Reward Processing in Healthy Offspring of Parents With Bipolar Disorder

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Importance Bipolar disorder (BD) is highly familial and characterized by deficits in reward processing. It is not known, however, whether these deficits precede illness onset or are a consequence of the disorder.

Objective To determine whether anomalous neural processing of reward characterizes children at familial risk for BD in the absence of a personal history of a psychopathologic disorder.

Design, Setting, and Participants This study compared neural activity and behaviors of children at high and low risk for mania while they anticipate and respond to reward and loss. The study was performed from September 15, 2009, through February 17, 2012, in a university functional magnetic resonance imaging facility and included 8- to 15-year-old children without disorders born to a parent with BD (n = 20 high-risk children) and demographically matched healthy comparison children (n = 25 low-risk children).

Main Outcomes and Measures Neural activity, as measured with functional magnetic resonance imaging, during anticipation and receipt of reward and loss during a monetary incentive delay task.

Results While anticipating losses, high-risk children had less activation in the pregenual cingulate than did their low-risk counterparts (t₁₉ = −2.44, P = .02). When receiving rewards, high-risk children had greater activation in the left lateral orbitofrontal cortex than did low-risk children (t₄₃ = −3.04, P = .004). High-risk children also had weaker functional connectivity between the pregenual cingulate and the right ventrolateral prefrontal cortex while anticipating rewards than did low-risk children (t₁₉ = −4.38, P < .001) but had a stronger connectivity between these regions while anticipating losses (t₂₄ = 2.76, P = .01). Finally, in high- but not low-risk children, novelty seeking was associated with increased striatal and amygdalar activation in the anticipation of losses, and impulsivity was associated with increased striatal and insula activation in the receipt of rewards.

Conclusions and Relevance Aberrant prefrontal activations and connectivities during reward processing suggest mechanisms that underlie early vulnerabilities for developing dysfunctional regulation of goal pursuit and motivation in children at high risk for mania. Longitudinal studies are needed to examine whether these patterns of neural activation predict the onset of mania and other mood disorders in high-risk children.

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Bipolar disorder (BD) is a debilitating disorder of motivational functioning that commonly begins during adolescence. Manic states of BD are typically characterized by increased risk-taking, novelty seeking, and impulsivity. Clinicians are frequently challenged to distinguish children who exhibit normal variants of adolescent behavior from children who engage in maladaptive forms of reward processing that are associated with mania. Given that the strongest risk factor for developing mania is a family history of BD, disturbances in core reward processing in children at familial risk for BD may provide a basis for understanding the origins of manic symptoms. Few studies, however, have examined the neural aspects of these aberrations, particularly in young offspring of parents with BD who may be predisposed to reward dysfunction even before the onset of mania.

Adults and children with BD have impaired reward learning, increased reward reactivity and greater arousal in reward conditions, greater attentional bias toward immediate rewards, and greater satisfaction with winning. Neuroimaging studies of reward processing in BD have had mixed results. Although one study found expected increases in activation in the ventral striatum during reward anticipation, another study found reduced activation in the nucleus accumbens on receipt of rewards. Other studies report increased prefrontal activations that may serve to regulate anticipation and response to reward. Singh et al found that adolescents with BD have decreased activation in the thalamus and inferior temporal gyrus while anticipating rewards and increased activations in the middle frontal gyrus and parietal cortices while anticipating losses. These studies suggest that adolescents and adults with BD have discordant behavioral and neural responses to reward, including enhanced motivation for seeking rewards and aberrant estimation of risks and punishments. However, these studies are confounded by comorbidities, medication exposures, and variable mood states. Emerging evidence also suggests that a neural network model provides the most comprehensive understanding of reward function in BD; however, to our knowledge, no studies in BD have examined the connectivities among key regions during reward processing. Additional studies are clearly needed to gain a better understanding of dysfunctional reward processing in the development of mania.

It is not clear whether previously reported neurobehavioral patterns of reward response reflect a developmental process that is more typical of children than adults, play an etiologic role in BD, or are a consequence of multiple mood episodes or medications. Another study examined whether anomalous neural processing of rewards is a trait feature found in families with BD. In individuals with BD and their relatives, reward-related increases in activations were found in the amygdala and the orbitofrontal cortex (OFC) and were associated with heightened sensitivity in response to reward and deficient prediction error signaling. These findings raise the intriguing possibility that impaired reward processing represents an early risk factor for developing BD and is a potential therapeutic target even in the absence of overt symptoms. Indeed, investigators have linked aberrant reward processing to trait impulsivity and to approach or novelty-seeking behaviors, characteristics that have been posited to be associated with BD and can lead to a more severe illness course. No study, to our knowledge, however, has examined the neural correlates of reward processing in young offspring without disorders born to parents with BD; these children may be at risk for trait impulsivity and novelty-seeking behaviors before the onset of mania.

The aim of the present study was to examine neural activations associated with reward processing in young offspring without disorders born to parents with BD. We used a monetary incentive delay task that has been used in children with and at risk for mood disorders and that reliably activates key reward neural circuitry, including medial and ventrolateral prefrontal cortices, OFC, dorsal and pregenual anterior cingulate cortex, and ventral striatum, during anticipation and receipt of rewards. On the basis of prior literature, we predicted that, compared with typically developing children at low risk for developing mania, offspring of parents with BD would have aberrations in frontostriatal activation and connectivity while processing rewards and losses. Given the likely relations between impulsivity and mania risk and between novelty seeking and mania risk, we also predicted that those high-risk participants with higher levels of trait impulsivity and novelty seeking would have greater activations in reward-related regions while processing rewards.

**Methods**

**Participants**

A total of 45 children through 15 years of age with no current or past Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) Axis I disorder participated in the study after they and their parents gave their assent and informed consent according to institutional guidelines for the protection of human subjects at Stanford University. Twenty children had one biological parent diagnosed as having bipolar I disorder (high risk), and 25 children had biological parents and first- and second-degree relatives with no history of any Axis I disorder (low risk). From September 15, 2009, through February 17, 2012, eligible children completed more extensive interviews and testing after parental written informed consent and child written assent (eMethods in the Supplement).

**Assessment of Psychiatric Health**

All participants were evaluated by semistructured clinical interviews by raters (M.K.S. and M.E.H.) masked to family history status and with established symptom and diagnostic reliability (κ>0.9) to rule out current and lifetime psychopathologic disorders (eMethods in the Supplement). To ensure that the 2 groups did not differ in levels of mania or depression in the absence of any psychiatric diagnoses, all youth were interviewed using the Young Mania Rating Scale and the Children’s Depression Rating Scale-Revised. Levels of anxiety were assessed by administering the Multidimensional Anxiety Scale for Children to the parents. Global func-
tioning was determined by the Children’s Global Assessment Scale. Level of trait impulsivity was assessed by the Barratt Impulsiveness Scale, which yielded attentional, motor, and nonplanning subscales. The Revised Dimensions of Temperament Survey was completed by all parents during euthymia about their offspring’s temperament. We focused on the Revised Dimensions of Temperament Survey approach-withdrawal score, which indexes the degree of novelty seeking (high scorers tend to approach or move toward new persons, objects, situations, or events) that may influence reward-related neural circuitry. Age, sex, socioeconomic status, pubertal stage, IQ, and handedness were also assessed.

Statistical Analysis
We administered the monetary incentive delay task during functional magnetic resonance imaging to participants, recording reaction time and accuracy on each trial. The monetary incentive delay task probes neural responses to anticipation and receipt of gains and losses using a set of cues to indicate whether participants can win or avoid losing money if they respond quickly enough to a target that follows a cue and anticipation period. Task design, functional magnetic resonance imaging data acquisition, preprocessing, and statistical analyses are detailed in the eMethods and eFigure in the Supplement.

Using a fixed-effects model in SPM8 statistical software (Wellcome Trust Centre for Neuroimaging), we computed statistical contrasts for anticipation and feedback phases of reward and loss. For anticipation, we compared trials with reward or loss cues to corresponding nonreward and nonloss trials. For feedback, we compared trials in which participants gained money to nonreward feedback trials, and we compared trials in which participants avoided losing money to nonloss trials. To examine group differences in brain activation during reward processing, we conducted a 2-way [group [high risk or low risk] by valence [reward or loss]] voxel-wise analysis of covariance for anticipation and feedback contrasts after adjusting for Young Mania Rating Scale, Children’s Depression Rating Scale–Revised, and Multidimensional Anxiety Scale for Children scores. We used a psychophysiological interaction analysis in SPM8 to evaluate functional connectivity between reward-related regions of interest from our voxel-wise analysis and the rest of the brain.

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Finally, we explored within-group correlations to examine associations among neural activations in the bilateral amygdala, insula, and NAcc regions of interest during reward processing across all conditions and trait impulsivity and novelty seeking. These regions of interest were selected based on reward findings in BD and from the existing reward literature. The region of interest significance levels were Bonferroni corrected for multiple comparisons. And, we used Fisher r-to-z transformations to determine whether the high- and low-risk groups differed significantly with respect to these within-group correlations.

Results
Participant Characteristics
Demographic and clinical characteristics are presented in the eTable in the Supplement. High-risk and low-risk children did not differ significantly with respect to age (P = .22), sex (P = .42), handedness (P = .23), IQ (P = .23), Young Mania Rating Scale score (P = .74), Children’s Depression Rating Scale–Revised score (P = .55), Multidimensional Anxiety Scale for Children score (P = .66), socioeconomic status (P = .66), or Tanner stage (P = .17).

Compared with low-risk children, high-risk children had lower Children’s Global Assessment Scale scores (t139 = 2.65, P = .01) and higher Barratt Impulsiveness Scale impulsivity subscale scores (P = .16 for the motor subscale, P = .60 for the nonplanning subscale, and P = .58 for the attention subscale), but the groups did not differ significantly with respect to these subscales. High-risk children also had higher Revised Dimensions of Temperament Survey approach-withdrawal scores (t139 = 2.68, P = .01), reflecting higher levels of novelty seeking. Between-group imaging results remained significant after covarying for these characteristics.

Behavioral Results
Two-way group-by-valence analyses of covariance of reaction times and accuracy yielded no significant main effects or interactions (P = .64, .65, .50, .38, .18, and .44 for reaction time as the main effect of group, reaction time as the main effect of valence, reaction time group-by-valence interaction, accuracy as the main effect of group, accuracy as the main effect of valence, and accuracy group-by-valence interaction, respectively) (eTable in the Supplement).

Voxel-wise Neuroimaging Results
Two-way group-by-valence analyses of variance compared voxel-wise activity of high-risk and low-risk participants in response to rewards and losses during anticipation and feedback conditions (P = .05, FWE corrected); significant effects were followed by within- and between-group post hoc t tests. Voxel-wise main effects of group, main effects of valence, and the interaction between group and valence during anticipation and feedback conditions are presented in the Table.

Anticipation
A significant interaction of group and valence was found in the pregenual cingulate during anticipation (F1,39 = 11.94, P = .001). Whereas low-risk children had greater pregenual cingulate activation during anticipation of loss than during anticipation of reward (t24 = -2.04, P = .05), high-risk children had the opposite result, with less activation in the same region during anticipation of loss than during anticipation of reward (t24 = -2.44, P = .02) (Figure 1). Low-risk children had greater pregenual cingulate activation than did high-risk children during the anticipation of loss (t139 = 2.35, P = .02) (Figure 1).
As a significant interaction of group and valence was found in the left lateral OFC during feedback ($F_{1,39} = 23.28, P < .001$) and in the bilateral OFC at a lower threshold ($P < .01$, uncorrected), high-risk children had greater left lateral OFC activation during feedback of successful rewards than during feedback of avoided losses ($t_{19} = 3.68, P = .002$), low-risk children had less activation in the same region during successful rewards than
During avoided losses ($t_{24} = -3.72, P = .001$) (Figure 2). Moreover, high-risk children had greater left lateral OFC activation in response to successful rewards than did low-risk children ($t_{24} = -3.04, P = .004$); in contrast, low-risk children had greater activation in response to avoided losses in the same region than did high-risk children ($t_{43} = 3.56, P = .001$) (Figure 2).

**Functional Connectivity Results**

Group and valence effects and interactions of voxel-wise connectivity with the pregenual cingulate during anticipation and with the left lateral OFC during feedback are presented in the Table.

**Anticipation**

Connectivity with the pregenual cingulate during anticipation yielded a significant interaction in the right ventrolateral prefrontal cortex (VLPFC) ($F_{1,39} = 20.04, P < .001$). Whereas high-risk children had less connectivity between the pregenual cingulate and right VLPFC during anticipation of reward than during anticipation of loss ($t_{19} = -4.38, P < .001$), low-risk children had greater connectivity between the same regions during anticipation of reward than during anticipation of loss ($t_{24} = 2.76, P = .005$). In addition, high-risk children had significantly greater connectivity between the pregenual cingulate and right VLPFC than did low-risk children during anticipation of loss ($t_{43} = -2.94, P = .005$) and weaker connectivity between the same regions during anticipation of gain ($t_{13} = 4.49, P < .001$) (Figure 3).

**Feedback**

No significant group or valence effects were found.
The pregenual cingulate typically functions in reward feedback in healthy offspring of mothers with depression. The pregenual cingulate during loss anticipation in high-risk children in the current study are consistent with previous investigations in patients with and at risk for BD, with some notable differences. Decreased activation in the pregenual cingulate during loss anticipation in high-risk children parallels deficits found in cingulate function during reward anticipation in euthymic adults with BD and during reward feedback in healthy offspring of mothers with depression. The pregenual cingulate typically functions in the regulation of emotion and to weigh cost against benefit in situations that require approach-avoidance decision-making.

Thus, reduced pregenual cingulate activation in high-risk youth may represent a neurobiological vulnerability that predisposes high-risk children to impaired hedonic function.

When high-risk children received feedback about receiving rewards, they activated the lateral OFC to a greater degree than did low-risk children, indicating an exaggerated prefrontal response during reward outcome. In healthy individuals, the OFC is involved in monitoring reward values, and the lateral OFC is especially likely to be activated when a response previously associated with a reward has to be suppressed, supporting its regulatory or inhibitory control function. Adults with mania have significant increases in activation in the left lateral OFC (Brodmann areas 11 and 47) while anticipating increasing rewards but not during reward outcome. Activation in the OFC, but in different conditions (anticipation vs outcome), may occur because we assessed children in this study before they experienced the typical increases in reward sensitivity during anticipation that are first observed in adolescence.

Alternatively, increased activation in the lateral OFC during reward outcome in the high-risk offspring may represent an immature or maladaptive engagement in immediate gratification. Distinguishing between this explanation and an account that suggests a regulatory response by the lateral OFC requires further investigation of how the prefrontal cortex is functionally connected during reward processing.

In our examination of prefrontal functional connectivity, we found that high-risk children aberrantly regulate their affective responses to reward. Specifically, compared with low-risk children, high-risk children had weaker connectivity between the pregenual cingulate and VLPFC during reward anticipation but stronger connectivity between these regions during anticipation of loss, suggesting impaired regulation of affect while anticipating rewards but excessive regulation while anticipating losses. The VLPFC may be functioning in synchrony with the pregenual cingulate to regulate emotional response to loss or to reinforce inhibitory control in the
context of deficient pregenual cingulate activation while anticipating losses to facilitate optimum behavior.\textsuperscript{52, 53} In contrast, VLPCF dysfunction may decrease pregenual cingulate-VLPCF connectivity, resulting in a failure to regulate emotion during reward anticipation. This explanation is consistent with other studies in individuals with\textsuperscript{54-55} and at risk\textsuperscript{56} for BD that have found VLPCF dysfunction to be associated with emotional dysregulation and mood shifts characteristic of BD.\textsuperscript{57}

In addition, high- and low-risk groups did not differ in ventrostriatal activation during reward anticipation, suggesting a lack of differential regard for reward magnitude during this condition\textsuperscript{12, 13, 28} but exaggerated prefrontal regulatory control during reward outcome.\textsuperscript{49} These findings suggest that the affective component of reward that relates to reward magnitude is less relevant to high-risk children than is prefrontally mediated reward probability and regulation. Furthermore, prefrontal dysfunction occurs in the absence of any symptoms and may precede striatal and limbic dysfunction commonly associated with BD.\textsuperscript{58-59} This finding has important implications for treatment, particularly with early-onset BD.\textsuperscript{60}

High-risk children had higher levels of trait novelty seeking than did low-risk children, suggesting heightened reward sensitivity, and trends for elevated attention, motor, and non-planning impulsivity compared with low-risk children. In high-risk children, trait novelty seeking was associated with increased striatal and amygdalar activation during loss anticipation, and trait impulsivity was associated with increased striatal and insula activation during receipt of rewards. Excessive striatal activations with reward value (anticipation) and prediction error (outcome) in children with higher trait novelty seeking parallel a study\textsuperscript{42} in adults with hypomania and suggest a mania-related enhanced perception of the value of goals that may lead to reward. Rodent models suggest that amygdala hyperactivity with novelty seeking represents a developmental vulnerability toward psychopathologic disorders.\textsuperscript{61} Finally, insula hyperactivity in response to reward outcome in more impulsive high-risk children is consistent with a bias toward an expectation of positive outcomes in decision-making situations.\textsuperscript{57} Together, these findings suggest that high-risk children with high trait novelty seeking and impulsivity have enhanced perception and representation of goal value coupled with a positive outcome expectancy bias, which could increase their risk of developing mania-related insatiable and indiscriminate reward seeking.

We should note a number of study limitations. First, we had a modest sample size; nevertheless, we found robust activation differences between groups. Second, to minimize motion artifact, only 9 replications of each trial type were presented, which may have reduced power to obtain significant effects. Third, our cross-sectional design without a bipolar comparison group did not allow us to determine whether findings in the high-risk group represented neural vulnerability (risk) vs neural adaptation (resilience). We tried to avoid comparisons in children who are in grossly different developmental stages on the bipolar continuum because of the potential for confounding from age, medication exposure, comorbidities, or mood state. Prospective studies are needed to determine reward-related vulnerabilities that predict clinical outcome. Fourth, self-report and parent questionnaires, rather than laboratory procedures, were used to assess impulsivity and temperament in children. Although there is a rich literature on how these traits impair neural responses to reward,\textsuperscript{18, 62, 63} few studies have directly examined their effect on neural predispositions for mania. Our study is the first, to our knowledge, to demonstrate the influence of trait novelty seeking and impulsivity on neural response to reward in children at risk for BD.

Conclusions

In this study, we present evidence that children without disorders born to parents with BD exhibit anomalous prefrontal function during reward processing that may represent a biomarker for developing mania. Future studies should examine the longitudinal trajectory of this dysfunction and its ability to predict the clinical onset of mania. Such research may facilitate the development of intervention strategies that use adaptive reward responses that could prevent the onset of mania.


