ORIGINAL ARTICLE

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

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Context: Deficits in reward processing and their neural correlates have been associated with major depression. However, it is unclear 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 diagnosable disorder.

Design: Comparison of neural activity among children at low and high risk for depression as they process reward and loss.

Setting: University functional magnetic resonance imaging facility.

Participants: Thirteen 10- to 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 using functional magnetic resonance imaging, 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 showed 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 before the onset of depressive symptoms. Longitudinal studies are needed to examine whether these characteristics predict the subsequent onset of depression.

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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,[1-3] 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 (**Table 1**). In unselected samples of participants, studies using functional magnetic resonance 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 have found loss anticipation and outcomes to be associated with activation in the insula and the caudate[13,14] and with deactivation in the mesofrontal cortex.[8,9] Regions such as the insula may have a role in 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 the dorsal anterior cingulate cortex (dACC), which is 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.

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In contrast, Eshel et al[19] found greater activation in the orbitofrontal cortex or ventrolateral prefrontal cortex and dACC 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 adults and children with depression. Knutson et al[21] examined patterns of neural activation in individuals diagnosed as having MDD as they anticipated and received monetary reward and punishment. In contrast to never-depressed control subjects, who exhibited dACC activation during anticipation of loss, participants with depression 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 adults with depression 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, adults with depression 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 as having MDD exhibited less activation in the anterior cingulate cortex (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 1-year follow-up assessment. In 2 subsequent studies, Forbes et al[26,27] found depression in children to be associated with reduced activation in reward-related brain areas during anticipation of reward and during reward outcome. Specifically, children with depression exhibited blunted responses in the ACC, bilateral caudate, and orbitofrontal cortex when anticipating and receiving reward. Forbes et al[27] replicated their findings of reduced striatal responding in children with depression during reward anticipation and outcome but also found greater activation among these participants in the dorsolateral and medial prefrontal cortex.

Therefore, it seems that adults and children with depression are characterized by unique patterns of neural activity during the processing of reward stimuli. However, the role of this neural functioning in the course of depression is unclear. For example, it is possible that neural or behavioral anomalies in reward responsivity are present before the first onset of a depressive episode and represent a vulnerability factor that has 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% of the offspring of mothers with depression will develop depression.[28-30] Therefore, 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 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 before 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 when passively viewing fearful faces and lower nucleus accumbens activation when viewing happy faces. However, no studies to date 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 past or current psychopathologic conditions. Because investigators have reported sex differences in the transmission and recurrence of depression in children,[27] in the present study we examined neural functioning in care-

Table 1. Overview of Neural Patterns of Activation and Deactivation in Response to Reward and Loss

Significant Region	Finding of Activation or Deactivation
Unselected Samples	
Striatum	Activation with reward,[8-10] deactivation of caudate with loss[13,14]
Insula	Activation with reward[8,9,11,12] and with loss[13,14]
Thalamus	Activation with reward[8,9,11,12]
Dorsal midbrain	Activation with reward[8,9,11,12]
Mesiofrontal cortex	Deactivation with loss[8,9]
Healthy Adults vs Healthy Children	
Nucleus accumbens	Activation in adolescents greater than in children and adults[18]
Orbitofrontal cortex or ventrolateral prefrontal cortex	Activation in adults greater than in adolescents[19]
Dorsal anterior cingulate cortex	Activation with reward,[21] deactivation with reward[22]
Adults With MDD	
Nucleus accumbens or ventral striatum	Deactivation with reward outcomes[22-24]
Caudate	Deactivation with reward outcomes[22]
Midbrain	Deactivation with reward[23]
Hippocampus	Deactivation with reward[23]
Anterior cingulate cortex	Deactivation with reward[26,27]
Medioorbitofrontal 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]

Abbreviation: MDD, major depressive disorder.

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fully 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 psychopathologic conditions. Drawing on findings obtained among individuals with depression,[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, when anticipating and receiving gains. We further predicted 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 past or current *DSM-IV* Axis I disorder. Thirteen girls had biological mothers with a history of recurrent MDD during their daughters' 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, Stanford, California. The mothers' responses to a telephone interview established that mothers and daughters were fluent in English, that daughters were between the ages 10 and 14 years, and that daughters were unlikely to have past or current psychopathologic conditions. 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) 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 *DSM-IV* Axis I Disorders (SCID)[33] to the mothers. To assess interrater reliability, an independent trained rater evaluated 30% of the K-SADS-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 interrater reliability.

Daughters in the high-risk group were eligible to participate in the study if (1) 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 (2) their mothers met *DSM-IV* criteria for at least 2 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. Daughters in the low-risk group were eligible to participate if (1) they did not meet criteria for any past or current Axis I disorder based on both the parent and child K-SADS-PL and (2) their mothers did not meet criteria for any past or current Axis I disorder.

To ensure that the 2 groups of girls did not differ in current levels of depressive symptoms, 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 years. Level of maternal depression was measured by the Beck Depression Inventory.[35] Levels of anxiety were assessed by administering the Multidimensional Anxiety Scale for Children[36] to the mothers and the Anxiety Sensitivity Index for Children[37] 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 imaging procedure was similar to the monetary incentive delay (MID) task described by Knutson et al.[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 imaging system. Participants were trained before imaging to test for explicit cue comprehension and were shown the prizes they could win during the task before entering the imaging system.

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 six-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 should 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 or square), lines within the cue signaled how much the trial was worth (1 line [1 point] or 2 lines [5 points]). Therefore, the following 5 possible cues were included in the anticipation phase that indicated whether participants should make a button press and the point level for that trial: (1) circle with 1 line (1 point), (2) circle with 2 lines (5 points), (3) square with 1 line (–1 point), (4) square with 2 lines (–5 points), or (5) triangle representing no response (0 points). During the feedback phase, for each trial participants received feedback about whether 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 nonincentive trials. Each cue type (circle, square, or triangle) appeared 20 times, and trial types were pseudorandomly distributed across the run. The cue during the anticipation phase was displayed for 250 milliseconds. Following the cue and a varying anticipation period (2000-2500 milliseconds), a target of varying duration was presented (250-350 milliseconds, determined from pilot testing to result in 75% accuracy), and participants were required to press a button as quickly as possible (circle or square) or to 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

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was exactly 6 seconds. The feedback phase informing participants whether they had lost or won points was displayed for 1650 milliseconds.

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 (ie, 1 and 5 points) were combined, as were trials presenting anticipation of loss cues. For the anticipation phase, trials with gain (circle) or loss (square) cues were compared with nonincentive trials (triangle). For the feedback phase, trials in which participants gained points were compared with nongain feedback trials, and trials in which participants lost points were compared with nonloss trials.

Functional Magnetic Resonance Imaging Data Acquisition and Analysis

Imaging was conducted on a 1.5-T imaging system (Signa; GE Medical Systems, Milwaukee, Wisconsin). Functional images were acquired using a T2-weighted spiral in/out pulse sequence[40] using the following parameters: 83-millisecond repetition time per section, 40-millisecond echo time, 90° flip angle, 24-cm field of view, and 2000-milliseconds acquisition time per frame, consisting of 24 sequential axial sections (3.75-mm^2 in-plane resolution, 3-mm through-plane resolution, and 1-mm gap). High-resolution structural images were obtained using a T1-weighted spoiled gradient-recalled acquisition in a steady state sequence (1-mm^2 in-plane resolution, 1.5-mm through-plane resolution, 7 ms echo time, and 15° flip angle).

Preprocessing and analysis of functional magnetic resonance (fMR) imaging data were conducted using software (Analysis of Functional Neural Images [AFNI]; National Institutes of Health, Bethesda, Maryland).[41] Time series data were section time corrected relative to the most ventroaxial section and were volume registered to correct for head translation and rotation during the image (2-pass Fourier interpolation). BOLD time series with sudden motion exceeding 2.0 mm were corrected using a software program (ArtRepair; Center for Interdisciplinary Brain Sciences Research, Stanford University)[42]; in this procedure, a subject's raw functional data were converted to statistical parametric mapping format (SPM Analyze; Wellcome Trust Centre for Neuroimaging, London, England), processed with ArtRepair (in MATLAB 7.3; MathWorks, Inc, Natick, Massachusetts), and then converted back to AFNI format for further processing. Data were spatially smoothed with a 4-mm gaussian smoothing kernel, band-pass filtered (0.011-Hz high-pass threshold and 0.15-Hz low-pass threshold), and normalized to percentage signal change. Functional images were coregistered to anatomic images and transformed into Talairach space.

STATISTICAL ANALYSIS

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

Preprocessed time series data for each individual were analyzed using the AFNI-based multiple regression program 3dDeconvolve. The regression model included the following 7 orthogonal regressors of interest: anticipation of gain, anticipation of loss, nonincentive, gain outcomes, nongain outcomes, nonloss outcomes, and loss outcomes. Nuisance covariates included in the model were 3 translational and 3 rotational head motion estimates and 6 regressors modeling zero- 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 vs nonincentive, anticipation of loss vs nonincentive, gain vs nongain outcomes, and loss vs nonloss outcomes.

For each contrast of interest, contrast coefficients for each group were compared by performing 2-sample *t* tests on a voxelwise basis within a mask constructed of several regions of interest. 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 were selected within the AFNI program. They included the caudate, putamen, globus pallidus, amygdala, cingulate cortex, medial prefrontal cortex, hippocampus, insula, thalamus, and hypothalamus. Together, these structures yielded a single mask composed of 2710 isotropic voxels (3.75 mm each). The voxel-level significance ($P=.05$) and cluster size ($k=10$) criteria used to hold familywise error at $P=.05$ were calculated using the AFNI program AlphaSim. This program generates null hypothesis distributions and corresponding statistical criterion values using Monte Carlo simulation. Parameters known to affect the shape of null hypothesis distributions of fMR imaging 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.

Table 2. Participant Characteristics and Behavioral Results

Variable	High-Risk Girls	Low-Risk Girls
White race/ethnicity, % (No./total No.)	69 (9/13)	77 (10/13)
Age, mean (SD), y	12.2 (1.7)	12.7 (1.4)
Wechsler Intelligence Scale for Children–IV vocabulary score, mean (SD)	52.5 (6.4)	50.7 (7.8)
Children's Depression Inventory score, mean (SD)[a]	1.5 (1.3)	0.6 (0.7)
Multidimensional Anxiety Scale for Children score, mean (SD)	33.3 (11.1)	38.6 (13.8)
Tanner breast score, mean (SD)	3.3 (1.2)	3.1 (1.1)
Tanner hair score, mean (SD)	3.3 (1.1)	3.0 (1.4)
Menses, %	44	56
Beck Depression Inventory score of mother, mean (SD)[a]	15.1 (12.5)	1.8 (2.2)
MDD episodes of mother, mean (SD)[a]	6.4 (5.0)	0
Hit rate overall, mean (SD), %	87 (7)	86 (9)
Reaction time overall, mean (SD), milliseconds	250 (41)	261 (38)

Abbreviation: MDD, major depressive disorder.
[a] $P \leq .05$.

RESULTS

PARTICIPANT CHARACTERISTICS

Demographic and clinical characteristics of the 2 participant groups are given in **Table 2**. No significant differences were noted between the 2 groups in age ($t_{24}=0.72$), Wechsler Intelligence Scale for Children–IV vocabulary score ($t_{24}=0.66$), Multidimensional Anxiety Scale for Children score ($t_{21}=1.04$), Anxiety Sensitivity Index for Children score ($t_{24}=0.68$), Tanner breast score ($t_{22}=0.52$), Tanner hair score ($t_{22}=0.67$), percentage of participants who were postmenarche ($\chi^2_{18}=0.63$), or race/ethnicity ($\chi^2_{26}=3.05$) ($P>.05$ for

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Table 3. Areas of Increased Activation in Response to Contrasts of Interest

Region	Brodmann Area	Side	x RL	y AP	z IS[a]	Between-Group Maximum *t*	No. of Voxels in Cluster[b]	Cohen *d*	Low-Risk *t*	High-Risk *t*
Anticipation of Gain vs Nonincentive										
High-risk > low-risk contrast										
Insula	13	R	38	–15	8	–3.24	18	1.27	–3.459	0.808
Low-risk > high-risk contrast										
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 Nonincentive (Low-Risk > High-Risk Contrast)										
Lentiform nucleus or globus pallidus		L	–18	0	7	3.81	74	1.49	3.831	–1.855
Midcingulate gyrus	24	L	–4	4	27	2.94	16	1.15	3.189	–0.923
Outcome of Gain vs Nongain (Low-Risk > High-Risk Contrast)										
Anterior cingulate gyrus	32	R	11	19	27	4.44	144	1.74	2.974	–1.103
Posterior cingulate gyrus	23	L	0	–26	31	4.41	83	1.73	2.735	–2.705
Midcingulate gyrus	24	L	–11	4	34	4.45	47	1.75	3.753	–0.919
Putamen or lentiform nucleus		L	–23	–4	4	3.50	17	1.37	1.900	–1.670
Anterior cingulate gyrus	32	L	–4	19	42	2.90	13	1.14	1.860	–2.400
Anterior thalamic nucleus		R	8	–4	12	3.35	11	1.31	1.567	–2.034
Anterior cingulate gyrus	32	L	–11	34	19	4.72	11	1.85	0.972	–3.130
Outcome of Loss vs Nonloss										
High-risk > low-risk contrast										
Cingulate gyrus		L	0	23	27	–2.93	10	1.15	0.525	3.280
Low-risk > high-risk contrast										
Caudate		R	17	19	1	4.30	15	1.69	1.262	–3.306
Putamen		L	–15	15	–7	2.90	11	1.14	0.236	–2.943

Abbreviations: AP, anterior/posterior; IS, inferior/superior; RL, right/left.
[a] Coordinates are in Talairach-Tournoux space; x, y, z coordinates refer to right/left (x: negative = right), anterior/posterior (y: negative = anterior), and inferior/superior (z: negative = inferior).
[b] Activations with greater than 10 contiguous voxels reported at a threshold of $P = .05$.

all). The mothers of the high-risk girls reported significantly higher Beck Depression Inventory scores than did the mothers of the low-risk girls (Table 2) ($t_{24} = 3.28$, $P < .01$). The high-risk girls obtained significantly higher scores on the CDI-S than did the low-risk girls ($t_{24} = 2.06$, $P = .05$). However, it is important to note that the mean CDI-S score for the high-risk group (1.5) was well below the cutoff 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, 1 mother of a daughter in the high-risk group was diagnosed as having past obsessive-compulsive disorder, 1 as having past posttraumatic stress disorder and panic disorder, and 1 as having past bulimia and specific phobia.

BEHAVIORAL FINDINGS

The 2-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 ($P > .05$ for all), indicating comparable performance of the 2 groups on the task. These results are summarized in Table 2.

NEUROIMAGING FINDINGS

No significant associations were obtained between the neuroimaging findings and pubertal stage, task performance, participants' current depressive symptoms, or level of maternal symptoms. Group analyses comparing low- vs high-risk participants yielded the following results (**Table 3** and **Figure**).

Anticipation of Gain vs Nonincentive

In response to anticipation of gain, low-risk participants exhibited greater activation than did high-risk participants in the left putamen and in the left insula. High-risk daughters exhibited greater activation than did low-risk daughters within the right insula.

Anticipation of Loss vs Nonincentive

During anticipation of loss, low-risk participants showed greater activation than did their high-risk counterparts within the left lentiform nucleus or globus pallidus and the left midcingulate gyrus (Brodmann area [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 several foci to a greater degree than did their high-risk counterparts, including the left putamen or lentiform nucleus, multiple regions within the cingulate gyrus (BAs 32, 24, and 23), and the right anterothalamic nucleus. High-risk participants did not display greater activation in any regions compared with low-risk participants.

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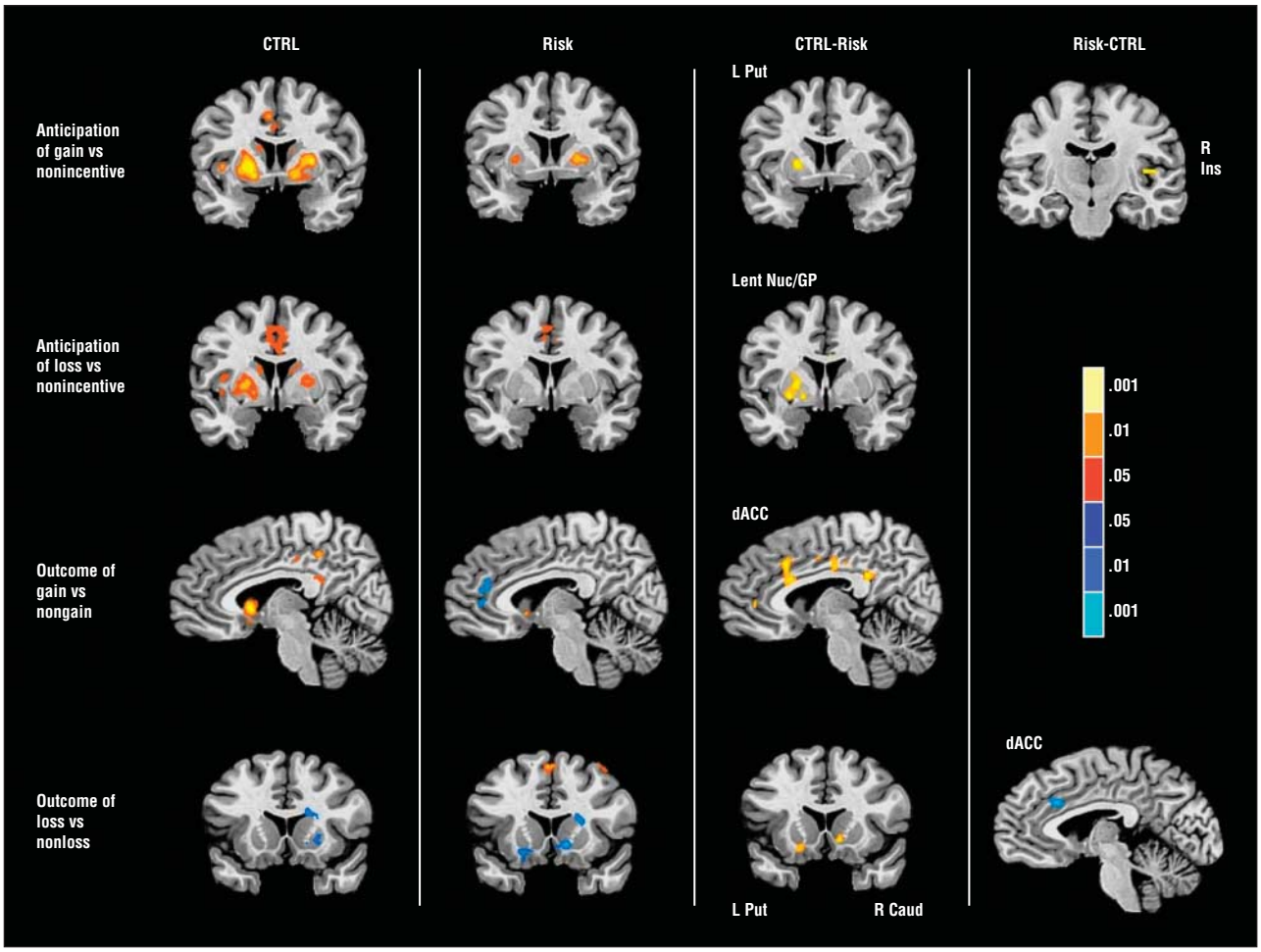

Figure. Activations (yellow) and deactivations (blue) within the groups of low-risk control (CTRL) and high-risk (Risk) daughters (2 left columns). Contrasts in the 2 right columns depict regions of activation comparing CTRL-Risk and Risk-CTRL (blue and yellow correspond with activation in the Risk-CTRL comparison). No between-group deactivations were identified. Activations with more than 10 contiguous voxels are reported at a threshold of $P=.05$. dACC indicates dorsal anterior cingulate cortex; Lent Nuc/GP, lentiform nucleus or globus pallidus; L Put, left putamen; R Caud, right caudate; and R Ins, right insula.

Loss vs Nonloss Outcomes

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

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 adolescents[26] and adults[21] with depression. 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 with the anticipation and receipt of gain and with the anticipation and receipt of loss, thereby providing an initial examination of the processing of 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 the anticipation and the receipt of reward. This finding mirrors previous work that has documented a blunting of reward-related activation in adolescents with current depression.[26] Therefore, even before the onset of a depressive disorder, high-risk daughters exhibit anomalous neural activations in response to reward stimuli. Both the present study and studies by Forbes et al[25-27] found overall reductions in activation in response to reward anticipation and outcome. In contrast, the adults with depression examined by Knutson et al[21] did not differ significantly from their nondepressed counterparts during reward anticipation. This difference may be attributable to 2 factors. First, both in the present study and in the studies by Forbes et al, points were used that were later redeemed for prizes or cash; in the study by Knutson et al, individuals played specifically for money. Money may be a stronger secondary reinforcer than are points and may actually attenuate (or override)

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depression-associated differences in activation among reward-related networks. Second, there are likely maturational differences between the developing adolescent neural system for reward and the more mature adult reward systems (Table 1). Other studies[16,18] have documented important developmental differences in the processing of reward examined across the life span. 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 4 comparisons (ie, during anticipation and outcome of reward and loss) low-risk daughters exhibited more regional activations than did high-risk daughters. The high-risk daughters showed greater activations in 2 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] However, Preuschoff et al[48] recently documented a unique contribution of the right insula during risk prediction error (ie, errors associated with predicting an uncertain outcome that may motivate subsequent behavioral adjustments). In this context, the insula has been posited to have 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 use 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 the dACC during reward outcomes suggests a general reduced sensitivity to reward or a diminished capacity to integrate reward outcomes over time in individuals at risk for depression. In contrast, the recruitment of the 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 seems that the reward processing system is critically impaired in daughters who are at elevated risk for depression, although they have not yet experienced a depressive episode. Moreover, high-risk daughters seem to have difficulty in being able to appropriately recruit the 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 children with depression 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 2 incentive levels may reflect anomalies in participant motivation but is also likely due to the fact that having only 2 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 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. Fifth, although 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.

In 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 the striatum and dACC during processing of reward and loss. Most important, we also document a prominent role of the insula as an index of 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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REFERENCES

1. Allen NB, Trinder J, Brennan C. Affective startle modulation in clinical depression: preliminary findings. *Biol Psychiatry*. 1999;46(4):542-550.
2. Sloan DM, Strauss ME, Quirk SW, Sajatovic M. Subjective and expressive emotional responses in depression. *J Affect Disord*. 1997;46(2):135-141.
3. Sloan DM, Strauss ME, Wisner KL. Diminished response to pleasant stimuli by depressed women. *J Abnorm Psychol*. 2001;110(3):488-493.
4. Rottenberg J, Kasch KL, Gross JJ, Gotlib IH. Sadness and amusement reactivity differentially predict concurrent and prospective functioning in major depressive disorder. *Emotion*. 2002;2(2):135-146.
5. Berenbaum H, Oltmanns TF. Emotional experience and expression in schizophrenia and depression. *J Abnorm Psychol*. 1992;101(1):37-44.
6. Henriques JB, Davidson RJ. Decreased responsiveness to reward in depression. *Cogn Emotion*. 2000;14(5):711-724.
7. Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *J Psychiatr Res*. 2008;43(1):76-87.
8. Knutson B, Fong GW, Adams CM, Varner JL, Hommer D. Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport*. 2001;12(17):3683-3687.
9. Knutson B, Wimmer GE, Kuhnen CM, Winkielman P. Nucleus accumbens activation mediates the influence of reward cues on financial risk taking. *Neuroreport*. 2008;19(5):509-513.
10. Ernst M, Nelson EE, McClure EB, Monk CS, Munson S, Eshel N, Zarahn E, Leibenluft E, Zametkin A, Towbin K, Blair J, Charney D, Pine DS. Choice selection and reward anticipation: an fMRI study. *Neuropsychologia*. 2004;42(12):1585-1597.
11. Bjork JM, Knutson B, Fong GW, Caggiano DM, Bennett SM, Hommer DW. Incentive-elicited brain activation in adolescents: similarities and differences from young adults. *J Neurosci*. 2004;24(8):1793-1802.
12. Galvan A, Hare TA, Davidson M, Spicer J, Glover G, Casey BJ. The role of ventral frontostriatal circuitry in reward-based learning in humans. *J Neurosci*. 2005; 25(38):8650-8656.
13. Elliott R, Friston KJ, Dolan RJ. Dissociable neural responses in human reward systems. *J Neurosci*. 2000;20(16):6159-6165.
14. Wächter T, Lungu OV, Liu T, Willingham DT, Ashe J. Differential effect of reward and punishment on procedural learning. *J Neurosci*. 2009;29(2):436-443.
15. Santesso DL, Dillon DG, Birk JL, Holmes AJ, Goetz E, Bogdan R, Pizzagalli DA. Individual differences in reinforcement learning: behavioral, electrophysiological, and neuroimaging correlates. *Neuroimage*. 2008;42(2):807-816.
16. Ernst M, Nelson EE, Jazbec S, McClure EB, Monk CS, Leibenluft E, Blair J, Pine DS. Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *Neuroimage*. 2005;25(4):1279-1291.
17. Van Leijenhorst L, Westenberg P, Crone E. A developmental study of risky decisions on the cake gambling task: age and gender analyses of probability estimation and reward evaluation. *Dev Neuropsychol*. 2008;33(2):179-196.
18. Galvan A, Hare TA, Parra CE, Penn J, Voss H, Glover G, Casey BJ. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *J Neurosci*. 2006;26(25):6885-6892.
19. Eshel N, Nelson EE, Blair RJ, Pine DS, Ernst M. Neural substrates of choice selection in adults and adolescents: development of the ventrolateral prefrontal and anterior cingulate cortices. *Neuropsychologia*. 2007;45(6):1270-1279.
20. Casey BJ, Getz S, Galvan A. The adolescent brain. *Dev Rev*. 2008;28(1):62-77.
21. Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH. Neural responses to monetary incentives in major depression. *Biol Psychiatry*. 2008;63(7):686-692.
22. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry*. 2009;166(6):702-710.
23. Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD. Abnormal temporal difference reward-learning signals in major depression. *Brain*. 2008;131(pt 8):2084-2093.
24. Steele JD, Kumar P, Ebmeier KP. Blunted response to feedback information in depressive illness. *Brain*. 2007;130(pt 9):2367-2374.
25. Forbes EE, Christopher May J, Siegle GJ, Ladouceur CD, Ryan ND, Carter CS, Birmaher B, Axelson DA, Dahl RE. Reward-related decision-making in pediatric major depressive disorder: an fMRI study. *J Child Psychol Psychiatry*. 2006;47(10): 1031-1040.
26. Forbes EE, Shaw DS, Dahl RE. Alterations in reward-related decision making in boys with recent and future depression. *Biol Psychiatry*. 2007;61(5):633-639.
27. Forbes EE, Hariri AR, Martin SL, Silk JS, Moyles DL, Fisher PM, Brown SM, Ryan ND, Birmaher B, Axelson DA, Dahl RE. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am J Psychiatry*. 2009;166(1):64-73.
28. Goodman SH, Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. *Psychol Rev*. 1999;106(3):458-490.
29. Hammen C, Brennan PA, Keenan-Miller D. Patterns of adolescent depression to age 20: the role of maternal depression and youth interpersonal dysfunction. *J Abnorm Child Psychol*. 2008;36(8):1189-1198.
30. Hammen C, Brennan PA, Keenan-Miller D, Herr NR. Early onset recurrent subtype of adolescent depression: clinical and psychosocial correlates. *J Child Psychol Psychiatry*. 2008;49(4):433-440.
31. Monk CS, Klein RG, Telzer EH, Schroth EA, Mannuzza S, Moulton JL III, Guardino M, Masten CL, McClure-Tone EB, Fromm S, Blair RJ, Pine DS, Ernst M. Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. *Am J Psychiatry*. 2008;165(1):90-98.
32. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980-988.
33. First MB Sr, Gibbon M, Williams JBW. *Structured Clinical Interview for* DSM-IV *Axis I Disorders: Patient Version*. New York: New York State Psychiatric Institute; 1996.
34. Kovacs M. The Children's Depression, Inventory (CDI). *Psychopharmacol Bull*. 1985;21(4):995-998.
35. Barrera M Jr, Garrison-Jones CV. Properties of the Beck Depression Inventory as a screening instrument for adolescent depression. *J Abnorm Child Psychol*. 1988; 16(3):263-273.
36. March JS, Sullivan K. Test-retest reliability of the Multidimensional Anxiety Scale for Children. *J Anxiety Disord*. 1999;13(4):349-358.
37. Deacon BJ, Valentiner DP, Gutierrez PM, Blacker D. The Anxiety Sensitivity Index for Children: factor structure and relation to panic symptoms in an adolescent sample. *Behav Res Ther*. 2002;40(7):839-852.
38. Pastovic JJ, Guthrie GM. Some evidence of the validity of the WISC. *J Consult Psychol*. 1951;15(5):385-386.
39. Tanner JM. *Growth at Adolescence*. Oxford, England: Blackwell Scientific; 1955.
40. Preston AR, Thomason ME, Ochsner KN, Cooper JC, Glover GH. Comparison of spiral-in/out and spiral-out BOLD fMRI at 1.5 and 3 T. *Neuroimage*. 2004;21(1):291-301.
41. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res*. 1996;29(3):162-173.
42. Mazaika PK, Whitfield-Gabrieli S, Reiss AL. Artifact repair of fMRI data from high motion clinical subjects, with new results from 3D large motion correction. Paper presented at: 13th Annual Human Brain Mapping Conference; June 2007; Chicago, Illinois.
43. Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT. Automated Talairach atlas labels for functional brain mapping. *Hum Brain Mapp*. 2000;10(3):120-131.
44. Rapoport JL, Castellanos FX, Gogate N, Janson K, Kohler S, Nelson P. Imaging normal and abnormal brain development: new perspectives for child psychiatry. *Aust N Z J Psychiatry*. 2001;35(3):272-281.
45. Critchley HD, Mathias CJ, Dolan RJ. Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron*. 2001;29(2):537-545.
46. Ernst M, Bolla K, Mouratidis M, Contoreggi C, Matochik JA, Kurian V, Cadet JL, Kimes AS, London ED. Decision-making in a risk-taking task: a PET study. *Neuropsychopharmacology*. 2002;26(5):682-691.
47. Huettel SA, Song AW, McCarthy G. Decisions under uncertainty: probabilistic context influences activation of prefrontal and parietal cortices. *J Neurosci*. 2005; 25(13):3304-3311.
48. Preuschoff K, Quartz SR, Bossaerts P. Human insula activation reflects risk prediction errors as well as risk. *J Neurosci*. 2008;28(11):2745-2752.
49. Paulus MP, Stein MB. An insular view of anxiety. *Biol Psychiatry*. 2006;60(4):383-387.
50. Simmons A, Matthews SC, Stein MB, Paulus MP. Anticipation of emotionally aversive visual stimuli activates right insula. *Neuroreport*. 2004;15(14):2261-2265.
51. Holroyd CB, Coles MG. Dorsal anterior cingulate cortex integrates reinforcement history to guide voluntary behavior. *Cortex*. 2008;44(5):548-559.
52. Walton ME, Croxson PL, Behrens TE, Kennerley SW, Rushworth MF. Adaptive decision making and value in the anterior cingulate cortex. *Neuroimage*. 2007; 36(suppl 2):T142-T154.
53. Velanova K, Wheeler ME, Luna B. Maturational changes in anterior cingulate and frontoparietal recruitment support the development of error processing and inhibitory control. *Cereb Cortex*. 2008;18(11):2505-2522.
54. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci*. 2000;4(6):215-222.

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