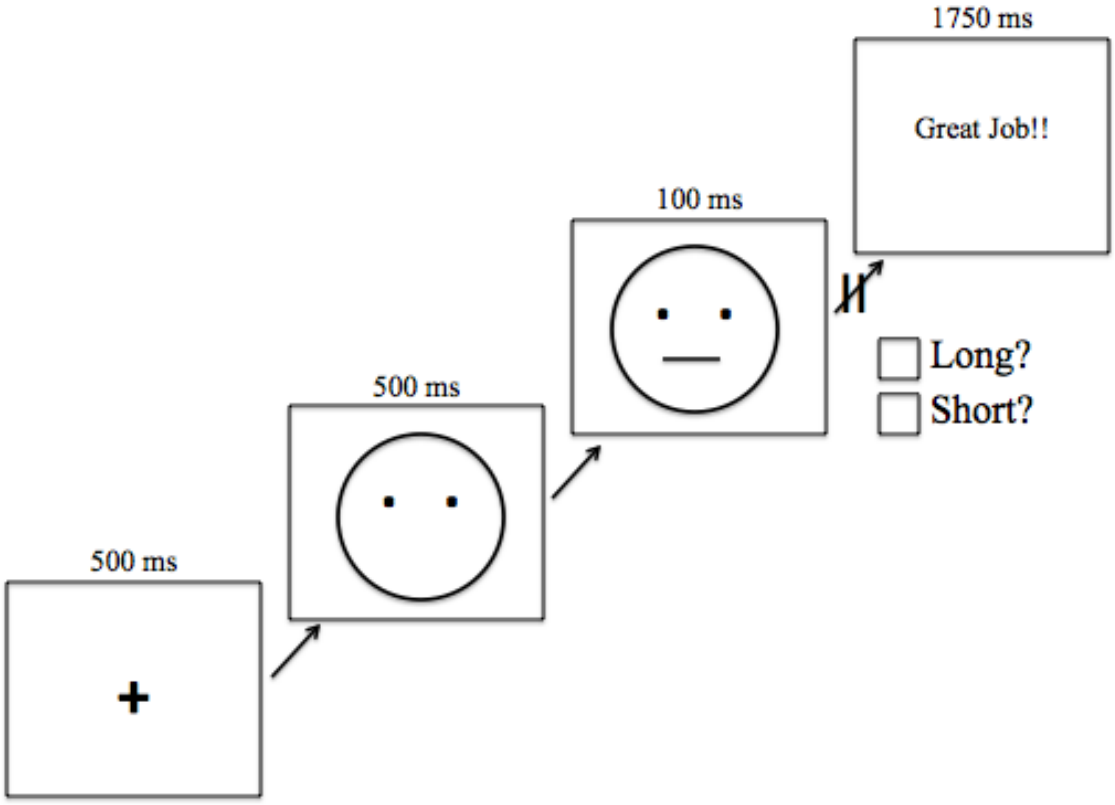
Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). The SHAPS is a 14-item self-report measure of hedonic capacity, and participants are asked to rate their level of pleasure when doing certain activities. For each item, participants indicate whether they *Strongly Agree, Agree, Disagree,* or *Strongly Disagree* with the statement. For scoring, both *Disagree* or *Strongly Disagree* result in a score of 1 while both *Agree* or *Strongly Agree* result in a score of 0 for the item. Total scores range from 0 to 14, and higher scores indicate greater anhedonia. Items from the SHAPS include, "I would enjoy being with my family or close friends" and "I would be able to enjoy my favorite meal." Past research has shown that the SHAPS demonstrates satisfactory validity and reliability (Snaith et al., 1995). In this study, the Cronbach's alpha was .86, indicating good internal consistency.

Multidimensional Anxiety Scale for Children (MASC; March, 1997). The MASC is a 39-item self-report measure of anxiety symptoms. In the current study, we utilized the social anxiety and harm avoidance subscales. Answers are given using a Likert scale from 0 (*Never true about me*) to 3 (*Always true about me*), and higher scores reflect greater levels of anxiety symptoms. Examples of items include, "I feel tense or uptight" and "I'm afraid that other kids will make fun of me." Past research demonstrated that the MASC is a valid and reliable measure of anxiety symptoms among children and adolescents 8 to 17 years (March et al., 1997). The Cronbach's alpha ranged from .73 to .82, indicating fair to good internal consistency.

Probabilistic Reward Task (PRT; Pizzagalli et al., 2005). The PRT is a computer-based task that examines reward responsiveness (see Figure 1). When completing the task, participants are instructed to distinguish between two cartoon face stimuli (short (11.5 cm) or long (13.0 cm) mouth). The task consists of 200 trials divided into 2 blocks separated by a 30 second break between each block. Each trial starts with a fixation cross (+) displayed for 500 milliseconds

(ms). After the fixation cross, a mouth-less cartoon face is presented for 500 ms, and then either a short or long mouth is presented in the face for 100 ms. The mouth is then removed and the mouth-less cartoon face remains until participants indicate whether a short or long mouth was presented by pressing either the "c" or "m" keys (counterbalanced across participants). Each block contains equal presentations of short and long mouths in a pseudorandomized sequence.

Figure 1. Probabilistic reward task schema



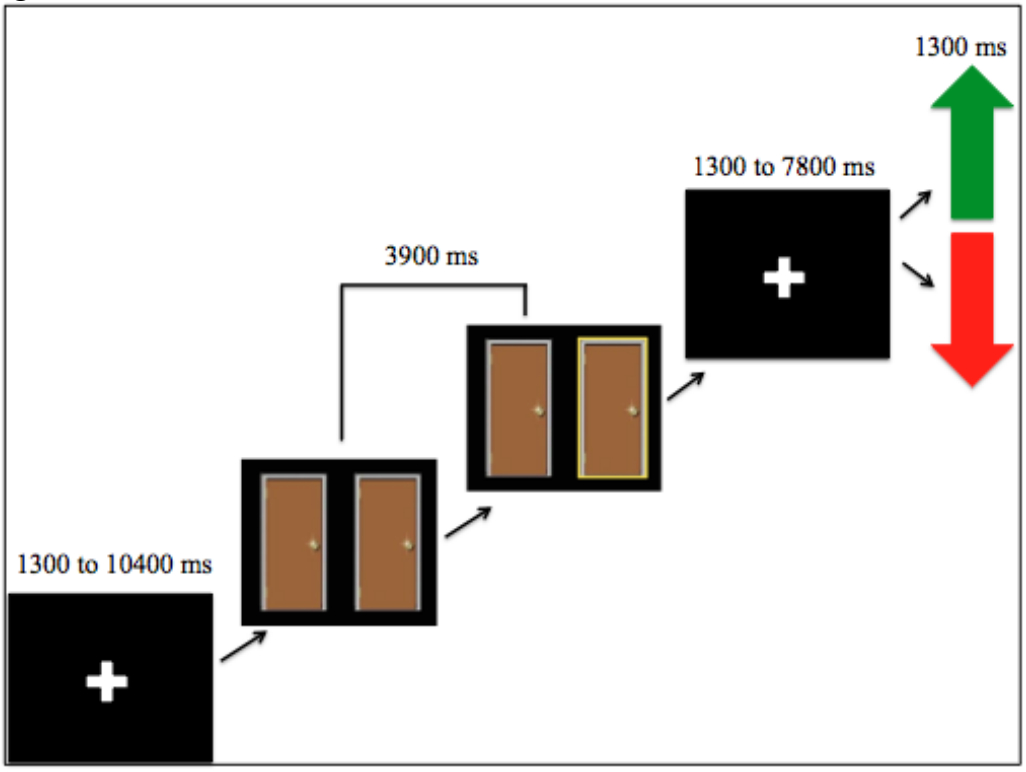
Note. Schema shows design of PRT trials with either a short or long mouth displayed on the face for 100 ms following the mouth-less presentation of the face for 500 ms. Inter-trial intervals (ITIs) included a fixation cross presented for 500 ms. Rewarding feedback was presented for 1750 ms, though not every trial included feedback.

Participants receive asymmetrical reinforcement for correct trials to produce a response bias toward the more frequently reinforced (rich) stimulus as opposed to the less frequently reinforced (lean) stimulus (McCarthy, 1991; Tripp & Alsop, 1999). Correctly identified rich trials were rewarded three times more often than correctly identified lean trials. Participants were informed that they would not receive feedback for all correct responses, and only 40 correct trials

(30 rich, 10 lean) were rewarded in each block of 100 trials. Those trials that did include feedback included "Great Job!" feedback screen presented for 1750 ms. Signal detection theory was utilized to calculate response bias (RB) – one's ability to moderate behavior as a result of differential reinforcement – was used as a measurement of reward responsiveness. Additionally, measures of reaction time (RT), accuracy, and discriminability (ability to differentiate between long and short mouths) also were computed. Past research has found that reduced response bias is associated with higher levels of anhedonia and depressive symptoms (Pizzagalli et al., 2005), and it is believed that the task is an objective measurement of hedonic capacity.

Doors Task (DT; Carlson et al., 2011). In this study, participants complete the DT while fMRI data were collected. The DT is a monetary reward task designed to assess neural responses to reward and loss (see Figure 2). The task includes 48 trials and lasts approximately 10 minutes. OptSeq2 was utilized to determine inter-stimulus interval (ISI) and inter-trial intervals (ITI) that optimize the hemodynamic response. Participants view two doors side by side for 3900 ms, and they are prompted to choose one door that contains a prize. If they fail to do so, a door will be randomly chosen for them. Based on the door selected, there is an opportunity to win (+50¢,) or lose (-25¢,) money on each trial. After their selection, the ISI fixation cross is presented from 1300 to 7800 ms, The ISI is followed by feedback on whether the participant won or lost money. Feedback for a correct answer is indicated by green up arrow (1300 ms), or an incorrect answer is indicated by a red down arrow (1300 ms). After receiving the feedback, the ITI fixation cross was presented (1300 to 10400 ms). The number of wins and losses is predetermined and presented in a pseudorandom order. Each participant earned a set amount ($12.00).

Figure 2. Doors task schema



Note. Doors were presented for 3900 ms, during which time participants chose which door they thought contained the prize. Following a varying inter-stimulus interval (ISI), reward or loss feedback was presented for 1300 ms. Inter-trial intervals (ITIs) varied from 1300 to 10400 ms.

Parent Instruments

Structured Clinical Interview for DSM (SCID; First et al., 2002). The SCID is a semi-structured clinical interview that assesses the presence of Axis I psychopathology among adults (APA, 2000). Previous research has indicated excellent inter-rater reliability (Ventura, Liberman, Green, Shaner, & Mintz, 1998). Postdoctoral fellows and graduate students administered clinical interviews after receiving 40 hours of training including didactics and mock interviews. All interviews were digitally recorded, and the principal investigator (RPA) randomly selected 25% of the interviews to assess inter-rater reliability in determining a history of depression. The Cohen's kappa coefficients were excellent ($\kappa = 1.00$).

Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II is a 21-item measure of severity of depressive symptoms over the past 2 weeks. Each item contains four

statements (scored from 0-3), and higher scores reflect more severe depressive symptoms. Cutoffs for the BDI-II are: (a) minimal depression = 13 and below, (b) mild depression = 14-19, (c) moderate depression = 20 and 28, and (d) severe depression = 29-63. Measure items include, "I feel guilty all of the time." Past research has shown high internal consistency (Beck et al., 1996), and in the current study, the Cronbach's alpha was .85, suggesting good internal consistency.

MRI Acquisition

Data acquisition during the Doors Task required approximately 12 minutes, and participants used a button box to select the left or right door on each trial. Imaging data were acquired at the McLean Imaging Center using a 3T Siemens Trim Trio system using a 32-channel brain array coil. During functional scans, gradient echo T2*-weighted echo-planar images were acquired using a multi-band sequence with TR/TE: 1300/32ms; FOV 212mm; matrix: 64X64; 72slices; in-plane resolution: 2mm; voxels 2x2x2mm. Head movement was minimized using a head cushion, and data from participants who moved more than 3mm during the scan were excluded from analyses. SPM8 was used for all pre-processing, which included motion/slice-time correction, removal of slow linear trends, intensity normalization, and spatial smoothing (6-mm).

Data Analytic Overview

Probabilistic Reward Task. Participants' baseline performance on the PRT was analyzed based primarily on response bias (RB). A higher RB indicates a greater ability to correctly identify the rich stimulus and greater preference for selecting the response associated with the rich stimulus. The RB was calculated using the following formula:

$$Log\ b = 1/2*\log*[(\text{RICH correct}*\text{LEANincorrect})/(\text{RICHincorrect}*\text{LEANcorrect})]$$

The primary analyses focused on RB, and a mixed analysis of variance (ANOVA) was conducted with *Group* (LR, HR) and *Block* (1, 2) as factors. A Greenhouse-Geisser correction was used to provide a more conservative test of hypotheses. Secondary analyses probed differences in RT, discriminability, and accuracy.

Doors Task. Structural data was collected for each participant prior to fMRI acquisition during the Doors Task. After preprocessing, analyses were conducted using a general linear model. Between-group whole-brain analyses with reward versus loss contrasts compared blood oxygen level dependent (BOLD) signals. After conducting whole brain analyses, secondary region of interest (ROI) analyses were conducted to examine differences in activation within mesolimbic regions, particularly, the nucleus accumbens, caudate, and putamen.

Results

Descriptive Statistics

Mean scores and standard deviations (SD) for baseline measures are reported in Table 1. Independent samples t-tests compared symptoms in the LR and HR groups. Importantly, there was no significant difference in depressive symptoms, $t(8.76) = -1.80$, $p = 0.106$; anhedonia symptoms, $t(9.01) = -1.23$, $p = 0.251$; harm avoidance anxiety symptoms, $t(10.40) = -0.09$, $p = 0.927$; and social anxiety symptoms, $t(19.40) = -0.85$, $p = 0.404$. As expected, there was a significant difference in maternal symptoms, with HR mothers reporting greater depressive symptom severity relative to LR mothers, $t(31) = 3.90$, $p = 0.021$.

Probabilistic Reward Task

Prior to analyses, outliers (LR = 3) were removed, as their performance on the task did not meet criteria to be usable data. Namely, participants were considered outliers if the number of valid trials was <80% for each block, the reward ratio of rich:lean was less than 3:1, the

number of outliers per block exceeded 20, and the accuracy was <55%. Consistent with prior studies, preliminary analyses tested group differences across discriminability, accuracy, and reaction time. Results indicated that there were group differences in discriminability in Block 1

	Low-Risk		High-Risk	
Measure	*Mean*	*SD*	*Mean*	*SD*
Age	13.13	0.850	13.00	0.87
Depressive Symptoms	4.08	4.63	12.11	13.08
Harm Avoidance Anxiety	17.74	2.99	17.88	3.68
Social Anxiety	8.00	4.05	9.11	3.02
Anhedonia Symptoms	0.21	0.66	0.89	1.62
Parental Depressive Symptoms	2.67	3.47	10.44	8.13

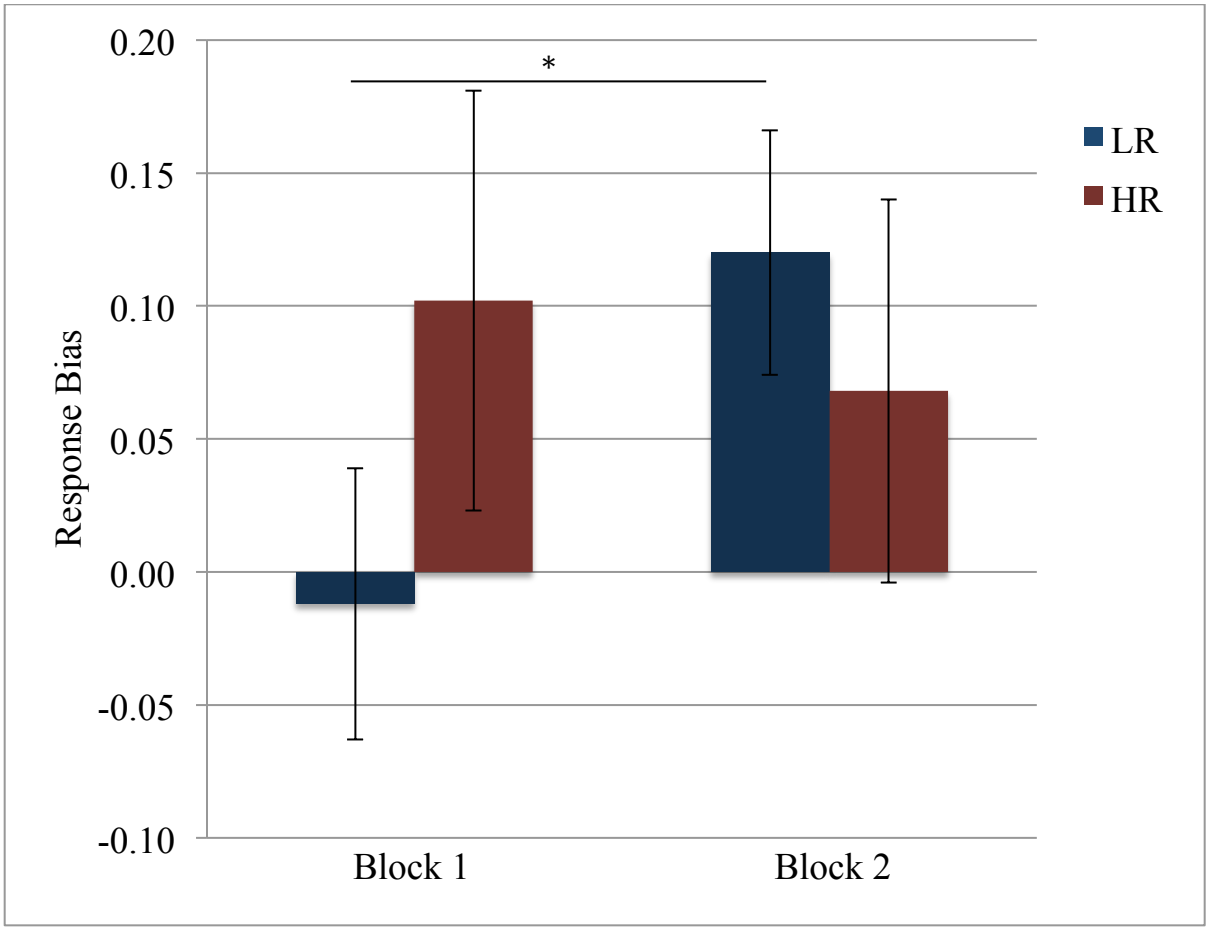
such that the LR group demonstrated higher discriminability (trend: $p = 0.06$). There were no other significant between-group effects (Ps > 0.12). Therefore, Block 1 discriminability was included as a covariate when examining response bias differences.

Table 1. Mean and standard deviations for baseline instruments in low- and high-risk adolescents

Note. $^{*}p < .05$; Depressive symptoms = MAFQ; Harm avoidance anxiety = MASC Harm Avoidance subscale; Social anxiety = MASC Social Anxiety subscale; Anhedonia symptoms = SHAPS; Parental depressive symptoms = BDI-II.

Response Bias. A *Group* (LR, HR) x *Block* (1, 2) ANCOVA was conducted to examine differences in response bias (RB). There was a significant *Group* x *Block* interaction effect on RB, $F(1,27) = 4.26$, $p = 0.049$; $\eta^2 = .14$. When probing the between-group simple effects, the LR group exhibited an increase in RB over blocks ($p = 0.004$), but there was no significant effect for the HR participants ($p = 0.604$) (see Figure 3). The interaction was not qualified by a main effect for *Group*, $F(1,27) = .14$, $p = 0.711$; $\eta^2 = 0.01$.

Figure 3. Changes in response bias over time



Note. $^{*}p < .05$; The LR (n = 29) group showed a significant increase in response bias from Block 1 to Block 2 (p = 0.004), while the HR (n = 9) group exhibited a non-significant decrease in response bias (p = 0.604).

Discriminability. A *Group* x *Block* ANOVA was conducted to examine differences in discriminability. There was no *Group* x *Block* interaction, $F(1,28) = 2.54$, $p = 0.122$; $\eta^2 = 0.08$, and additionally, there was no main effect for *Group*, $F(1,28) = 1.62$, $p = 0.213$; $\eta^2 = 0.06$.

Accuracy. A *Group* x *Block* ANOVA revealed no significant interaction effect for accuracy, $F(1,28) = 3.24$, $p = 0.083$; $\eta^2 = 0.10$, and there was no main effect of *Group*, $F(1, 28) = 2.06$, $p = 0.163$; $\eta^2 = 0.07$.

Reaction Time. A *Group* x *Block* ANOVA was conducted, which showed no significant interaction effect on RT, $F(1, 28) = 2.92$, $p = 0.098$; $\eta^2 = 0.09$. There was no main effect of *Group*, $F(1, 28) = 0.06$, $p = 0.811$; $\eta^2 = 0.002$.

Doors Task

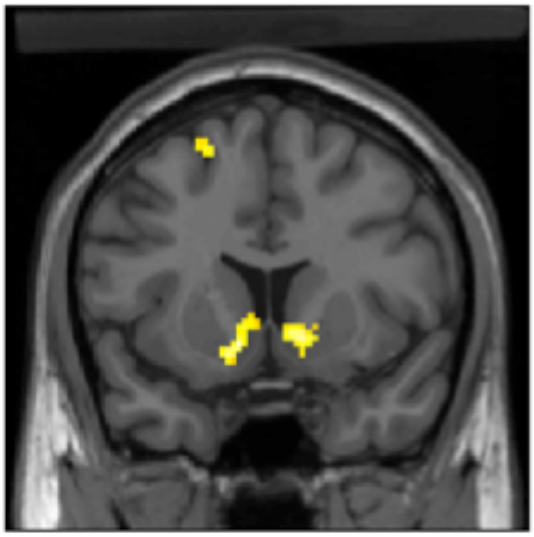
Prior to analyses, the task was examined to ensure that it was probing the hypothesized brain regions associated with reward processing. One LR participant was excluded as an outlier from analyses of the left NAcc because the activation was more than two SDs below the mean activation level, which may be an indicator of task noncompliance.

Whole Brain Analyses. Prior to conducting between-group comparisons, we examined whether there was differential activation to wins versus losses. Comparisons across participants showed greater bilateral activation in the nucleus accumbens (NAcc) for wins versus losses (right NAcc: $t(29) = 2.28$, $p = 0.030$; left NAcc: $t(28) = 3.01$, $p = 0.005$; see Figure 4). In contrast to our hypothesis, no between-group differences emerged. Between groups comparisons in the right NAcc revealed no difference in activation between LR and HR for wins ($t(29) = 0.09$, $p = 0.930$) and losses ($t(29) = 0.05$, $p = 0.962$). Similar comparisons of the left NAcc revealed no difference in activation between LR and HR for wins ($t(29) = 0.46$, $p = 0.650$) and losses ($t(28) = 0.04$, $p = 0.967$). However, when probing activation within the LR and HR youth separately, interesting findings emerged. In the NAcc, the LR showed greater activation for wins versus losses in the right ($t(20) = 2.35$, $p = 0.029$) and left ($t(19) = 2.96$, $p = 0.008$) NAcc. In contrast, the HR showed no difference in activation for wins versus losses in the right ($t(8) = 0.88$, $p = 0.305$) and left ($t(8) = 1.10$, $p = 0.305$; see Figure 5) NAcc. Additional ROI analyses were conducted in reward-related regions.

ROI Analyses. Win-loss contrasts probed activation in mesolimbic regions implicated in reward processing, including the putamen, caudate, and NAcc. Eigen values were extracted from ROIs that were determined anatomically using Wake Forest University School of

Medicine's PickAtlas maps (v3.0.5; Maldjian, Laurienti, Burdette, & Kraft, 2003). When extracting values from these regions, no within- or between-group differences emerged.

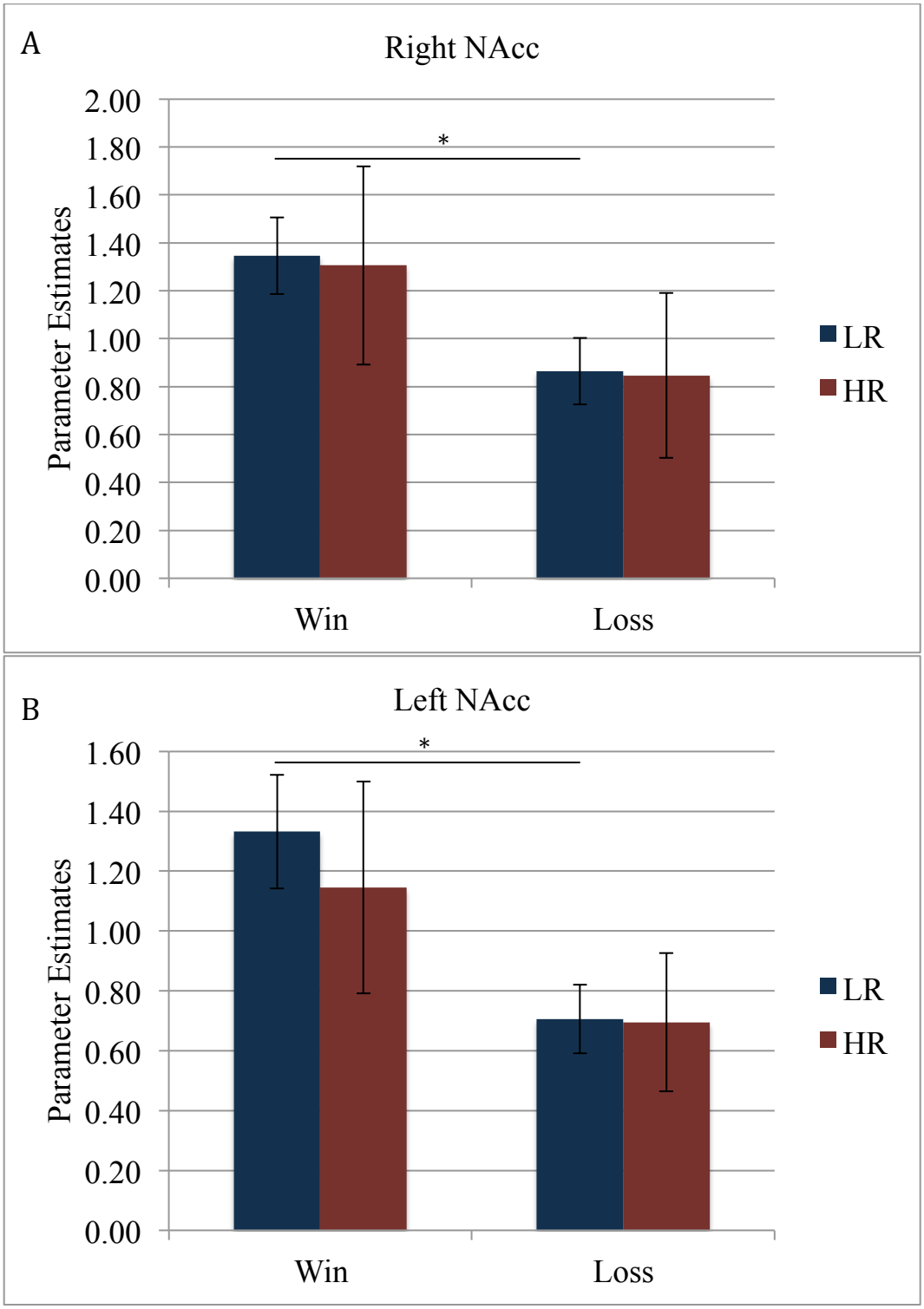
Figure 4. Bilateral activation in the nucleus accumbens (NAcc) across participants



Note. Win-Loss contrast across participants ($p < 0.001$, uncorrected); (A) Right NAcc: x=12, y=10, z=-6);z=4.38; cluster = 154; (B) Left NAcc: x=-10, y=10, z=-8; z=4.46; cluster size = 128.

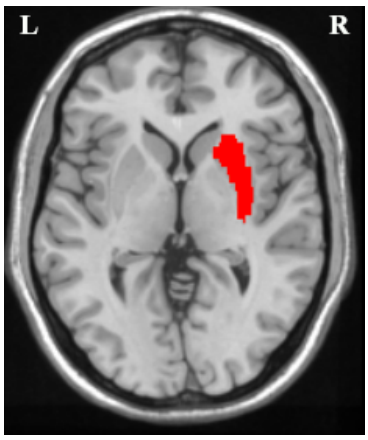
Correlation. A Pearson's correlation examined the association between adolescent depressive symptoms (MAFQ) and activation within the ROI for the right putamen (win-loss contrast; see putamen ROI Figure 6). A significant negative correlation was found across groups ($r = -0.439$, $p = 0.017$; see Figure 7), suggesting that a smaller difference in activation to wins versus losses was associated with greater depressive symptom severity at baseline.

Figure 5. Activation in right and left nucleus accumbens (NAcc) in response to wins and losses



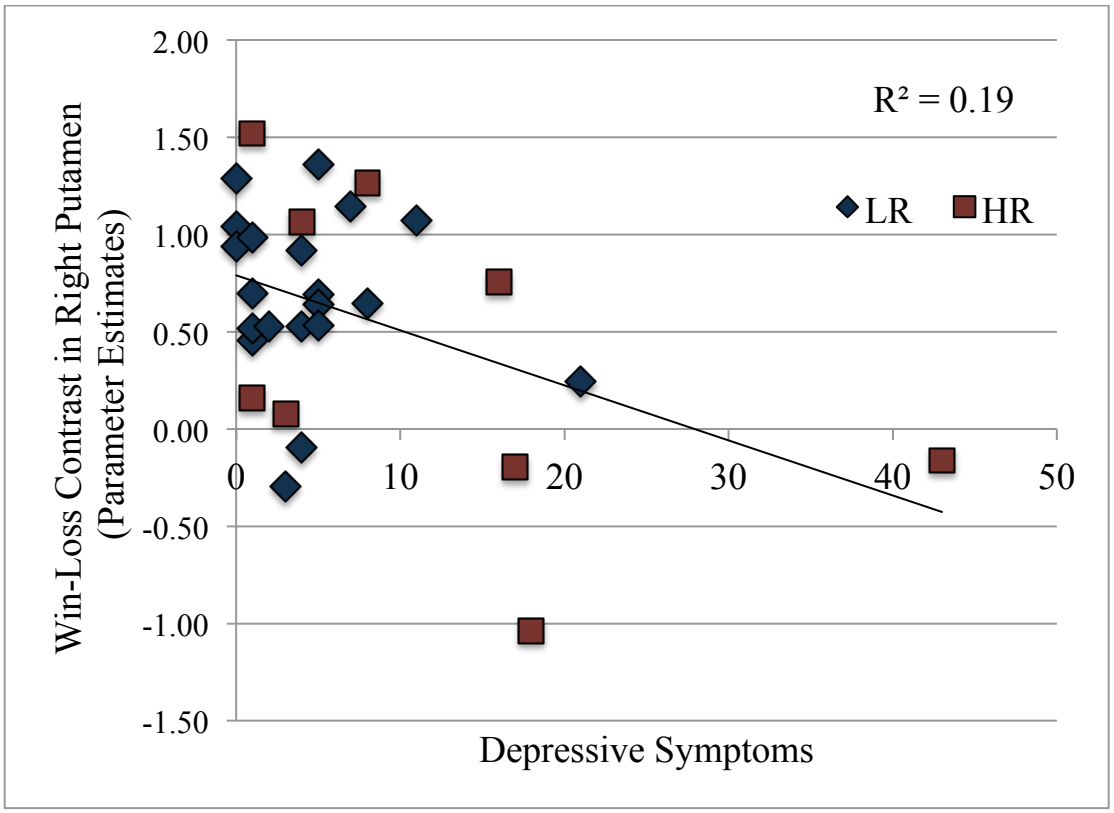
Note. * $p < 0.05$; Between-group analyses examined differences in (A) the right NAcc showed a significant difference in activation between wins and losses for the LR ($t(29) = 2.35$, $p = 0.029$) but not HR ($t(8) = 0.88$, $p = 0.407$) and (B) the left NAcc revealed similar differences in the LR ($t(28) = 2.96$, $p = 0.008$). but not HR ($t(8) = 1.10$, $p = 0.305$).

Figure 6. Right putamen region-of-interest (ROI)



Note. Prior studies have shown activation in the putamen during reward processing.

Figure 7. Correlation between right putamen activation (win-loss contrast) and depressive symptoms



Note. A negative correlation between depressive symptoms and right putamen activation (r = -0.439, n = 29, p = 0.017).

Discussion

The main goal of this thesis was to identify behavioral indicators and biomarkers associated with reward processing that may contribute to depression onset (Steele et al., 2007; Pizzagalli et al., 2008). Consistent with our hypothesis, we found a significant difference in response bias between LR and HR groups, such that the HR group failed to demonstrate an increase in response bias over time. However, contrary to our hypothesis, no between-group differences emerged when examining differential neural activation following wins and losses. Several findings warrant additional discussion.

Initial Reward Responsiveness

Despite exhibiting no differences in depressive and anxious symptoms, LR youth exhibited an increased response bias over time whereas the HR adolescents showed a blunted response bias. This finding is interesting, as it may demonstrate that HR youth possess *abnormal* reward processing prior to the onset of depressive symptoms. Past research has consistently shown that depressed individuals demonstrate a blunted response bias compared to healthy controls, (Pizzagalli et al., 2008) and identifying the same mechanisms in healthy, high-risk individuals may indicate an underlying risk factor for depression. This is the first study to examine reward responsiveness within a high-risk design, and moving forward, it will be important to determine whether blunted reward responsiveness prospectively predicts depressive symptoms. These findings could, potentially, be used in the early identification of depression. Moreover, if this reward responsiveness emerges as a promising phenotype, it also may have important implications for timing and type of treatment.

Differential Neural Activation to Wins vs. Losses

In contrast to our hypothesis, we found no between-group differences in neural activation following wins or losses in reward-related regions (i.e., caudate, putamen, NAcc). Though no group differences emerged, across participants, there was greater bilateral activation in the NAcc when contrasting wins versus losses, though this difference was only significant in the LR group. We also found a significant negative correlation across participants between depressive symptoms and neural activation (i.e., contrasting wins vs. losses) in the right putamen. Sharp and colleagues (2014) demonstrated reduced response to wins in the right ventral striatum in both currently depressed female adolescents and female adolescents with a maternal history of depression. In a similar study, high-risk female adolescents demonstrated greater dorsal anterior cingulate activation in response to losses compared to low-risk counterparts (Gotlib et al., 2010). Both studies showed abnormal functioning of reward response pathways in girls with a familial history of depression that precedes the onset of depressive symptoms. Our inability to detect between-group differences may be due, in part, to a small sample size. As data collection continues, we may see differences emerge that mirror those found in previous studies.

Another possible reason for our inconclusive results is that the current study uses a monetary reward task. Other studies of high-risk adolescents used card guessing and probability tasks to probe reward responsivity (Sharp et al., 2014, Forbes et al., 2009). Gotlib and colleagues (2010) adapted a monetary incentive delay task for their study of high-risk adolescents, but it was modified to use points as opposed to actual monetary reward. It is possible that monetary rewards may not be as salient for adolescents as compared to other forms of reward. Social reward tasks related to peer acceptance and rejection may be more relevant to adolescents, and future studies may benefit from investigating reward responsivity with tasks that probe social

connectedness and support. The larger study, that this thesis draws data from, examines such social interaction in a Chatroom task (Guyer et al., 2012). As peer interactions are increasingly important during adolescence, this task may evoke a differential response to social acceptance and rejection between groups.

When examining factors across participants, we found a correlation between depressive symptoms and activation in the right putamen. This is expected, considering not all HR participants are expected to develop MDD and some LR participants may develop MDD without having a family history of the disorder (scores ranged from 0 to 43 across participants). It is important to look at this relationship across participants because familial risk is not the only factor that contributes to depression vulnerability. Despite a low sample size, this effect is promising and as the study continues, it may be useful in predicting later onset of depression. This may be a potential target for early identification of depression in adolescence and can inform intervention targets and treatment efforts.

Limitations and Future Directions

There are a number of limitations worth noting in this study. First, the sample size was relatively small, especially in the HR group. This limits generalizability and our ability to detect group differences. As the ongoing study progresses, revisiting these hypotheses with a larger sample is essential. Second, although there is a high rate of intergenerational transmission of MDD from mother to daughter, the study is limited by inclusion of mothers and the exclusion of fathers. Future research would benefit from examining the depression history in both biological parents. Last, this study included girls but not boys in light of increased risk among female adolescents to experience MDD during adolescence (Hankin et al., 2007). Nonetheless, it will be

important to examine whether putative mechanisms implicated in MDD onset among female adolescents are also implicated in depressive disorders in male adolescents.

Clinical Implications

Depression in adolescents remains an enormous public health concern, and this study provides an important examination of behavioral indicators and biomarkers that may underlie risk for depression in adolescents. Based on our findings, risk markers related to reward processing exist in adolescents with a family history of depression that differ from individuals without a family history of the disorder. Moving forward, we hope to tease apart differential behavioral and neural components that may predict later onset of depressive symptoms. Increased understanding of risk factors for adolescent depression, ultimately, may improve our early identification of high-risk individuals, which allows earlier prevention and potentially more effective treatment.

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