

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 rewards⁴⁻⁶ 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-sectional¹⁷ and longitudinal¹⁸ 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



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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,

anxiety disorders, or substance abuse/dependence) did not significantly differ between risk groups (all $p > .05$). Two high-risk fathers met criteria for MDD, 2 low-risk fathers met criteria for anxiety disorders, and 4 fathers (HR $n = 2$) met criteria for substance abuse/dependence. Results were qualitatively similar when excluding low-risk children of fathers with any disorder.

Symptom Measures

Children and mothers completed a variety of self-report measures regarding depressive symptomology, affective reactivity/regulation, and incentive sensitivity. Current analyses focus on dimensional measures of child depressive symptoms obtained via the Child Depression Inventory–Child report (CDIC).³³ Maternal report of child depressive, anxious, and attention-deficit/hyperactivity disorder (ADHD) symptoms were assessed via the Child Depression Inventory–Parent report (CDIP)³⁴ and Child Behavior Checklist (CBCL).³⁵ Age- and sex-adjusted t scores are reported and used in the current analyses with particular focus on the anhedonia and negative mood subscales from the CDIC (possible t score values are 33–100). The CDIC anhedonia subscale includes items assessing the experience of pleasure, loss of energy, sleep and appetite problems, and a sense of isolation.³⁶ The CDIC negative mood subscale includes items assessing feelings of sadness, crying, worry, and indecisiveness.³⁶ It should be noted that the anhedonic and negative mood subscales were strongly positively correlated ($r = 0.71$) in the current sample. Both subscales have shown adequate internal consistency in previous studies^{36,37} and are scored such that higher values reflect greater severity. *DSM*-oriented scales were used from the CBCL.

Materials and Tasks

Participants played a child-friendly card guessing game (Figure 1), modified from a well-validated adult version³⁸ and previously used in adults and children.^{23,39} Children guessed whether the number on a mystery card (represented by a “?”) was more or less than 5, after which candy was won for correct guesses, lost for incorrect guesses, or neither won nor lost if the card number was 5. Participants chose whether to play for Skittles or M&Ms and received a lump sum of candy at the conclusion of the experiment.

fMRI Data Processing and Analyses

Data Processing. The fMRI data were collected using the 3T Siemens Connectome scanner at Washington University in St. Louis with a 32-channel head coil using sequences developed for the Human Connectome Project (HCP).⁴⁰ Data were processed using the HCP minimal preprocessing pipeline.⁴¹ Previously validated corrections

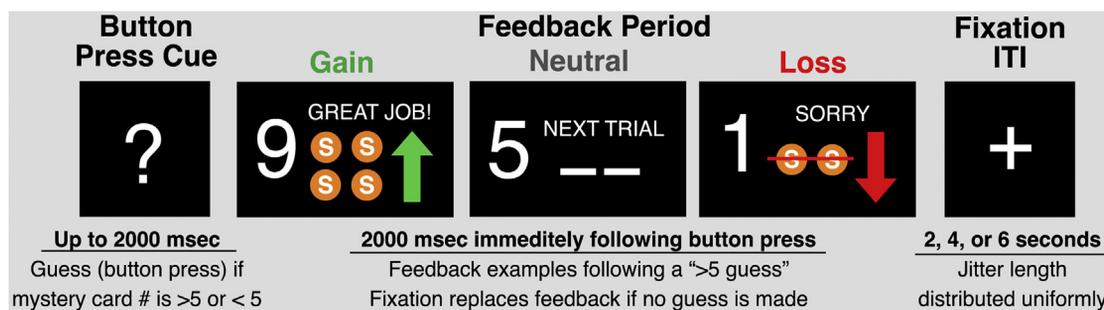
for head motion⁴² were applied; importantly, neither the relative displacement nor the number of frames remaining after scrubbing significantly differed between high-risk and low-risk groups for runs included in general linear models (GLMs; all $p > .10$). GLMs that assumed a canonical statistical parametric mapping (SPM) hemodynamic response were estimated using in-house Washington University software. Responses to each feedback type (gain, neutral, loss) were estimated relative to the intertrial interval (ITI) beginning with the onset of the mystery card cue; a separate anticipatory period could not be modeled, as feedback immediately followed response to the cue. Additional information regarding the task, fMRI acquisition, preprocessing steps, motion correction/data quality checks, and GLM creation procedures is provided in Supplement 1, available online.

Data Analyses Investigating MDD Risk. A voxelwise repeated-measures analysis of variance (ANOVA) was conducted to investigate how responses to candy incentive feedback differed based on MDD risk. Feedback type (gain, neutral, loss) was the repeated measure, and risk group (low, high) was a between-subjects factor. An anatomically defined mask covering regions previously implicated in the pathophysiology of MDD/risk, including the amygdala, hippocampus, striatum/basal ganglia, insula, and ACC, was applied to ANOVA output maps before thresholding (Figure S1, available online). Masked results were thresholded based on Monte Carlo simulations (3dClustSim, afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) at $z \geq 2.5$ and ≥ 62 contiguous voxels to achieve a false-positive rate of $p < .01$ across the mask. Maps were then partitioned such that peaks of activity were considered separate regions if they were more than 12 mm apart based on a peak-finding algorithm.⁴³ Percent signal change, averaged across a given region, was extracted for each feedback type for use in post hoc tests. Post hoc tests relevant to our hypotheses are considered significant and discussed when $p < .01$.

For regions showing a main effect of feedback type, planned post hoc analyses included 1-sample t tests for each feedback type (identifying activation or deactivation) and paired t tests comparing feedback types. For regions showing an interaction of feedback type and risk group, planned post hoc independent-samples t tests were conducted to evaluate whether responses to feedback types differed between risk groups (we focus on the difference between response to gain versus neutral and loss versus neutral in text). Exploratory post hoc regressions for these regions investigating the effects of comorbid maternal anxiety and substance abuse/dependence diagnosis on activation within the high-risk group, and whether risk-group effects remain after controlling for depressive/anxious symptoms, are presented in Supplement 1, available online.

Two additional planned sets of post hoc tests were conducted to evaluate the relative relationships between risk group and response

FIGURE 1 Card guessing game schematic. Note: Example of all feedback options following a “greater than 5” button press guess. ITI = intertrial interval.



to gain-neutral and loss-neutral feedback. First, the size of group differences for each feedback type was compared using the *cocor* package⁴⁴ implemented in R. The *cocor* package allows statistical comparison of dependent correlations (i.e., correlated correlations within the same sample). Thus, we compared point-biserial correlations (special case of Pearson's correlations used when 1 variable is dichotomous) between the following: risk group (0 = LR, 1 = HR) and gain-neutral, and risk group and loss-neutral. Second, post hoc binomial logistic regressions, with response to gain-neutral and loss-neutral predicting risk group, were conducted to evaluate whether response to gain and loss were unique or common predictors of MDD risk. Regressions were conducted only for regions where response to both gain-neutral and loss-neutral significantly differed based on risk group in the *t* tests described above.

Data Analyses Investigating Symptoms. A voxelwise linear regression was conducted to investigate unique effects of anhedonic symptoms and negative mood symptoms, while also controlling for risk group status, on response to gain versus loss feedback. Planned post hoc regressions with anhedonic symptoms, negative mood symptoms, and risk group predicting gain versus loss, gain, or loss responses were conducted for each region identified in the voxelwise analysis.

RESULTS

Sample Characteristics

Risk groups did not significantly differ in age, sex/ethnicity distributions, family income, candy liking (see Supplement 1, available online), negative mood symptoms, or ADHD symptoms (Table 1). High-risk children did report elevated general depressive (CDIC total score) and anhedonic symptoms, and mothers of high-risk children reported higher levels of general depressive (CDIP total score) and anxiety problems in their children.

Neuroimaging Results

Regions Showing a Main Effect of Feedback Type. A number of regions spanning the dorsal and ventral striatum, ACC, amygdala, and hippocampus/parahippocampal gyrus showed a main effect of feedback type (Table S1, Figure S2, available online). Children showed greater activation following gain than both neutral and loss feedback, particularly within the dorsal striatum. Children showed loss-related deactivation, particularly within the ventral striatum, amygdala, and hippocampus/parahippocampal gyrus.

Regions Showing a Main Effect of Risk Group. No regions showed a significant main effect of risk group.

Regions Showing an Interaction of Feedback Type and Risk Group. Several regions within the ventral striatum, anterior insula, and parahippocampal gyrus showed a feedback type by risk group interaction (Figure 2, Figure S3 [available online], Table 2). We focus on gain versus neutral and loss versus neutral contrasts in the text (other contrasts/feedback types; see Table S2, available online).

Blunted Responses to Gain Versus Neutral Feedback in High-Risk Children

High-risk children showed significantly reduced activation to gain (versus neutral) compared to low-risk children within the lateral ventral striatum, caudate body, and anterior insula (Table 2, Figure 2).

Enhanced Responses to Loss in High-Risk Children

Within all regions showing a feedback type-by-risk group interaction, including those discussed above, high-risk children showed significantly greater deactivation/reduced

TABLE 1 Clinical and Demographic Characteristics of Low- and High-Risk Groups

Characteristic	Low-Risk (n = 32)				High-Risk (n = 16)				<i>t</i> / χ^2
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Sex (% female)	53.12	—	—	—	50.00	—	—	—	0.04
Ethnicity (% white)	75.00	—	—	—	75.00	—	—	—	<0.01
Child age	9.28	1.00	7.44	10.80	9.05	1.14	7.37	10.83	0.70
Family income	14.66	6.27	4	21	13.31	8.01	1	21	0.64
CDIC total <i>t</i> score ^c	44.63	9.99	37	83	53.19	14.76	37	77	-2.09 ^b
CDIC Negative Mood subscale <i>t</i> score ^c	48.69	11.05	39	85	54.56	16.74	39	80	-1.27
CDIC Anhedonia subscale <i>t</i> score	46.00	9.98	37	83	52.69	10.47	37	75	-2.15 ^b
CDIP total <i>t</i> score ^c	40.31	3.79	34	48	48.06	7.52	40	67	-3.88 ^a
CBCL Anxiety Problems subscale <i>t</i> score ^c	51.28	2.95	50	63	55.75	6.51	50	70	-2.62 ^b
CBCL ADHD Problems subscale <i>t</i> score ^c	51.38	2.88	50	63	54.38	7.01	50	75	-1.64
Candy liking rating	4.60	0.55	3	5	4.69	0.45	4	5	-0.52
Age of maternal MDD onset (y)	—	—	—	—	19.44	7.04	11	39	—
Number of maternal lifetime MDD episodes	—	—	—	—	9.06	8.81	1	20	—

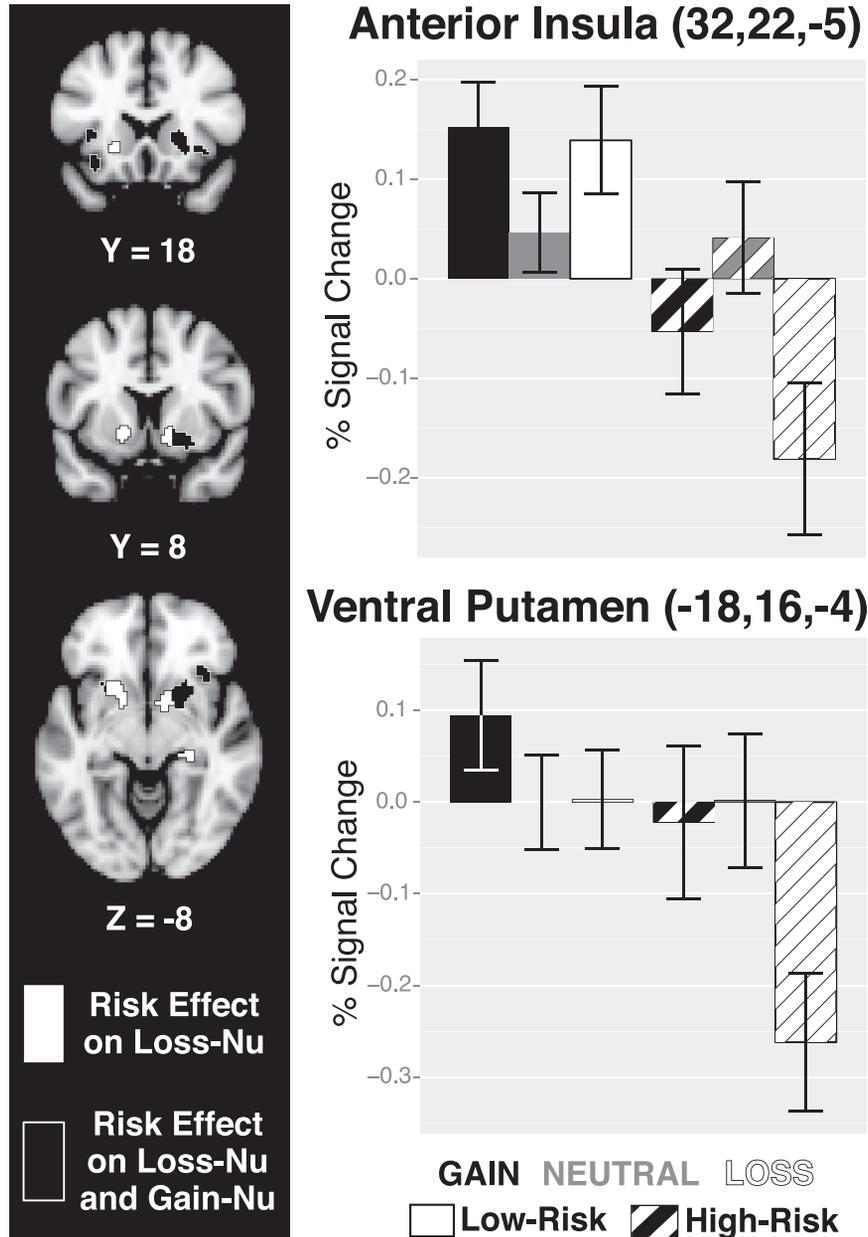
Note: Family income level coded in 21 increments of \$5,000 starting with 1 = \$1–\$5,000 and ending with 21 ≥ \$100,000. ADHD = attention-deficit/hyperactivity disorder; CBCL = Child Behavior Checklist; CDIC = Child Depression Inventory—Child Version; CDIP = Child Depression Inventory—Parent Version; Max = maximum; MDD = major depressive disorder; Min = minimum.

^a*p* < .01.

^b*p* < .05.

^cAssumption of equality of variances *p* < .05.

FIGURE 2 Regions showing a feedback-type × risk-group interaction. Note: Regions where response to loss-neutral (Nu) feedback significantly differed between risk groups are depicted in red. Regions where both response to loss-Nu feedback and response to gain-Nu feedback significantly differed between risk groups are depicted in purple. Magnitude estimates for responses to gain (blue), neutral (gray), and loss (red) feedback are depicted for the low-risk (solid) and high-risk (patterned) groups. Error bars reflect +/− one standard error of the mean.



activation to loss (versus neutral) than low-risk children (Table 2, Figure 2). Of note: within the high-risk group, neither maternal anxiety nor substance abuse/dependence diagnoses significantly predicted response to either gain-neutral or loss-neutral (Table S3, available online), and risk effects on gain/loss response were qualitatively similar when controlling for child depressive and anxious symptoms (Table S4, available online).

Relationships Between MDD Risk and Blood Oxygen Level-Dependent (BOLD) Response Are Larger for Loss Than for Gain

Risk group differences were significantly larger for responses to loss-neutral than for gain-neutral within the striatum (effects did not differ within the left ventral putamen) and parahippocampal gyrus (Table S5, available online). Effects of risk group on response to gain and loss did

TABLE 2 Post Hoc Independent-Samples *t* Tests Investigating the Interaction of Feedback Type and Risk Group

MNI Coordinates			Cluster Size	Region	Gain-Neutral			Loss-Neutral		
X	Y	Z			<i>t</i>	<i>d</i>	<i>p</i>	<i>t</i>	<i>d</i>	<i>p</i>
20	17	0	115	Caudate body	2.73	0.84	.009	5.15	1.59	<.001
-18	16	-4	112	Ventral putamen	1.54	0.47	.131	4.03^a	1.24	.001
24	7	-10	134	Ventral putamen	3.74	1.15	<.001	4.18	1.29	<.001
-16	-1	-14	57	Medial globus pallidus	2.16	0.66	.036	4.58	1.41	<.001
9	4	-11	74	Medial globus pallidus	2.43	0.75	.019	4.27	1.31	<.001
26	-25	-12	87	Parahipp gyrus BA28	0.22	0.07	.825	4.38	1.35	<.001
-34	21	6	92	Anterior insula BA13	4.11	1.26	<.001	2.85	0.88	.007
-33	16	-13	44	Anterior insula BA13	2.79	0.86	.008	2.89	0.89	.006
32	22	-5	93	Anterior insula BA13/47	3.08	0.95	<.001	4.41	1.36	<.001

Note: Boldface data reflect significant group differences where $p < .01$. See Table S3 (available online) for additional post hoc independent-samples *t* test results.
d = Cohen's *d*; Parahipp = Parahippocampal.
^aAssumption of equality of variances unmet.

not significantly differ in magnitude within the anterior insula.

Blunted Response to Gain and Enhanced Deactivation to Loss Are Independent Predictors of Risk Group

Within the striatum, gain-neutral response was no longer a significant predictor of risk group after adding loss-neutral response to the model (Table S6, available online). However, response to loss-neutral continued to significantly predict risk group even with gain-neutral response in the model. Patterns were mixed for anterior insula regions (Table S6, available online). The right ventral anterior insula showed the same pattern as striatal regions. However, in the left dorsal anterior insula, gain-neutral response predicted risk group with loss-neutral in the model, and loss-neutral was no longer a significant predictor with gain-neutral in the model.

Anhedonic and Negative Mood Symptoms as Possible Differential Predictors of Reward Response

Anhedonia, over and above negative mood and risk group, significantly negatively predicted response to gain-loss within the insula and anterior cingulate in the voxelwise regression (Table S7, available online), indicating reduced differentiation between responses to gain and loss feedback with increasing anhedonic symptoms. Negative mood, over and above anhedonia and risk group, significantly positively predicted response to gain-loss, within overlapping and extended insula and cingulate regions as well as within the ventral striatum/subgenual cingulate (Brodmann area [BA] 25) (Table S7, available online; Figure 3), indicating greater differentiation between responses to gain and loss feedback.

Interactions between risk group and each symptom measure were added to the post hoc regressions as an additional exploratory step to evaluate whether the relationship between symptoms and gain-loss response differed based on risk group. Risk group interactions with either symptom did not significantly predict gain-loss response for any region (Table S7, available online), indicating that high- and low-risk

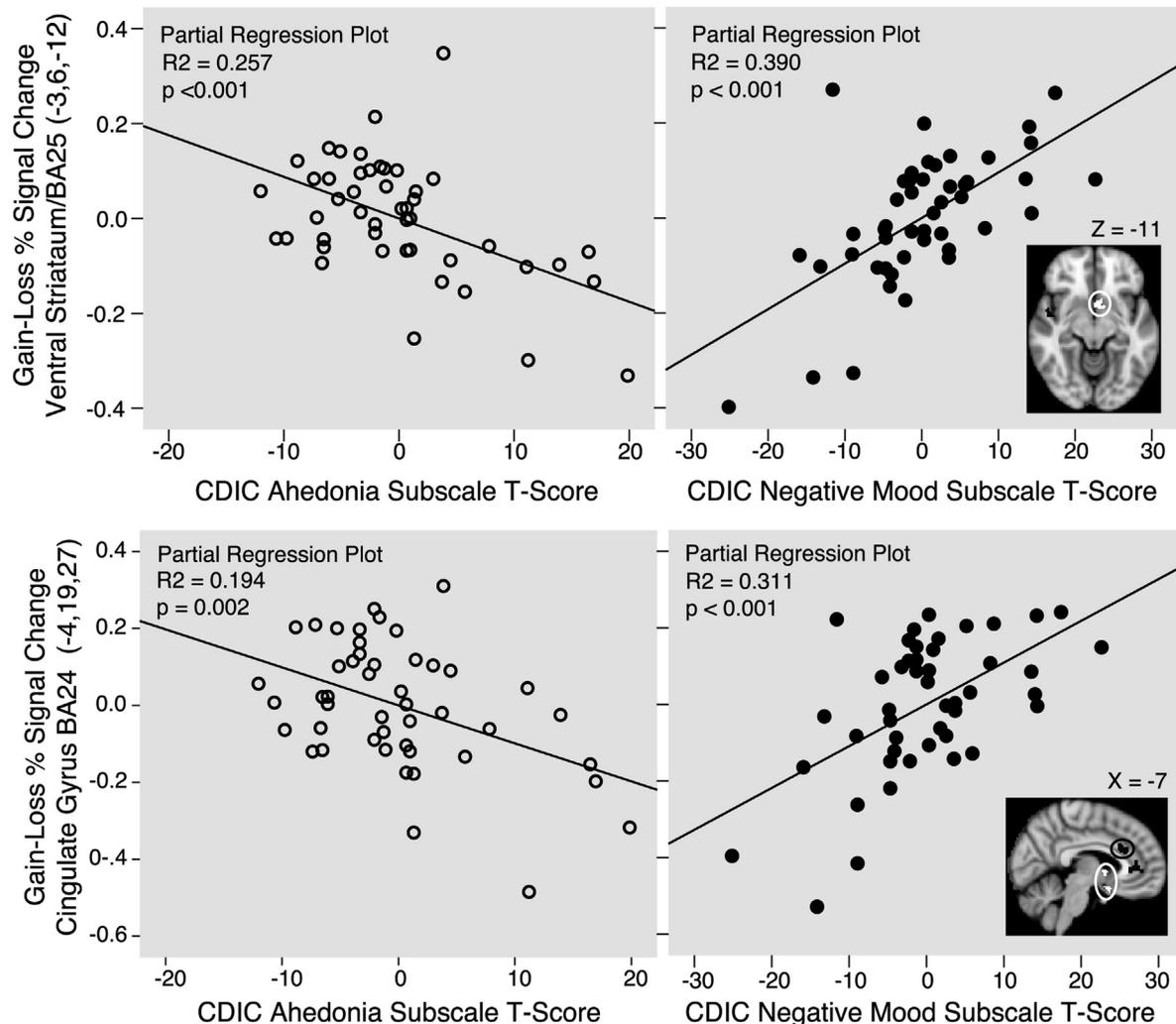
groups showed similar relationships between activation and anhedonic versus negative mood symptoms. However, there was a trend toward an interaction of anhedonia and risk group ($p = .03$) within the anterior cingulate, with anhedonia negatively predicting gain-loss response only within the low-risk group.

To further isolate the source of effects of symptoms on gain-loss response, planned post hoc regressions revealed that, across all regions, neither anhedonia nor negative mood significantly predicted response to gain feedback (all p values $>.10$; see Tables S8 and S9, available online). Conversely, within ventral striatal, cingulate, and posterior insula regions, anhedonia predicted reduced deactivation to loss feedback, whereas negative mood predicted enhanced deactivation to loss feedback (all p values $<.05$; see Tables S8–S9, available online).

DISCUSSION

The goal of the current study was to investigate how depression risk and specific depressive symptom domains related to neural responses to both gain and loss of reward in healthy school-aged children. As hypothesized, high-risk children showed blunted response to gain feedback within the striatum and anterior insula. However, high-risk children also showed greater deactivation to loss within these same regions and within additional ventral striatal and parahippocampal regions. Importantly, the effect of MDD risk on striatal response to loss was significantly larger than that on gain, with striatal loss-related deactivation significantly predicting risk-group status above and beyond blunted gain responses. These findings demonstrate that alterations in reward processing are evident as early as school age in offspring of mothers with MDD. However, our results indicated a stronger relationship between MDD risk and response to loss than to gain, a pattern consistent with behavioral/neural findings indicating greater salience of loss in late childhood more generally.^{23,24,26} Another set of key findings were the unique and opposing relationships anhedonic and negative mood symptom severity showed with

FIGURE 3 Anhedonia and negative mood symptoms predicting the difference in response to gain versus loss within the ventral striatum (white circle) and cingulate gyrus (black circle). Note: Partial regression plots controlling for risk group and the alternate symptom subscale. BA = Brodmann area; CDIC = Child Depression Inventory–Child report.



gain-loss feedback responses. These effects were largely driven by blunted deactivation to loss in children reporting elevated anhedonia and enhanced deactivation to loss in children reporting elevated negative mood. Collectively these results, in regard to gain, are consistent with the extant adolescent MDD risk literature.⁴⁻⁶ However, they extend this literature by elucidating unique relationships between gain/loss responses, depression risk, and specific depressive symptom domains, areas that have not been thoroughly investigated in childhood or older ages.

High-risk children showed blunted responses to reward within regions, such as the ventral striatum and anterior insula, involved in reward learning and affective responding.^{11,45,46} patterns also observed in adolescent MDD risk.^{4,5,14} This finding is consistent with the hypothesis that blunted response to reward is a trait marker of depression risk, evident even in late childhood, before the onset of the normative increase in reward responsivity

associated with adolescence. However, as the size of this effect within the ventral striatum was somewhat smaller (Cohen's $d = 0.75-1.15$) than those reported in other similarly powered adolescent studies (i.e., Gotlib *et al.*⁴; Cohen's $d = 1.37$), it remains possible that the relationship between MDD risk and blunted reward responses increases further over adolescence. Future longitudinal studies are needed to directly test this hypothesis and to evaluate whether blunted reward responsiveness during childhood is predictive of change in reward responsiveness over adolescence. Additional studies are also needed to investigate mechanisms mediating the relationship between maternal MDD and offspring reward response. Twin and other family studies have begun to suggest that behavioral and neural response to reward is somewhat heritable^{47,48}; thus, it is possible that the blunted reward responsiveness that we observe in high-risk children results from reward system dysfunction putatively passed on genetically from mothers with depression to

their children. However, it is likely that other factors that co-occur with maternal depression also relate to blunted reward responding, such as exposure to stress/trauma or specific parenting styles.^{49,50} This familial environment and parental characteristics may also mediate/moderate the relationship between striatal reward response and depression risk. Future studies investigating both maternal and child response to reward, along with other genetic and environmental factors, are needed to evaluate these potential mechanisms.

Blunted striatal response to reward is the most commonly reported finding in the adolescent MDD and MDD risk incentive literatures. However, a very salient finding in the current study was enhanced deactivation to loss of reward in high-risk children. This pattern was universal across regions showing a risk group interaction in the voxelwise ANOVA. The only other study investigating response to loss of reward in a high-risk group also reported greater ventral striatal deactivation to loss (versus nonloss) feedback in high-risk adolescents.⁴ Few fMRI studies have investigated normative ventral striatal responses to loss of reward in childhood, and thus there is also little work investigating relationships between deactivation to loss and sensitivity/affective response to that feedback within childhood. However, we interpret the enhanced deactivation to loss observed within the high-risk group to reflect heightened sensitivity to loss, given that, in adults, ventral striatal deactivation is observed when outcomes are worse than expected (i.e., negative prediction error),⁵¹ and with increasing losses.⁵²

It is unclear whether the large effect of MDD risk on ventral striatal response to loss, versus gain, observed in this study is unique to childhood, as no other studies have compared effect sizes of group differences for gain and loss within the same region. It is also important to note that blunted striatal gain responses no longer significantly predicted risk group after adding loss into the model, and that enhanced striatal deactivation to loss was a unique predictor of risk group. This indicates that loss-related deactivation not only explains the variance in risk group status predicted by blunted striatal gain response, but also predicts additional variance in MDD risk. Future studies are needed to evaluate the unique contributions of loss and gain responsiveness to MDD risk across developmental stages.

The interpretation that loss-related deactivation within the ventral striatum reflects greater sensitivity to loss is also consistent with the observed relationships between loss responsiveness and severity of anhedonic versus negative mood symptoms. Children reporting elevated negative mood, associated with enhanced loss-avoidance behavior,²⁷ showed enhanced deactivation to loss feedback within the ventral striatum, insula, and anterior cingulate. Conversely, children reporting elevated anhedonic symptoms, associated with blunted gain-approach and loss-avoidance behaviors,²⁷ showed blunted deactivation to loss within similar regions. Importantly, these symptoms related to loss responses over and above MDD risk, suggesting that although elevated self-reported anhedonic symptoms were observed in the high-risk group, the relationships between loss response and anhedonia occur independent of risk

group status. It was surprising that response to gain feedback did not significantly relate to anhedonic symptoms, as elevated anhedonia predicts reduced response to monetary gain in adolescents^{5,8,9,22,53} and reduced gain-approach behavior in children.²⁷ Given the extant literature, we are hesitant to interpret this null result in a child sample without replication.

Although additional work is needed to prospectively examine the relationship between hyperresponsiveness to loss and future depression/symptoms, this cross-sectional work suggests that such hyperresponsiveness is a unique marker of childhood depression risk and negative mood symptom severity. This hyperresponsiveness may prove to be a new mechanism of risk that can be targeted by novel treatments. For example, trying to reduce response to negative stimuli, such as losses, would likely prove beneficial in the context of childhood risk and elevated negative mood more generally, whereas this approach would likely be less beneficial for children exhibiting elevated anhedonic symptoms.

This study had several limitations. Both maternal and child mental health histories were determined based on retrospective reporting. Although such methods are routinely applied in the literature and have been validated as an appropriate measure of historical disorder, it is possible that children may have experienced disorder or that mothers may have been misclassified. However, as this would likely have reduced differences between high- and low-risk groups (particularly for risk-group misclassification), it is unlikely that the current results are due to misclassification. Future studies investigating neural response to gains/losses are needed within child samples that have been followed since early life and/or are the offspring of women who have been engaged in longitudinal studies of mental health. Another limitation is that only maternal MDD history was used to define risk groups. Paternal mental health also has an impact on offspring psychopathology risk,⁵⁴ as do other environmental factors such as exposure to trauma/stress⁵⁵; however, given the current study's sample size and recruitment design, it was not possible to investigate these sources of risk. Future studies actively investigating other sources of risk will be important for examining whether other risk factors relate to altered response to incentives. The study's sample size should also be considered when interpreting sizes of reported effects; thus, larger studies are needed to replicate current findings.

In sum, the current results suggest that enhanced responsiveness to loss of reward is a strong correlate of MDD risk and depressive symptomology in school-aged children. Although children who have never been depressed but are at high risk for developing MDD show blunted striatal and anterior insular responses to candy gain feedback, enhanced ventral striatal deactivation to candy loss feedback is a stronger predictor of maternally defined MDD risk. Furthermore, individual differences in the severity of core depressive symptoms, anhedonia, and negative mood showed strong and opposing relations to loss responsiveness, whereas neither symptom construct significantly related to gain responsiveness. Given these results, and the fact that childhood is normatively a time of increased sensitivity to loss,^{23,24,56} identifying mechanisms

for reducing reactivity to loss of reward/negative stimuli and negative mood may prove to be a useful, preventive strategy for mental health intervention in childhood. &

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