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Neural Processing of Reward and Loss in Girls at Risk for Major Depression

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Abstract

Context—Deficits in reward processing and their neural correlates have been associated with major depression. It is unclear, however, if these deficits precede the onset of depression or are a consequence of this disorder.

Objective—To determine whether anomalous neural processing of reward characterizes children at familial risk for depression in the absence of a personal history of psychopathology.

Design—Comparing neural activity of children at low and high risk for depression as they process reward and loss.

Setting—University fMRI facility.

Participants—Thirteen 10– 14-year-old never-disordered daughters of mothers with recurrent depression (“high risk”) and 13 age-matched never-disordered daughters with no family history of depression (“low risk”).

Main Outcome Measure—Neural activity, as measured with fMRI, in key reward and attention neural circuitry during anticipation and receipt of reward and loss.

Results—While anticipating gains, high-risk participants showed less activation than did their low-risk counterparts in the putamen and left insula, but greater activation in the right insula. When receiving punishment, high-risk participants showed greater activation in the dorsal anterior cingulate gyrus than did low-risk participants, who showed greater activation in the caudate and putamen.

Conclusions—Familial risk for depression affects neural mechanisms underlying the processing of reward and loss; young girls at risk for depression exhibit anomalies in the processing of reward and loss prior to the onset of depressive symptoms. Longitudinal studies are needed to examine whether these characteristics predict the subsequent onset of depression.

Keywords

depression; reward; anticipation; incentive; familial risk

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[1]After reviewing the SCID interviews, one mother was found to meet current diagnostic criteria for obsessive-compulsive disorder; excluding this mother’s daughter from the analyses did not change the results.

INTRODUCTION

A hallmark characteristic of Major Depressive Disorder (MDD) is the diminished experience of pleasure or reward. For example, compared with nondepressed persons, depressed individuals have been found to be characterized by attenuated reactivity to slides depicting pleasant scenes,[1,2, 3] to amusing film clips,[4] to pleasant drinks,[5] and to monetary reward contingencies.[6] Moreover, Pizzagalli et al.[7] found that depressed individuals are impaired in their ability to integrate reinforcement history over time in a probabilistic reward task.

Recently, investigators have begun to examine neural aspects of responsivity to positive stimuli (see Table 1). In unselected samples of participants, studies using functional imaging have found reward processing to be associated with increased activation in the striatum[8–10], insula, thalamus, and dorsal midbrain[8,9,11,12], and loss anticipation and outcomes to be associated with activation in the insula and the caudate[13,14], and with deactivation in the mesial frontal cortex[8,9]. Regions such as the insula may play a role in both reward and loss processing by responding to uncertain reward and risk conditions. Moreover, faster learning of reward contingencies has been found to be associated with greater activation in dorsal anterior cingulate cortex (dACC), important for action and conflict monitoring, and in the basal ganglia[15]. Although adolescents have generally been found to exhibit neural responses to reward stimuli similar to those found in adults[16,17], there are exceptions to this pattern. For example, Galvan et al.18 reported greater nucleus accumbens, relative to prefrontal, activity in adolescents than in children and adults during reward processing. In contrast, Eshel et al.[19] found greater activation in the orbitofrontal cortex/VLPFC and dorsal ACC in adults than in adolescents when making risky monetary decisions. In a recent review, Casey et al.[20] postulated that increased risk-taking behavior in adolescence is associated with a shift in activation of prefrontal regions from diffuse to more focal recruitment over time, and with elevated recruitment of subcortical regions.

Researchers have begun to extend the investigation of neural aspects of reward processing to depressed adults and children. Knutson et al.21 examined patterns of neural activation in individuals diagnosed with MDD as they anticipated and received monetary reward and punishment. In contrast to never-depressed controls, who exhibited dACC activation during anticipation of loss, depressed participants were characterized by dACC activation during anticipation of reward, suggesting that they experience conflict when they anticipate receiving positive stimuli. Pizzagalli et al. 22 found that depressed adults had significantly less activation to rewarding outcomes in the left nucleus accumbens and bilateral caudate than did healthy controls, indicating dysfunction in the basal ganglia in MDD, particularly during the consummatory phase of reward processing. Kumar et al.23 found that, compared with healthy controls who received an acute dose of antidepressant medication, depressed adults receiving long-term antidepressant treatment exhibited significantly reduced activations in the ventral striatum, rostral and dorsal anterior cingulate, retrosplenial cortex, and midbrain and hippocampus. Steele et al.[24] similarly reported that adults diagnosed with MDD exhibited less activation in the ACC in response to negative (lose) feedback and less activation in the ventral striatum in response to win feedback than did healthy controls.

In the first behavioral study of reward-related processing in boys with current depression, Forbes et al.[25] reported that depression was associated with a reduced ability to distinguish between low- and high-magnitude rewards, which predicted depressive symptoms in a one-year follow-up assessment. In two subsequent studies, Forbes et al.[26,27] found depression in children to be associated with reduced activation in reward-related brain areas during both anticipation of reward and reward outcome. Specifically, depressed children exhibited blunted responses in ACC, bilateral caudate, and OFC while both anticipating and receiving reward. Forbes et al.[27] replicated their findings of reduced striatal responding in depressed children

during reward anticipation and outcome, but also found greater activation in these participants in dorsolateral and medial prefrontal cortex.

It appears, therefore, that depressed adults and children are characterized by unique patterns of neural activity during the processing of reward stimuli. The role of this neural functioning in the course of depression, however, is not clear. It is possible, for example, that neural and/or behavioral anomalies in reward responsivity are present before the first onset of a depressive episode and represent a vulnerability factor that plays a role in the development of this disorder. Examining this possibility requires investigators to assess individuals before they experience their first episode of this disorder. In this context, it is well documented that approximately 40 percent of the offspring of depressed mothers will themselves develop depression.[28–30] Thus, examining functional brain responses to the anticipation and receipt of reward and loss in children at high familial risk for depression who have not yet experienced a depressive episode themselves should help to identify patterns of neural activation that are involved in vulnerability to developing MDD.

To date, few investigators have examined reward processing in asymptomatic children who have a familial vulnerability for MDD prior to the onset of their first episode of depression. In a notable exception, Monk et al.[31] found that children at familial risk for depression showed greater amygdala and nucleus accumbens activation while passively viewing fearful faces and lower nucleus accumbens activation while viewing happy faces. No studies, however, have examined reward processing in a sample of high-risk children who have not yet experienced any Axis I disorder. Investigating the neural bases of reward processing in such a sample would allow us to understand the nature of depression-associated difficulties in reward processing independent of current or past psychopathology. Because investigators have reported gender differences in the transmission and recurrence of depression in children[27], in the present study we examined neural functioning in carefully diagnosed, never-disordered daughters of mothers who have experienced recurrent episodes of MDD during their daughters' lifetime and in age-matched control daughters of mothers with no past or current psychopathology. Drawing on findings obtained with depressed individuals[21–27], we predicted that, compared with daughters of never-disordered mothers, daughters of mothers with recurrent MDD would exhibit reduced activation in brain regions associated with reward-processing, including the striatum, insula, and ACC while anticipating and receiving gains. We predicted further that, while they anticipate and receive losses, daughters of mothers with recurrent MDD would show greater activation than would daughters of low-risk mothers in brain regions associated with conflict monitoring and harm avoidance, including the ACC and insula.

METHODS

Participants

Participants were 26 girls between the ages of 10 and 14 years with no current or past Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM–IV) Axis I disorder. Thirteen girls had biological mothers with a history of recurrent MDD during their daughter's lifetime, and 13 girls had biological mothers with no history of any Axis I disorder. Girls were recruited with their mothers through internet and print advertisements in the local community and through the Department of Psychology and the Department of Psychiatry and Behavioral Sciences at Stanford University. The mothers' responses to a telephone interview established that both mothers and daughters were fluent in English, that daughters were between 10 and 14 years of age, and that daughters were unlikely to have past or current psychopathology. Those daughters who were considered likely to be eligible for participation were invited to the laboratory for more extensive interviews and testing.

Assessment of psychopathology

Trained interviewers assessed the diagnostic status of the daughters by administering the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL), which has been shown to generate reliable and valid child psychiatric diagnoses.32 Interviewers had previous training and experience with this interview, and administered it separately to the daughters and their mothers (about the daughters) in order to assess current and lifetime diagnoses for affective, psychotic, anxiety, behavioral, substance abuse, and eating disorders. A different interviewer administered the Structured Clinical Interview for the DSM–IV (SCID)33 to the mothers. To assess inter-rater reliability, an independent trained rater evaluated 30% of the K-SAD-PL and SCID interviews by randomly selecting audiotapes of equal numbers of high-risk and healthy control (low-risk) pairs. In all cases, these diagnoses matched the diagnoses made by the original interviewer, $\kappa=1.00$, indicating excellent inter-rater reliability.

Daughters in the high-risk group were eligible to participate in the study if (a) they did not meet criteria for any past or current DSM-IV Axis I disorder according to both the parent and child K-SADS-PL; and (b) their mothers met DSM-IV criteria for at least two distinct episodes of MDD since the birth of their daughters but did not meet criteria for current MDD or any other Axis I disorder, although they could meet criteria for a past Axis I disorder in addition to MDD (see Footnote 1). Daughters in the low-risk group were eligible to participate if (a) they did not meet criteria for any past or current Axis I disorder based on both the parent and child K-SADS-PL; and (b) their mothers did not meet criteria for any past or current Axis I disorder.

To ensure that the two groups of girls did not differ in current levels of depressive symptom, all girls completed the short form (10-item) of the Children's Depression Inventory (CDI-S), [34] a self-report measure of depressive symptoms developed for children between the ages of 8 and 17. Level of maternal depression was measured by the Beck Depression Inventory.35 Levels of anxiety were assessed by administering the MASC36 to the mothers and the ASIC37 to the daughters. To ensure that any group differences were not a function of intelligence, the Vocabulary subscale of the Wechsler Intelligence Scale for Children–IV was administered to all girls.[38] Finally, to assess pubertal development, daughters were also administered the Tanner stages questionnaire[39].

Procedure

Monetary Incentive Delay Task—The scanning procedure was similar to the Monetary Incentive Delay (MID) task described by Knutson and colleagues.[21] We modified the MID task for children (KIDMID) by replacing the rewarding stimulus, money, with points that could be used to redeem prizes that the participants selected before beginning the task in the scanner. Participants were trained prior to the scan to test for explicit cue comprehension and shown the prizes they could win during the task prior to entering the scanner.

Designed to probe neural responding to the anticipation and receipt of reward and punishment outcomes, the KIDMID task uses a set of cues to indicate whether the participants can win points or avoid losing points if they are fast enough to hit a target. The KIDMID task consists of a single run of 100 6-second trials. Each trial was composed of an anticipation phase and a feedback phase. During the anticipation phase, a cue was presented that signified whether the participant should respond to a subsequently presented target (circle or square) or withhold a response (triangle). A circle indicated that the participant could win points if she was fast enough to hit the target; a square indicated that the participant could avoid losing points if she was fast enough to hit the target. On trials in which the participant was required to respond (circle, square), lines within the cue signaled how much the trial was worth (one line = 1 point;

2 lines = 5 points). Thus, five possible cues were included in the anticipation phase that indicated both whether participants should make a button press and the point level for that trial (circle with one line = response, +1 point; circle with two lines = response, +5 points; square with one line = response, −1 point; square with two lines = response, −5 points; triangle = no response, 0 points). During the feedback phase, for each trial participants received feedback about whether or not they had gained or lost points, and how many; for triangle trials, a '0' was presented because participants could neither win nor lose points on these non-incentive trials. Each cue type (circle, square, triangle) appeared 20 times and trial types were pseudo-randomly distributed across the run. The cue during the anticipation phase was displayed for 250 ms. Following the cue and a varying anticipation period (2000–2500 ms), a target of varying duration was presented (250–350 ms, determined from pilot testing to result in 75% accuracy), and participants were required to press a button as quickly as possible (circle, square) or withhold their response (triangle). A variable delay period separated the offset of the target stimulus from the onset of the feedback phase that informed participants whether they had lost or won points. This delay period was varied so that the length of the entire trial was exactly 6 seconds. The feedback phase informing participants whether they had lost or won points was displayed for 1650ms.

Statistical contrasts were conducted separately on blood oxygen level dependent (BOLD) data from anticipatory and outcome periods. Because reaction times did not differ as a function of incentive level, to increase statistical power trials presenting anticipation of gain cues (i.e., 1 and 5 points) were combined as were trials presenting anticipation of loss cues. For the anticipation phase, trials with gain or loss cues (circle and square, respectively) were compared to non-incentive trials (triangle). For the feedback phase, trials in which participants gained points were compared to non-gain feedback trials, and trials in which participants lost points were compared to non-loss trials.

fMRI data acquisition and analysis—Scanning was conducted on a 1.5T GE Signa Scanner. Functional images were acquired using a T2*-weighted in-/out- spiral pulse sequence[40] using the following parameters: repetition time [TR] = 83 ms/slice, echo time [TE] = 40 ms, flip angle = 90°, field of view [FOV] = 24 cm, acquisition time = 2000 ms per frame, consisting of 24 sequential axial slices (in-plane resolution = 3.75 mm2; through-plane resolution = 3 mm, 1 mm gap). High-resolution structural scans were collected using a T1-weighted spoiled grass sequence (1 mm^2 in-plane and 1.5 mm through-plane resolution, TE = min, flip angle = 15°).

Preprocessing and analysis of fMRI data were conducted using Analysis of Functional Neural Images (AFNI) software.41 Time-series data were slice-time corrected relative to the most ventral axial slice, and volume registered to correct for head translation and rotation during the scan (Fourier interpolation, two-pass). BOLD time series with sudden motion exceeding 2.0 mm were corrected using ArtRepair42; in this procedure, subject's raw functional data were converted to SPM Analyze format, processed with ArtRepair in Matlab 7.3, and then converted back to AFNI format for further processing. Data were spatially smoothed with a 4mm Gaussian smoothing kernel, and band-pass filtered (high-pass threshold = 0.011 Hz, low-pass threshold = 0.15 Hz), and normalized to percent signal change. Functional images were co-registered to anatomical images and transformed into Talairach space.

Statistical analysis—Reaction time and accuracy was recorded on each trial of the task. Mixed-model analyses of variance (ANOVAs) were conducted on individual hit rates, mean reaction times, and total points gained, with group (high-risk, low-risk) as the between-subjects factor and trial type (gain, loss) as the within-subject factor.

Preprocessed time series data for each individual were analyzed with 3dDeconvolve, an AFNI-based multiple regression program. The regression model included a set of seven orthogonal regressors of interest: anticipation of gain, anticipation of loss, non-incentive, gain outcomes, nongain outcomes, nonloss outcomes and loss outcomes. Nuisance covariates included in the model were three translational and three rotational head-motion estimates and six regressors modeling zeroth- through fifth-order polynomial trends in the BOLD time series. At the individual subject level, the following contrasts were performed on the beta coefficients from the multiple regression: anticipation of gain versus non-incentive; anticipation of loss versus non-incentive; gain versus nongain outcomes; and nonloss versus loss outcomes.

For each contrast of interest, contrast coefficients for each group were compared by conducting two-sample t-tests on a voxel-wise basis within a mask constructed of several regions of interest (ROIs). In creating the mask, multiple bilateral regions were selected to cover limbic and paralimbic structures and the striatum, which includes the combined volumes of the caudate, putamen, and lentiform nucleus. These structures were Talairach[43] defined and selected within the AFNI program. They included caudate, putamen, globus pallidus, amygdala, cingulated cortex, medial prefrontal cortex, hippocampus, insula, thalamus, and hypothalamus. Together, these structures yielded a single mask composed of 2710 3.75mm isotropic voxels. The voxel-level significance (p = .05) and cluster size (k = 10) criteria used to hold family-wise error at p = .05 were calculated with the AFNI program AlphaSim. This program generates null-hypothesis distributions and corresponding statistical criterion values through the use of Monte Carlo simulation. Parameters known to affect the shape of null hypothesis distributions of fMRI data, such as the number of voxels compared and their effective size, the per-voxel statistical criterion, and the definition of voxel clustering used, are modeled in these Monte Carlo simulations.

RESULTS

Participant Characteristics

Demographic and clinical characteristics of the two participant groups are presented in Table 2. There were no significant differences between the two groups in age, t(24) = 0.72; Wechsler Intelligence Scale for Children-IV Vocabulary scores, t(24) = 0.66; MASC scores, t(21) = 1.04; ASIC scores, t(24) = 0. 68; Tanner breast, t(22) = 0.52, Tanner hair, t(22) = 0.67; percent of participants who were post-menarche, $\chi 2(N=18) = 0.63$, or ethnicity, $\chi 2(N=26) = 3.05$, all p > .05 . The mothers of the high-risk girls reported significantly higher BDI scores (M = 13.23, SD = 11.74) than did the mothers of the low-risk girls (M = 2.23, SD = 2.80; t(24) = 3.28, p < .01. The high-risk girls obtained significantly higher scores on the CDI-S than did the low-risk girls, t(24) = 2.06, p =.05. It is important to note, however, that the average CDI-S for the high-risk group (1.46) was well below the cut-off of 10 typically used to identify probable clinically significant depression. Moreover, including levels of both children's and mothers' depressive symptoms as covariates in the analyses did not change our results. Finally, one of the mothers of a daughter in the high-risk group was diagnosed with past obsessive-compulsive disorder (OCD), one with past posttraumatic stress disorder and panic disorder, and one with past bulimia and specific phobia.

Behavioral Results

The two-way (group by trial type) ANOVAs conducted on hit rate, reaction times, and number of total points gained yielded no significant main effects or interactions for any variable (all ps>.05), indicating comparable performance of the two groups on the task (see Table 2).

Neuroimaging Results

Group analyses comparing low- vs. high-risk participants yielded the following results (presented in Table 3 and Figure 1).

Anticipation of Gain vs. Non-incentive—In response to anticipation of gain, low-risk participants exhibited greater activation than did high-risk participants in the left putamen as well as the left insula. High-risk daughters exhibited greater activation than did low-risk daughters within the right insula.

Anticipation of Loss vs. Non-incentive—During anticipation of loss, low-risk participants showed greater activation than did their high-risk counterparts within the left lentiform nucleus/globus pallidus and the left middle cingulate gyrus (BA 24). High-risk participants did not demonstrate any areas of increased activation relative to low-risk participants.

Gain vs. Nongain Outcomes—In response to gain outcomes, low-risk participants activated a number of foci to a greater degree than did their high-risk counterparts, including the left putamen/lentiform nucleus, multiple regions within the cingulate gyrus (BA 32, 24, and 23), and the right anterior thalamic nucleus. High-risk participants did not display greater activation in any regions compared with low-risk participants.

Loss vs. Nonloss Outcomes—Loss Outcomes activated the dorsal cingulate gyrus (BA 32) to a greater extent in high- than in low-risk participants. Low-risk participants exhibited greater activation than did high-risk daughters in the right caudate and left putamen.

Finally, no significant associations were obtained between the neural findings and pubertal stage, task performance, participants' current depressive symptoms, or level of maternal symptomatology.

COMMENT

The present study was designed to examine neural functioning during the processing of reward and loss in never-disordered daughters of mothers with a history of recurrent MDD, compared with age-matched daughters of mothers who have never experienced an Axis-I disorder. Functional anomalies in reward-processing have been found in both depressed adolescents[26] and depressed adults.[21] By examining reward-related neural responding in daughters who are at familial risk for the development of depression before the onset of disorder, we are able to identify patterns of activation indicative of aberrant reward functioning that may represent a vulnerability factor for depression. Moreover, given the structure of the task used in this study, we were able to examine neural responses associated both with the anticipation and receipt of gain and with the anticipation and receipt of loss, thereby providing an initial examination of the processing of both reward and punishment in daughters at risk for depression.

As predicted, we found that high-risk daughters exhibited attenuated neural responding during the processing of reward. Specifically, high-risk daughters were characterized by marked reductions in striatal activation during both the anticipation and the receipt of reward. This finding mirrors previous work that has documented a blunting of reward-related activation in currently depressed adolescents.[26] Thus, even prior to the onset of a depressive disorder, high-risk daughters exhibit anomalous neural activations in response to reward stimuli. Interestingly, both the present study and Forbes et al. found overall reductions in activation in response to both reward anticipation and outcome. In contrast, the depressed adults examined by Knutson et al. did not differ significantly from their nondepressed counterparts during reward anticipation. This difference may be attributable to two factors. First, both in the present study

and in Forbes' study, points were used that were later redeemed for prizes or cash; in Knutson's study, individuals played specifically for money. Money may be a stronger secondary reinforcer than are points, and may actually attenuate (or over-ride) depression-associated differences in activation in reward-related networks. Second, there are likely maturational differences between the developing adolescent neural system for reward and the more mature adult reward systems (see Table 1). Other studies have also documented important developmental differences in the processing of reward examined across the lifespan[16,18]. Collectively, these studies underscore the importance of contextualizing potential developmental differences in neural activation during reward processing in vulnerable populations that may still be undergoing cortical maturation.[44]

Perhaps most striking, across all four comparisons, i.e., during anticipation and outcome of both reward and loss, low-risk daughters exhibited a greater number of regional activations than did high-risk daughters. Interestingly, the high-risk daughters showed greater activations in two conditions. First, during gain anticipation, high-risk daughters exhibited higher right insula activation than did low-risk daughters. The insula has been implicated frequently in probes of reward processing that involve probabilistic gains.13,45–47 Recently, however, Preuschoff et al.[48] documented a unique contribution of the right insula during risk prediction error (i.e., errors associated with predicting an uncertain outcome that may motivate subsequent behavioral adjustments). In this context, the insula has been posited to play a role as an interoceptive marker linking risk predictions with anxious affect[49]; the right insula, in particular, has been found to be activated during anticipation of aversive stimuli.50 Given the finding in the present study of right insula activation in the high-risk daughters, it is plausible that high-risk daughters differentially evaluate the risk of receiving anticipated gains which, in turn, may increase risk prediction errors. Because our task design did not permit behavioral measurement of risk prediction or risk prediction error, it is important to emphasize that these evaluations might only occur at an implicit level.

A second region in which high-risk daughters exhibited greater neural activation than did their low-risk counterparts was the dACC (BA 32) during loss outcome. This finding is notable because, while the high-risk daughters failed to show the activation in this region during gain outcomes exhibited by the low-risk daughters, they recruited the dACC during loss outcomes, while the low-risk daughters did not. This dissociation in dACC function suggests an aberrant signal in response to reward and loss outcomes. Current theories posit a role of the dACC in the integration of reinforcement history over time in the service of adaptively guiding behavior.[51,52] Indeed, stronger dACC activation in response to rewarding outcomes is associated with improved learning of reward contingencies.15 Age-related improvements in performance during reward paradigms have also been linked to increased utilization of the dACC associated with error regulation and error feedback.53 Moreover, previous work has documented that adolescents show less activation in the dACC during reward than do adults, which is posited to contribute to their greater risk-taking behavior.[19] The failure of the high-risk daughters to recruit dACC during reward outcomes suggests a general reduced sensitivity to reward and/or a diminished capacity to integrate reward outcomes over time in individuals at risk for depression. In contrast, the recruitment of dACC by the high-risk daughters during loss outcomes may indicate a greater facilitation in integrating loss or punishment information. Considered together with reduced activation in the striatal areas commonly observed during reward, it appears that the reward processing system is critically impaired in daughters who are at elevated risk for depression, even though they have not yet experienced a depressive episode. Moreover, high-risk daughters appear to have difficulty in being able to appropriately recruit dACC, which is involved primarily in assessing the salience of emotional and motivational information and the regulation of emotional responses.[54] Clearly, longitudinal studies are needed to determine whether the anomalous activations observed in this study

during the processing of rewards and losses are associated with the subsequent onset of depression.

We should note several limitations of this study. First, the lack of a comparison group of depressed children and an absence of brain-behavior associations limit conclusions we can draw regarding how anomalies in the neural processing of reward and loss in the high-risk participants are related to the development of depression. Second, the lack of significant reaction-time differences between the two incentive levels may reflect anomalies in participant motivation, but is also likely due to the fact that having only two reward levels in the task constrains meaningful correlations with behavioral data. Third, in terms of the task, the "control" cue did not require a motor response, making it difficult to disambiguate a potential interaction or main effect of response preparation and incentive effects. As a related point, participants receive fewer gain and loss outcome trials than anticipation trials on the MID task, rendering estimates of activations to anticipation more reliable than of activations to outcome. Fourth, we had a relatively small sample size in this study, although the effect sizes for group differences in neural functioning were all large, indicating that these differences are reliable and robust. Finally, while we conducted a comprehensive assessment of maternal psychopathology, we did not assess paternal functioning. Therefore, it will be important in future research to assess and examine the effects of paternal psychopathology on children's neural and behavioral functioning.

CONCLUSION

Familial risk for depression affects mechanisms underlying the processing of reward and loss. In this study we present evidence that even before the onset of depressive symptoms, young girls at risk for depression exhibit anomalies in striatum and dACC during processing of reward and loss. Importantly, we also document a prominent role of the insula as an index of both normal and disordered reward functioning; this structure may be a promising candidate for a biological marker of risk for the development of a depressive disorder. Future research is needed to examine the longitudinal trajectories of these characteristics and their ability to predict the subsequent onset of depression.

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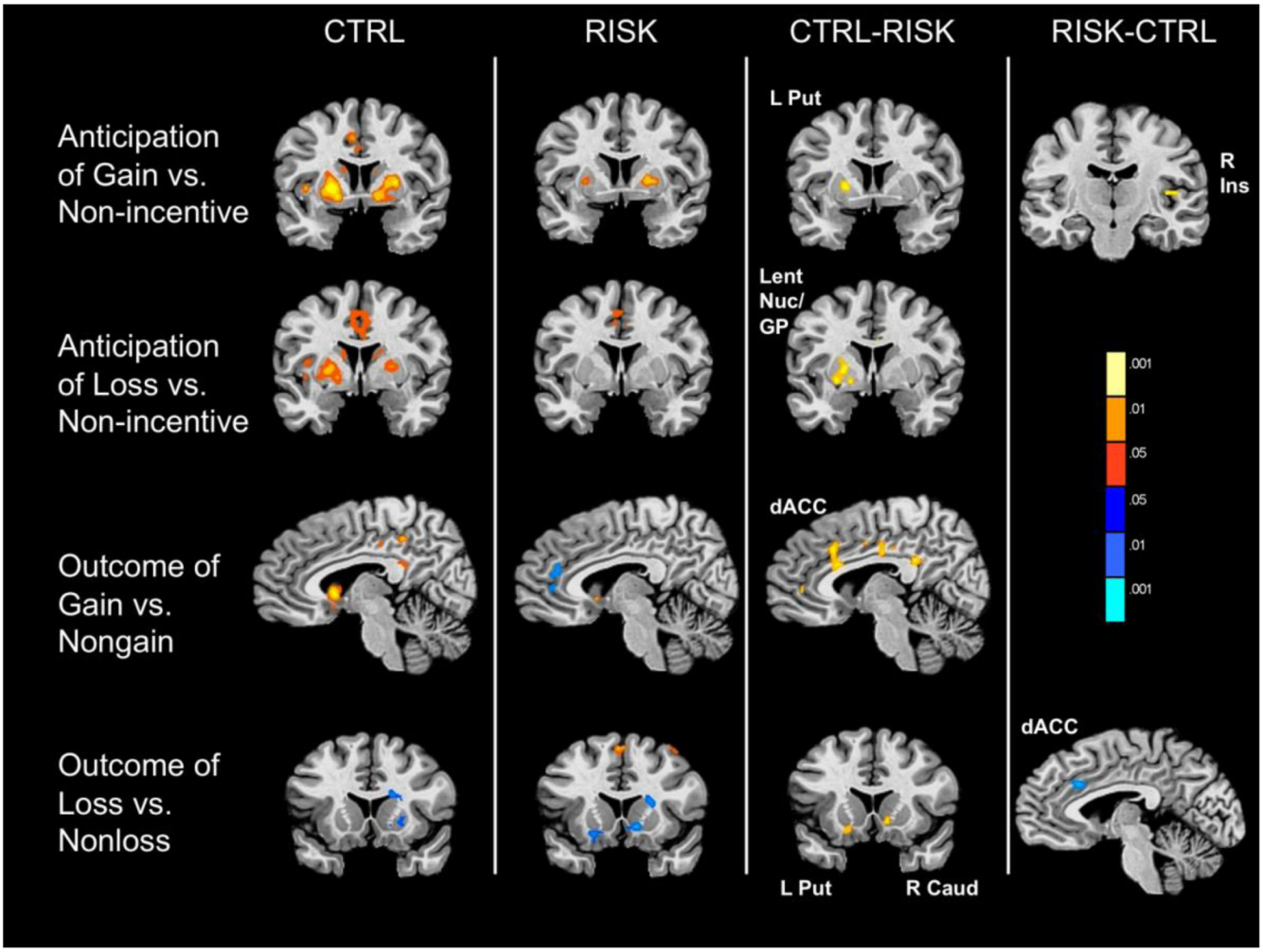

Figure 1.

Activations depicted in yellow and deactivations in blue within the groups of low-risk control (CTRL) and high-risk (RISK) daughters (two left columns). Contrasts in two right columns depict regions of activation comparing CTRL-RISK and RISK-CTRL (both blue and yellow correspond with activation in the RISK-CTRL comparison). R = right; L = left; threshold of p=.05, 10 or > voxels. No between-group deactivations were identified. L Put = left putamen; Lent Nuc/GP = lentiform nucleus/globus pallidus; dACC = dorsal anterior cingulate cortex; R Ins = right insula.

Table 1

Overview of neural patterns of activation and deactivation in response to reward and loss.

Type of Sample	Significant Regions	Finding (Activation/Deactivation)
Unselected samples	Striatum	Activation with reward[8–10] Deactivation of caudate with loss[13,14]
	Insula	Activation with reward,[8,9,11,12] Activation with loss[13,14]
	Thalamus	Activation with reward,[8,9, 11,12]
	Dorsal Midbrain	Activation with reward,[8,9, 11,12]
	Mesial Frontal Cortex	Deactivation with loss,[8,9]
Healthy Adults versus Healthy Children	Nucleus accumbens	Activation in adolescents> children, adults[18]
	Orbitofrontal Cortex/Ventrolateral Prefrontal Cortex	Activation adults > adolescents[19]
	Dorsal Anterior Cingulate Cortex	Activation with reward[21] Deactivation with reward[22]
Adults with MDD	Nucleus accumbens/Ventral Striatum	Deactivation with reward outcomes[22,23,24]
	Caudate	Deactivation with reward outcomes[22]
	Midbrain	Deactivation with reward[23]
	Hippocampus	Deactivation with reward[23]
	ACC	Deactivation with reward[26,27]
	Medial Orbitofrontal Cortex	Deactivation with loss[24]
Children with MDD	Caudate	Deactivation with reward[26,27]
	Orbitofrontal Cortex	Deactivation with reward[26,27]
	Dorsolateral and Medial Prefrontal Cortex	Activation with reward[27]
Children at risk for MDD	Amygdala	Activation with fearful faces[31]
	Nucleus Accumbens	Activation with fearful faces[31]
	Nucleus Accumbens	Deactivation with happy faces[31]

Table 2

Participant Characteristics and Behavioral Results

	High-Risk Girls			Low-Risk Girls		
Variable	**Mean**	**SD**	**%**	**Mean**	**SD**	**%**
Caucasian			69			77
Age (years)	12.21	1.7		12.65	1.4	
WISC-IV	52.5	6.4		50.7	7.8	
CDI-S*	1.46	1.33		0.62	0.65	
MASC	33.25	11.1		38.6	13.8	
Tanner (breast)	3.33	1.23		3.08	1.08	
Tanner (hair)	3.33	1.07		3.00	1.35	
Menses (% Yes)			44			56
BDI-II (Mother)*	15.1	12.5		1.83	2.17	
Number of MDD Episodes (Mother)*	6.42	4.96		0	0	
Hit Rate (% overall)	87	7		86	9	
Reaction Time (overall msec)	250	41		261	38	

* $p \leq 0.05$

Table 3

Areas of increased activation in response to contrasts of interest

Contrast	Region	BA	Side	X RL	Y AP	Z IS	Between Groups *t*	Vox	*d*	Low-Risk *t*	High-Risk *t*
Anticipation of Gain vs. Non-incentive											
(Gain-Non-incentive Anticipation)											
High-Risk > Low-Risk	Insula	13	R	38	−15	8	−3.24	18	1.27	−3.459	0.808
Low-Risk > High-Risk	Putamen		L	−19	0	4	3.84	17	1.51	5.535	0.406
	Insula	13	L	−34	−11	16	3.61	12	1.42	2.304	−2.865
Anticipation of Loss vs. Non-incentive											
(Loss-Non-incentive Anticipation)											
Low-Risk > High-Risk	Lentiform Nucleus/ Globus Pallidus		L	−18	0	7	3.81	74	1.49	3.831	−1.855
	Mid Cingulate Gyrus	24	L	− 4	4	27	2.94	16	1.15	3.189	−0.923
Outcome of Gain vs. Nongain											
(Gain-Nongain Outcome)											
Low-Risk > High-Risk	Ant Cingulate Gyrus	32	R	11	19	27	4.44	144	1.74	2.974	−1.103
	Post Cingulate Gyrus	23	L	0	−26	31	4.41	83	1.73	2.735	−2.705
	Mid Cingulate Gyrus	24	L	−11	4	34	4.45	47	1.75	3.753	−0.919
	Putamen/ Lentiform Nucleus		L	−23	−4	4	3.50	17	1.37	1.900	−1.670
	Ant Cingulate Gyrus	32	L	−4	19	42	2.90	13	1.14	1.860	−2.400
	Ant Thalamic Nucleus		R	8	−4	12	3.35	11	1.31	1.567	−2.034
	Ant Cingulate Gyrus	32	L	−11	34	19	4.72	11	1.85	0.972	−3.130
Outcome of Loss vs Nonloss											
(Loss-Nonloss Outcome)											
High-Risk > Low-Risk	Cingulate Gyrus		L	0	23	27	−2.93	10	1.15	0.525	3.280
Low-Risk > High-Risk	Caudate		R	17	19	1	4.30	15	1.69	1.262	−3.306

Contrast	Region	BA	Side	X RL	Y AP	Z IS	Between Groups *t*	Vox	*d*	Low-Risk *t*	High-Risk *t*
	Putamen		L	−15	15	−7	2.90	11	1.14	0.236	−2.943

Activations with greater than 10 contiguous voxels reported, thresholded at p= .05. R = right; L = left; BA = Brodmann's Area; Coordinates are in Talaraich-Tournoux space; x, y, z coordinates refer to left/right (x: negative = right), anterior/posterior (y: negative = anterior), and inferior/superior (z: negative = inferior); Max t indicates *t* score at the peak activation of each loc; Vox indicates number of voxels in cluster; *d* indicates effect size (Cohen's *d*).