Depression Risk Predicts Blunted Neural Responses to Gains and Enhanced Responses to Losses in Healthy Children

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Objective: Maternal major depressive disorder (MDD) increases risk for MDD and predicts reduced reward responding in adolescent offspring. However, it is unclear whether alterations in neural response to reward can be detected in school-aged children at high risk before the typical increase in reward response observed in adolescence.
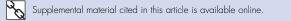
Method: To assess relationships between neural response to gain/loss feedback, MDD risk, and child depressive symptoms, 47 psychiatrically healthy 7- to 10-year-old children (16 at high risk given maternal MDD) completed questionnaires and a functional magnetic resonance imaging (fMRI) card-guessing game in which candy was gained and lost.

Results: High-risk children showed both blunted response to gain and greater deactivation/reduced activation to loss within the ventral striatum and anterior insula. Within the striatum, risk-group differences in response to loss feedback were significantly larger than for gain, with greater deactivation to loss predicting risk-group status above and beyond blunted gain activation. Anhedonia was related to reduced deactivation to loss (i.e., reduced sensitivity to loss), whereas negative mood was related to enhanced deactivation to loss (i.e., enhanced sensitivity to loss) in the ventral striatum.

Conclusion: High-risk children showed blunted ventral striatal activation to gain feedback, but ventral striatal deactivation to loss was a stronger predictor of MDD risk. Furthermore, relationships between response to loss and elevated depressive symptoms within the ventral striatum and cingulate differed depending on the type of depressive symptom. Together these results highlight the potentially important role of response to loss of reward in childhood risk for depression.

Key words: depression risk, reward, punishment, fMRI, children

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Identifying how risk factors for psychopathology manifest as functional deficits that predate/predict clinical symptom onset is critical for identifying targets for preventive intervention. To this end, a growing literature has begun to examine how risk factors for depression, such as a maternal history of major depressive disorder (MDD),[1] relate to neural responses to incentives, a domain altered in MDD.[2,3] However, this literature has largely focused on response to reward gain within adolescent groups. This leaves open several key questions: First, does maternally defined MDD risk relate to reward processing earlier in development, that is, before the normative adolescent rise in reward responsiveness? Second, does MDD risk also predict altered neural response to loss? Third, do specific depressive symptoms predict deficits in response to gain and loss feedback? These questions could have important treatment implications, given that mental health interventions may be more effective earlier in development.

Risk for MDD and Response to Reward

Adolescents with elevated MDD risk show reduced striatal activation to monetary rewards[4-6] and positive faces,[7] with reduced striatal response to reward predicting reduced experience of positive affect[5,8,9] and future increases in depressive symptoms.[10] Blunted response to rewards in high-risk adolescents has also been observed within other regions linked to affective processing and learning/behavioral responses to reward feedback,[11-13] such as the anterior insula (AI) and anterior cingulate cortex (ACC).[4,14,15] Together these lines of evidence suggest that adolescents who had never been depressed but were high-risk show blunted responses to multiple types of rewards within the extended reward/limbic system, similar to adults and adolescents with depression.[2,3,6,16]

Importantly, the reduced reward responsiveness associated with adolescent MDD risk occurs within a developmental context of normatively increasing reward responses. Given the now sizable cross-sectional[17] and longitudinal[18] literature documenting increasing striatal sensitivity to reward receipt across adolescence, an important developmental question remains regarding whether effects of MDD risk on reward response can be detected before this normative change. If blunted reward responsiveness is a trait characteristic of elevated MDD risk, then it should be observed during childhood. Alternatively, effects of MDD risk may interact with typical developmental processes; for example, individuals at high risk may fail to show the increasing response to reward during adolescence, with such effects being small or nonexistent in childhood. As no

functional magnetic resonance imaging (fMRI) studies to date have examined effects of maternal MDD on response to reward in school-aged children, investigating such questions is an important first step in characterizing the relationships between neural response to reward and risk states across development.

Risk for MDD and Response to Loss of Reward

Unlike the reward literature, the literature investigating neural responses to loss of reward is sparse and mixed. In adult MDD, some studies report blunted striatal and affective responses to negative stimuli/feedback,[19] whereas others report enhanced response within limbic regions, including the amygdala.[20,21] The only fMRI study investigating response to loss of reward feedback in adolescents with depression reported greater response to loss in healthy controls relative to adolescents with depression within the caudate and ACC.[22]

Adolescent MDD risk studies consistently report elevated responsivity to loss/negative stimuli, as high-risk groups show greater deactivation to monetary loss within the ventral striatum,[4] enhanced activation to aversive taste in the lateral orbitofrontal cortex (OFC),[14] and enhanced amygdala activation to negative faces.[7,15] The normative developmental literature, although small, consistently highlights elevated behavioral/neural response to loss/punishment in childhood/adolescence relative to adulthood, with children showing strong loss-avoidance behavior.[23-26] Thus, enhanced responsiveness to loss may be particularly characteristic of childhood MDD risk. As such, we would expect high-risk children to show greater ventral striatal deactivation and potentially greater amygdala activation to loss.

Role of Symptom Type and Severity

There is emerging behavioral work suggesting that specific types of depressive symptoms show differing associations with incentive and affective functioning. For example, in children, response to loss/negative stimuli is positively predicted by depressed/negative mood but is negatively predicted by anhedonia.[27] Furthermore, there is evidence for changes in the relative prevalence of specific depressive symptoms across development (e.g., prevalence of anhedonic symptoms increases in adolescence).[28] Thus, given the growing interest in relationships between specific symptom constructs and function,[29] it is also crucial to examine differential relationships of anhedonia versus negative mood symptoms, even at subclinical levels, with incentive responses.

Current Study

The goal of the current study was to investigate the effects of maternal MDD and child depressive symptomatology on neural responses to gain and loss of reward in healthy school-aged children. We hypothesized that healthy high-risk children would show both blunted responses to gain feedback (within the striatum, anterior insula, and anterior cingulate) and enhanced responses to loss feedback (within the striatum and amygdala). We also hypothesized that

group differences in response to loss would be larger than group differences in response to gain feedback, given the findings on normatively stronger responses to loss during this developmental period. Finally, we investigated whether levels of specific depressive symptoms, namely, anhedonia and depressed/negative mood, were related to different patterns of gain/loss responsiveness. Specifically, we hypothesized that elevated anhedonic symptoms would relate to blunted responding to both gain and loss, whereas elevated negative mood would relate to enhanced loss responses.

METHOD

Participants

A total of 130 mothers and their 7- to 10-year-old children were screened for inclusion/exclusion in a multi-session behavioral and neuroimaging study. Behavioral data regarding gain approach and loss avoidance from this study have been published previously.[27] Families were recruited from the St. Louis, MO metropolitan area via flyers/brochures distributed through schools and posted in the community as well as via the Research Participant Registry at Washington University School of Medicine. Mothers provided written informed consent, and children provided written assent. All study procedures were approved by the Washington University in St. Louis Institutional Review Board.

Maternal and child psychopathology was assessed via the Structured Clinical Interview for *DSM* Disorders (SCID)[30] and Kiddie-Structured Assessment for Affective Disorders–Present and Lifetime Version (KSADS),[31] respectively. Master's-level clinicians who were trained to reliability administered both measures. Demographic exclusion criteria for children included age beyond 7 to 10 years, menarche, prohibition of candy, gestational age less than 35 weeks, learning/major medical disorder, psychotropic medication (past or present), or prenatal exposure to alcohol/illegal drugs (maternal report). Children meeting diagnostic criteria for any disorder (past or present) based on combined maternal/child reports were excluded, as were children of mothers who met criteria for any disorder but not MDD, or both MDD and psychosis. Children of mothers who had no history of any psychiatric disorder were considered to be at low risk (LR) for depression; children of mothers who had experienced at least 1 depressive episode were considered to be at high risk (HR) for depression.

A total of 70 mother–child pairs (HR n = 26), only 1 child per mother, met all inclusion criteria and were invited to participate in a neuroimaging session. Of these children, 46 (HR n = 16) provided sufficient high-quality data (described in Supplement 1, available online) and are included in the current analyses. Of the high-risk mothers, 8 met criteria for MDD and an anxiety disorder, 3 met criteria for MDD and substance abuse/dependence, 2 met criteria for MDD, an anxiety disorder, and substance abuse/dependence, and the remaining 3 had no comorbid diagnoses. Four mothers had current diagnoses (all MDD). The majority of high-risk mothers experienced recurrent depressive episodes during the child's lifetime (n = 13 of 16); results were qualitatively similar when analyses were restricted to children of these mothers. Two high-risk mothers experienced episodes before the child's birth, and 1 high-risk mother experienced a single episode during the child's life. No high-risk mothers experienced only gestational or postpartum depressive episodes.

Although not the focus of the current study, paternal psychopathology was assessed via mother report using the Family Interview for Genetic Studies.[32] Rates of paternal diagnoses (i.e., MDD,