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Neural Correlates of Positive Emotion Processing That Distinguish Healthy Youth at Familial Risk for Bipolar Versus Major Depressive Disorder

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Abstract

Objective: Familial risk for bipolar (BD) or major depressive (MDD) disorder may lead to differential emotion processing signatures, resulting in unique neural vulnerability.

Method: Healthy offspring of a parent with BD (n=29, "BD-risk") or MDD (n=44, "MDD-risk") and youth without any personal or family psychopathology (n=28, "HC") ages 8-17 (13.64 ± 2.59) completed an implicit emotion perception functional magnetic resonance imaging task. Whole-brain voxel-wise and psychophysiological interaction analyses examined neural differences in activation and connectivity during emotion processing. Regression modeling tested for neural associations with behavioral strengths and difficulties and conversion to psychopathology at follow-up (3.71 ± 1.91 years).

Results: BD-risk youth showed significantly reduced bilateral putamen activation, and decreased connectivity between the left putamen and the left ventral anterior cingulate cortex (vACC) and the right posterior cingulate cortex (PCC) during positive-valence emotion processing compared to MDD-risk and HC (Z >2.3; p <.001). Decreased left putamen- right PCC connectivity correlated with subsequent peer problems in BD-risk (β = −2.90; p <.05) and MDD-risk (β = −3.64; p <.05). Decreased left (β = −.09; p < .05) and right putamen activation (β = −.07; p = .04) were associated with conversion to a mood or anxiety disorder in BD-risk. Decreased left putamen-right PCC connectivity was associated with a higher risk of conversion in BD-risk (HR = 8.28 , p < .01) and MDD-risk (HR = 2.31, p = .02).

Conclusion: Reduced putamen activation and connectivity during positive emotion processing appear to distinguish BD-risk youth from MDD-risk and HC youth, and may represent a marker of vulnerability.

INTRODUCTION

Identifying unique neurobiological markers that distinguish risk for bipolar disorder (BD) from risk for major depressive disorder (MDD) may be key to improving timely and accurate diagnosis and treatment. Although behavioral manifestations of BD and MDD represent distinct disruptions in emotion processing,[1] these disorders may present similarly with respect to clinical symptoms, frequently leading to misdiagnosis and improper treatment.[2] For example, youth with BD or at familial risk for BD who present with depressive symptoms are often treated with antidepressants,[3,4] which can induce a switch into mania, potentially worsening disease course.[5] Thus, elucidating reliable and early biological factors that can distinguish these disorders is of critical importance.[6] Further, identifying early biological markers could provide key insights into understanding risk and future behavioral outcomes for these distinct mood disorders.

Family history of a mood disorder is among the most important risk factors for developing a major mood disorder.[7,8] Thus, studies of child offspring of parents with mood disorders are ideally suited to investigate neural substrates that distinguish these disorders. Further, dysfunction in emotion processing underlies core clinical symptoms of both BD and MDD. The amygdala, striatum, anterior cingulate cortex (ACC), and regions of the prefrontal

cortex (PFC) comprise neural circuitry implicated in emotion processing.[9,10] Although differences in the neural circuitry of emotion processing have been observed between BD and MDD,[11-14] few studies have directly compared youth at risk for BD relative to youth at risk for MDD. Previous studies comparing youth offspring of parents with BD and youth offspring of parents with non-BD psychopathology including offspring of parents with MDD have demonstrated increased functional connectivity between the left ACC and amygdala in response to fearful faces in BD-risk youth relative to offspring of parents with non-BD psychopathology,[15] reduced right amygdala-ACC functional connectivity in BD-risk youth relative to offspring of parents within non-BD psychopathology during the implicit processing of emotional faces,[16] and increased right amygdala-left ventrolateral PFC functional connectivity for happy faces in BD-risk offspring compared to offspring of parents with non-BD psychopathology.[16] Further, studies in adults directly comparing BD to MDD suggest that certain disruptions in emotion processing may be specific to BD, including increased activation in the parahippocampal gyrus, the amygdala, and the ACC[17-19] and decreased activation in the striatum, insula, and thalmus relative to MDD.[20] These distinctions may, in part, explain why youth with BD experience more severe depression compared to youth with MDD.[21] Indeed, youth with and at familial risk for BD have demonstrated aberrant fronto-striatal function in response to fearful and happy facial expressions compared to healthy youth[22-24] including greater ACC activity when regulating attention to happy faces,[15] and abnormal functional connectivity between the ventrolateral PFC and caudate and between the amygdala and pregenual cingulate cortex.[25] Further, studies have shown that youth with BD view neutral faces as hostile[26] and show disruptions in emotion processing that are associated with psychosocial impairments, such as deficient social reciprocity and dysfunctional family relationships.[27] Thus, the interpersonal challenges observed in BD could stem from disruptions in emotion processing, such as misinterpreting facial expressions that could lead to significant impairments in socially driven behaviors.[28]

Thus, the extant literature implicates that aberrant emotion processing circuitry plays a central role in BD and MDD. Most studies to date, however, have focused on characterizing emotion processing after disorder onset. We and others have reported that aberrant brain abnormalities, such as amygdala hyperactivity and abnormal prefrontal activation and connectivity precede the onset of BD in high risk youth,[29,30] suggesting discriminability between risk status and the effects of repeated mood episodes. Although previous studies have compared youth offspring of parents with BD and youth offspring of parents with non-BD psychopathology, including unipolar MDD,[15,16] no study to date has directly compared emotion processing in BD-risk and MDD-risk, or examined whether differential neural markers of risk relate to future behavioral outcomes or risk for psychopathology. The aim of this study was to identify neural markers of emotion processing that distinguish youth at familial risk for BD (BD-risk) from youth at familial risk for MDD (MDD-risk) relative to youth without any personal or family history of psychopathology (HC). Based on prior studies,[23,24,31,32] we hypothesized that youth in the BD-risk group would demonstrate *decreased* activation in fronto-striatal reward regions while processing positive-valence (i.e., happy) facial expressions, and *increased* activation of the amygdala while processing negative-valence (i.e. fearful) facial expressions compared to MDD-risk and HC youth.

Based on previous studies,[25,33] we further hypothesized that the BD-risk group compared to the MDD-risk and HC groups would exhibit decreased striatal to frontal (VLPFC and cingulate) connectivity while processing facial expressions. Lastly, given that disruptions in emotion face processing in youth with BD are associated with significant psychosocial impairments,[27] we performed exploratory analyses to examine whether neural differences in emotion processing demonstrated between the BD-risk and MDD-risk groups prior to symptom onset were related to behavioral outcomes or conversion to psychopathology at longitudinal follow-up.

METHOD

Participants

Participants were sampled from a longitudinal study of youth at familial risk for BD and MDD. 110 youth aged 8 to 17 years without a *DSM-IV-TR Axis I* diagnosis who completed an implicit emotion face processing task were longitudinally followed in 18 month to 4 or more year intervals for 3.71 ± 1.91 years. 31 youth had at least one parent diagnosed with bipolar I disorder (BD-risk), 47 youth had at least one parent diagnosed with major depressive disorder (MDD-risk), and 32 youth had no personal or parents and first- and second-degree relatives with a history of any Axis I disorder (HC). Youth were recruited from an academic mood disorders program and from the surrounding community. Exclusion criteria for all groups included: 1) currently taking medication or receiving psychotherapy for any psychiatric disorder; 2) having a current or lifetime diagnosis of any psychiatric or substance use disorders, or neurological disorders; 3) MRI contraindications including orthodontic braces; and 4) intellectual quotient (IQ) <80 assessed by the Weschler Abbreviated Scale of Intelligence (WASI).[34] The University's Institutional Review Board approved the study, and written informed assent and consent were obtained from all youth and their parents, respectively, prior to study procedures.

Clinical Assessment and Behavioral Functioning

At baseline and follow-up, all participants were assessed for psychiatric symptoms by trained interviewers masked to family history status, to evaluate for psychiatric health at baseline and to identify psychiatric diagnoses at longitudinal follow-up. Interviews were administered separately to participants and their parents (regarding the participants) using the mood sections of the Washington University in St. Louis Kiddie-Schedule for Affective Disorders and Schizophrenia (WASH-U KSADS)[35] and the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (KSADS-PL).[36] The Structural Clinical Interview for the DSM-IV-*TR* (SCID-IV)[37] was administered to both parents to assess parental family history of mood and other psychiatric disorders. Diagnostic interviews were confirmed by a board-certified child and adolescent psychiatrist. To ensure the groups did not differ on levels of mania or depression in the absence of any psychiatric diagnoses, all youth were interviewed using the Children's Depressive Rating Scale-Revised (CDRS-R)[38] by raters blind to group status (to reduce bias in assessment) to confirm absent or low baseline depression symptom severity, and the Young Mania Rating Scale (YMRS),[39] to confirm absent or low baseline mania symptom

severity. The Children's Global Assessment Scale (CGAS)[40] was administered to assess overall global functioning.

Parents of participants completed the Strengths and Difficulties Questionnaire (SDQ)[41] at both baseline and follow-up to assess psychosocial strengths through the Prosocial Behaviors subscale and psychopathological difficulties through the subscales on Emotional Problems, Peer Problems, Conduct Problems, and Hyperactivity. If the parent with psychopathology completed the SDQ, they were euthymic or not in episode while completing the SDQ.

Implicit emotion perception task

Participants completed the *Happy Café Task*[33] within the fMRI scanner to assess implicit emotion processing. This task has been validated in youth to assess perceived valence of facial expression.[33] During this task, participants viewed images of happy, fearful, and calm facial expressions, and scrambled images presented in a block design (Figure 1). Scrambled images were created by randomly rearranging voxels of the facial expression pictures into an unrecognizable pattern. To assess *implicit* emotion processing, participants were instructed to identify the gender of the face presented by using a button box to push button 1 for female faces and button 2 for male faces, and alternating buttons 1 and 2 during the scrambled pictures blocks. Happy and fearful faces were used to probe positive- and negative- valence emotion processing, and calm faces were used as the comparison condition to subtract activation associated with happy and fearful face processing. Calm faces were selected as the comparison condition instead of neutral faces because previous studies suggested that neutral faces activate emotion processing regions such as the amygdala possibly due to neutral faces being perceived as threatening.[42] All faces were selected from the MacArthur facial expressions set ('NimStim'; http://www.macbrain.org/resources.htm). Facial expressions were balanced and matched on racial background and gender. Blocks of each facial expression and scrambled images were alternated throughout the task. Each block contained 8 different faces of the same expression presented individually for 3 seconds. This pattern was repeated 4 times. The entire task lasted 6 min and 24s. The task was presented using ePrime version 3.0 software (www.pstnet.com), which also collected reaction time and accuracy of behavioral responses.

Neuroimaging data acquisition

Before the fMRI scan, participants were familiarized with the scanning environment and trained to minimize head motion using a mock scanning procedure. MRI images were acquired on a 3 Tesla GE Signa scanner (General Electric Co., Milwaukee, WI) using an 8-channel head coil. High resolution anatomical images were acquired to optimize normalization of functional images to a standard template (3D FSPGR pulse sequence; TR = 8.5 ms, TE = 3.32 ms, TI = 400 ms, flip angle = 15°, field of view = 25.6 cm, 186 slices in the axial plane, resolution=1 cubic millimeters). Functional images were collected using a spiral in-out pulse sequence[43] with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 80°, field of view (FOV) = 22 cm, number of slices = 30 slices in the axial plane, and slice thickness = 4 mm with a gap of 1 mm. A high-order shim was used to improve field homogeneity.

Neuroimaging Preprocessing Steps

Preprocessing was completed using the fMRI Expert Analysis Tool (FEAT) function in FMRIB's Software Library (FSL)[44] and included slice-timing correction, motion correction with MCFLIRT, brain extraction, smoothing with a Gaussian filter (5 mm full width at half-maximum) and volume registration to MNI152 standard space. Participants were excluded due to motion if their absolute or relative mean displacements exceeded 2 mm or more than one-third of volumes had values for spatial standard deviation of successive difference images (DVARS) exceeding the threshold of the 75th percentile plus 1.5 times the interquartile range. Individual participants' first level analyses were performed using FEAT in FSL.

Whole-brain fMRI Data Analysis

Functional data were processed using FSL. For individual subject statistical maps, the timeseries of each voxel was modeled with a general linear model (GLM). Happy, fear, and calm conditions were modeled as regressors of interest. Scrambled blocks and 24 motion correction parameters were included as regressors of non-interest. We also included time points that exceeded the DVARS motion threshold of 75th percentile plus 1.5 times the interquartile range as regressors of non-interest to remove the effects of these timepoints in our analyses.[44] Group comparisons were conducted with voxelwise whole-brain F-tests using FSL's FLAME (FMRIB's analysis of mixed effects),[45] covarying for sex, mean-centered age, and mean-centered CDRS-R scores for the following contrasts: Happy > Calm and Fear > Calm. Statistically significant clusters were identified by thresholding Z-statistic images ($Z > 2.3$) with a FWE-cluster corrected probability of $p < .05$.[46] We extracted mean parameter estimates from significant clusters using fslmeants to determine the direction of activation differences. As an exploratory analysis, we also conducted follow-up two-group comparisons to examine emotion processing differences between high-risk (BD-risk + MDD-risk) and low-risk (healthy controls) participants (Supplement 1:S1, see Table S1, available online). We also conducted exploratory whole-brain fMRI analyses to examine sex differences in emotion processing (Supplement 1:S2, see Figure S1, available online).

Psychophysiological interaction (PPI) analyses

Psychophysiological interaction (PPI) analyses were conducted in FEAT to examine group differences in context-dependent functional connectivity associated with the processing of happy (vs. calm) faces. PPI analyses were conducted using the left putamen and the right putamen as seed regions of interest (ROI). These ROIs were selected because they exhibited significant group differences during Happy > Calm within our primary fMRI whole-brain analysis. ROIs were anatomically defined using FSL's Harvard-Oxford Subcortical Structural Atlas and transformed into individual subject space to create masks. Mean temporally filtered timeseries for each individual were then extracted from each ROI. Within each GLM analysis, the time course for each seed region was entered as a regressor of interest in addition to the main effect of task regressor and an interaction regressor. The interaction regressor was computed as the product of the mean extracted timeseries for the seed ROIs and our contrasts of interest: Happy > Calm. We also included the other original task regressor, fear, scrambled blocks, and 24 motion correction parameters as regressors of

non-interest. Similar to our whole-brain analyses, we included time points that exceeded the DVARS motion threshold calculated as regressors of non-interest to remove the effects of these timepoints in our analyses. Group comparisons were conducted using FLAME in FSL, covarying for sex, mean-centered age, and mean-centered CDRS-R scores. Significant group differences were identified using a threshold of $Z > 2.3$ with a FWE-cluster corrected significant threshold of $p < .05$.[46] A post-hoc Bonferroni correction was then applied for testing two seed regions ($p = .05/2$) for a final adjusted p value of $< .025$. Mean parameter estimates from significant PPI clusters were then extracted using fslmeants to determine the direction of group differences.

Statistical Analyses of Clinical and Behavioral data

All statistical analyses were conducted using SPSS Version 25 and R Version 3.6. We conducted one-way analyses of variance (ANOVAs) to test for a main effect of group in clinical and behavioral characteristics based on scores from the WASI, CDRS-R, YMRS, CGAS, and SDQ. We also conducted repeated measures ANOVAs to test for a main effect of group on change from baseline to follow-up on the SDQ.

We performed secondary hypothesis-generating linear regression analyses within the BD-risk and MDD-risk groups incorporating age, gender, and baseline SDQ scores as covariates, to explore whether activation or connectivity within regions of emotion processing circuitry that significantly differed between BD-risk and MDD-risk were associated with behavioral outcomes assessed using the SDQ at follow-up. Further, we performed exploratory logistic regression analyses, with age and gender as covariates, within the BD-risk and MDD-risk groups to test whether activation or connectivity within emotion processing regions that significantly differed between BD-risk and MDD-risk were associated with conversion status (i.e., development of a *DSM-IV* Axis I psychiatric diagnosis) at follow-up. We applied a false discovery rate (FDR) correction for multiple tests to account for testing six regressions (5 linear regressions and 1 logistic regression) in each group. To account for variability in longitudinal follow-up, we ran cox regression analyses with age and gender as covariates within the BD-risk and MDD-risk groups to examine whether a decrease in brain region activation or connectivity was associated with a greater risk of conversion (variables did not violate linearity in the logit or proportional hazards). As an exploratory analysis, we also examined age-varying differences during emotion processing and interactions between age and group (Supplement 1:S3, available online).

RESULTS

Participant Demographics and Clinical Characteristics

From the original 110 participants included in this study, four participants from the HC group, two participants from the BD-risk group, and three participants from the MDD-risk group were excluded due to excessive head motion in the scanner. Thus, the final sample consisted of 29 BD-risk, 44 MDD-risk, and 28 HC youth.

Participant demographic, clinical, and behavioral characteristics, as well as psychiatric diagnoses at follow-up are presented in Table 1. There were no significant group differences

in age, length of follow-up, IQ, ethnicity, YMRS score, motion artifact, or task accuracy and reaction time (all $ps > .05$). The three groups significantly differed in baseline CGAS scores ($p < .01$). Post hoc t-tests revealed that the BD-risk and MDD-risk groups had significantly lowered CGAS scores compared to the HC group (both $ps < .01$) and there were no significant differences between the BD-risk and MDD-risk group ($p = .93$). The three groups also significantly differed on baseline CDRS-R scores ($p = .04$). Post hoc t-tests revealed that youth in the BD-risk group had significantly higher CDRS-R scores compared to the HC group ($p = .04$); however, CDRS-R scores within the BD-risk group were below clinically meaningful thresholds (e.g. CDRS-R scores of 30 or above) (mean = 22.75, SD = 8.23). There were no significant differences in CDRS-R scores between the BD-risk and MDD-risk groups ($p = .98$) or between the MDD-risk and HC groups ($p = .20$). There were no significant differences between the three groups at baseline on all the subscales of the SDQ (all $ps > .05$). There was a significant group difference for follow-up SDQ Emotional Problems, $F(2,72) = 3.49$; $p = .04$, and Conduct Problems, $F(2,73) = 3.41$; $p = .04$. Post hoc t-tests revealed the BD-risk and MDD-risk groups had significantly higher scores for follow-up SDQ Emotional Problems (BD-risk vs HCs: $t(44) = 2.36$; $p = .02$; MDD-risk vs HCs: $t(47) = 2.76$; $p = .01$) and Conduct Problems (BD-risk vs HCs: $t(45) = 2.44$; $p = .02$; MDD-risk vs HCs: $t(48) = 2.44$; $p = .02$) compared to HCs. The BD-risk and MDD-risk did not statistically differ on follow-up SDQ Emotional and Conduct Problems subscale scores ($ps > .05$). There were no other group differences at follow-up on the Prosocial, Peer Problems, or Hyperactivity SDQ subscales (all $ps > .05$).

We also explored whether there were significant between-group differences in change in SDQ from baseline to follow-up. There was a significant group difference in SDQ Peer Problems changes from baseline to follow-up, $F(2,45) = 3.45$; $p = .04$. Post-hoc analyses revealed that the MDD-risk group had a significantly greater increase than the HC group ($p = .04$). There were no other significant group differences in change from baseline to follow-up on other SDQ subscales (all $ps > .05$).

Happy Café Task performance

There were no significant differences in task accuracy among the BD-risk, MDD-risk, and HC groups when implicitly viewing happy faces, $F(2,99) = .69$, $p = .51$), fearful faces, $F(2,99) = .78$, $p = .46$), or calm faces, $F(2,99) = .11$, $p = .90$. There were no significant differences in response time among the groups for happy faces, $F(2,99) = .69$, $p = .51$, fearful faces, $F(2,99) = 1.04$, $p = .36$, or calm faces, $F(2,99) = 1.02$, $p = .37$.

FMRI whole brain voxel-wise results for Happy Café Task

The BD-risk group showed significantly decreased activation in the left and right putamen compared to MDD-risk and HC groups when processing positive-valence emotional expressions (i.e. *happy faces*), shown in Figure 2A and Table 2. There were no significant differences in brain activation among the groups when processing negative-valence emotional expression (i.e., *fearful faces*)

Functional connectivity of Left and Right Putamen for Happy Café Task

Functional connectivity results are shown in Figure 2B and Table 2. When viewing happy faces, the BD-risk youth showed decreased left putamen connectivity with the vACC and decreased left putamen connectivity with the right PCC compared to MDD-risk and the HC youth. There were no significant group differences in left putamen connectivity between the MDD-risk and HC groups. No regions had significant functional connectivity with the right putamen.

Relation between baseline emotion processing, behavior, and conversion at follow-up

Linear regression results are shown in Table 3. Within the BD-risk group, decreased connectivity between the left putamen and right PCC was significantly associated with increased SDQ Peer Problems at follow-up ($\beta = -2.90$; $p < .05$, FDR-corrected). Within the MDD-risk group, decreased connectivity between the left putamen and right PCC was significantly associated with increased peer problems $\beta = -3.64$; $p = .03$, FDR-corrected) and increased connectivity between the left putamen and right PCC was significantly associated with increased SDQ Prosocial Behaviors ($\beta = 4.26$; $p = .03$, FDR-corrected). No other significant behavioral associations between neural activation and connectivity and follow-up SDQ scores were observed (all ps > .05).

Within the BD-risk group, decreased right ($\beta = -.09$; $p < .05$) and left ($\beta = -.07$; $p = .04$) putament activation were significantly associated with conversion to any *DSM-IV* Axis I disorder at follow-up (summarized in Table 1). Left putamen-vACC and left putamen- right PCC connectivity were not associated with conversion status at follow-up in the BD-risk group. Left and right putamen activation and left putamen-ACC and left putamen-right PCC connectivity were not associated with conversion status at follow-up for either the MDD-risk or HC groups (all *p*s > .05) (Table 3). Logistic regressions did not survive FDR-correction for multiple comparisons. Our cox regression models demonstrated that a one standard deviation unit decrease in left putamen-right PCC connectivity was associated with an increased risk of converting to a mood or anxiety disorder within the BD-risk group (HR = 8.28, $p < .01$) and the MDD-risk group (HR = 2.31, $p = .02$) (Table 3).

DISCUSSION

This study identified neural markers of emotion processing that distinguish healthy youth at familial risk for BD from youth at familial risk for MDD and low-risk healthy controls. During emotion processing of positively valenced stimuli, BD-risk youth demonstrated putamen hypoactivation relative to MDD-risk and HC youth, and hypoconnectivity between the left putamen and the left ventral anterior cingulate cortex (vACC) and the left putamen and the right posterior cingulate cortex (PCC) relative to MDD-risk and HC youth. Exploratory linear regression modeling demonstrated that reduced putamen-PCC connectivity was significantly associated with subsequent peer problems within the BD-risk and the MDD-risk groups. Conversely, greater putamen-PCC connectivity at baseline was associated with increased prosocial behaviors at follow-up within the MDD-risk group but not within the BD-risk group. Lastly, baseline putamen hypoactivation was associated with clinical conversion to any *DSM-IV Axis I* disorder at longitudinal follow-up in the BD-risk

group, and decreased left putamen- right PCC connectivity within the MDD-risk and BD-risk groups was significantly associated with a decreased risk of conversion when accounting for follow-up time.

During processing of positively valenced emotional stimuli, the BD-risk group demonstrated significantly reduced bilateral putamen activation compared to MDD-risk and HC youth, suggestive of a unique biological marker for familial risk to BD. The putamen, located within the dorsal striatum, is critically involved in reward processing and relaying information about the salience of rewarding stimuli to direct motivation and goal-directed behavior.[47,48] Indeed, happy faces are among the most intrinsically rewarding natural stimuli, signaling social reward.[9] Divergent relations between depression severity and social reward response among patients with BD and MDD have been previously documented; greater depression severity significantly correlates with reduced striatum and orbitofrontal activation in response to social reward in adult bipolar disorder but not unipolar depression. [49] Despite being phenotypically healthy, blunting of putamen activation when processing positively valenced facial expressions suggests a selective impairment in deriving pleasure from intrinsically rewarding social and emotional interactions prior to symptom onset in youth at familial risk for BD. Indeed, youth with and at-risk for BD exhibit aberrant frontal and striatal activity when anticipating and processing rewards,[30,50,51] including happy faces. [22,52] Therefore, it is plausible that they find happy faces less socially rewarding.[53] Although reduced bilateral putamen activation in response to social reward (i.e., happy faces) was exclusive to youth at familial risk for BD in the present study, we note that blunted putamen activation in response to monetary rewards has been previously reported in youth at familial risk for MDD.[54,55] Thus, different types of rewards (e.g., monetary, social) may yield varying results in youth at risk for different mood disorders. Specifically, blunted putamen activity in response to socially salient positive-valence stimuli may be a risk factor unique to familial BD risk, whereas blunted putamen activity in response to monetary reward may be more characteristic of MDD-risk youth. Youth with BD may have an abnormal bias toward positive emotional stimuli during mania, but youth at risk for BD may experience extended periods of low mood states preceding the onset of mania[2,56] and have neural phenotypes that are more consistent with MDD or risk for MDD. The decreased neural responsiveness toward a reinforcing social reward could also contribute to the generation of depressive symptoms,[57,58] and could explain the differences in reward sensitivity during depressed versus hypomanic/manic mood states.[59] Indeed, putamen activity in response to rewards may be more complex than what would be expected for seemingly dissociable mood states, [60-63] emphasizing the need for future studies to examine reward-processing in youth along a clinical risk and staging continuum, and across varying mood states.

Reduced connectivity between the putamen and left vACC and between the putamen and right PCC during positively valenced emotion processing was also found in BD-risk youth, but not MDD-risk youth, relative to HC youth. The vACC is important for identifying the valence and salience of rewards, and thus drives motivation to perform behaviors necessary to attain specific rewards in the environment.[64] The PCC is a highly connected brain region that has been implicated in functions such retrieval of information relevant to salient input, consciousness, regulating the focus of attention, and awareness.[65] Baseline putamen-vACC and putamen-PCC hypoconnectivity within the BD-risk group in response to positive

valence facial expressions may reflect deficient social reward processing. For example, we could speculate that a lack of awareness of or reduced salience for positive social stimuli could herald the development of peer problems, as previously described in youth offspring of bipolar parents.[66] Conversely, baseline putamen-PCC hyperconnectivity within the MDD-risk group could result in regulated affective processing in the context of social behaviors that may reinforce social reward and increase social behavior, which has been reported to buffer against the development of depression in at-risk youth.[67] Indeed, the processing of salient social cues such as emotional facial expressions undergoes important developmental changes during adolescence.[68] Further, differences in association of social behaviors at follow-up based on baseline connectivity patterns identified in BD-risk versus MDD-risk groups could indicate that these risk groups process social reward differently. Studies that compare emotional processing in youth with depression to those yet at risk for depression are needed to further evaluate these findings.

Further, we found that the degree of bilateral putamen hypoactivation in BD-risk youth was significantly associated with an increased future risk of psychopathology, and when we accounted for differences in longitudinal follow-up time, increased left putamen-right PCC connectivity was associated with a decreased risk of conversion within the BD-risk and MDD-risk groups. These preliminary finding are consistent with prior studies that have demonstrated abnormal putamen activation and connectivity to be associated with risk status[54,55,58] and bipolar disorder.[69] Interestingly, all psychiatric diagnoses at follow up were internalizing mood or anxiety disorders, suggesting that youth at familial risk for mood disorders cluster along a spectrum of internalizing disorders.[7,70,71] Future studies with larger sample sizes are needed to replicate and expand upon these interpretations.

In contrast to our hypothesis, we did not find any significant activation differences during the processing of negative valence (i.e. fearful) emotional stimuli that distinguish youth at risk for BD from those at familial risk for MDD or healthy controls. However, when we combined BD-risk and MDD-risk groups and compared them to HCs, lower putamen activation was observed in the fear versus calm contrast (Supplement 1:S1, see Table S1 and Figure S2, available online), raising the possibility that there may be a broader vulnerability during negative emotion processing that is not specific to a bipolar versus unipolar depression risk. Previous studies have shown evidence of alterations in limbic, subcortical, and prefrontal regions during the processing of fearful face stimuli in both MDD-risk and BD-risk.[29,72,73] Most risk studies to-date, however, have evaluated youth who already developed symptomatology,[74,75] raising the possibility that observed differences were related to symptoms that were already beginning to manifest.

We acknowledge limitations of our current work. First, neuroimaging data was only collected at one time point. This precludes us from determining whether the identified differences in reward circuitry between BD-risk youth and MDD-risk youth represent markers of neural vulnerability or compensatory adaptation. Future studies should evaluate neural markers longitudinally in order to examine changes in brain activation and connectivity over time and further delineate distinct neural biomarkers of BD relative to MDD-risk in youth. Second, a relatively wide age range of youth participated in the present study and though there were no significant between group differences in age or significant

interactions between age and group (Supplement 1:S3, available online), differential patterns of activation within the striatum and other reward regions may undergo change across longitudinal trajectories of development. Third, there were a greater number of participants in the MDD-risk group compared to the participants in the BD-risk and HC groups. This imbalance between the group sample sizes could potentially confound study findings; however, there were no significant differences in age, gender, and motion outliers among the three groups. Fourth, although all subjects were phenotypically healthy at baseline, we note that the BD-risk group exhibited significantly elevated CDRS-R scores compared to the HC group ($p = .04$), and therefore the subjects in the BD-risk group could be considered subsyndromal. There were no significant differences in depressive symptoms between the BD-risk and the MDD-risk groups at baseline, and CDRS-R scores overall were well below the clinically meaningful thresholds for depression severity (CDRS-R score < 35) across all participants (BD-risk group (mean (SD)): 22.75 (8.23); MDD-risk group (mean (SD)): 20.30 (3.80) ; HC group (mean (SD)): 19.00 (2.81)). There were no significant differences in baseline mania symptoms among the three groups. Fifth, the SDQ was completed by parental report. Parents with MDD or BD who completed the SDQ were euthymic or not in episode while completing the SDQ. Teacher reports may be useful to verify parent reports in future studies. Sixth, an inherent limitation to our methodological approach is that we do not have an exact time of psychiatric disorder onset. Thus, future longitudinal studies with interval assessments at regular short-term intervals are needed to confirm and expand upon the present findings. Lastly, although the present study is, to our knowledge, the largest study comparing neural markers of risk in youth at familial risk for BD and MDD in relation to subsequent behavioral and psychiatric outcomes the study sample is relatively small to conduct subgroup comparisons and future studies with larger samples are needed to replicate these findings.

Despite these limitations, this study identifies reward circuitry activation and connectivity biomarkers during processing of social rewards that distinguish youth at familial risk for BD relative to MDD and HC at an early presymptomatic stage. This highlights potential differential vulnerabilities for BD-risk compared to MDD-risk that are well contextualized in studies that differentiate these disorders when the full syndromes are expressed. We further demonstrate that differential profiles of reward-related brain networks in response to processing positively valenced facial expression in BD and MDD-risk groups were significantly linked to subsequent behavioral and psychiatric outcomes. Thus, differential activation and connectivity profiles of frontostriatal reward circuitry during implicit emotion processing of socially salient stimuli has implications for risk stratification and personalized prevention and treatment in at-risk youth. Measuring frontostriatal reward circuitry during emotion processing in the context of concordant or discordant parental mood disorders should be a focus of future research in high-risk populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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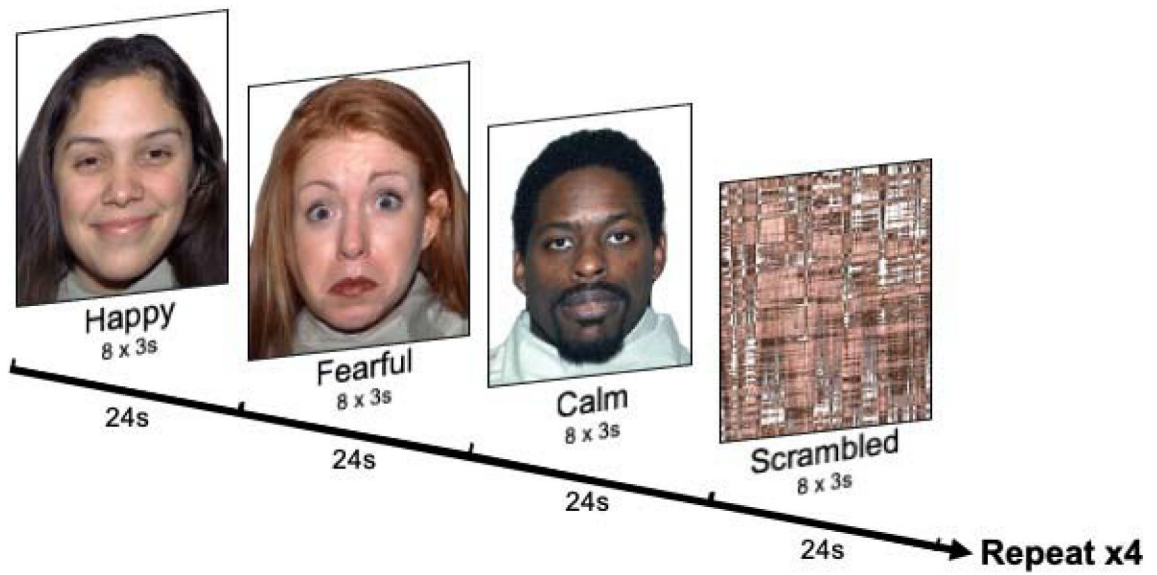
Figure 1. Schematic of Implicit Emotion Perception Task.
Note: Emotional facial expressions selected and adapted from the MacArthur facial expressions set ('NimStim'; http://www.macbrain.org/resources.htm) and a 'scrambled' picture were presented in a block design. Four blocks of each condition were shown, and each block contained 8 different pictures. Each picture was shown for 3 seconds. Subjects pressed button 1 for female and button 2 for male models. Subjects alternately pushed buttons 1 and 2 for the scrambled stimuli. This pattern was repeated 4 times.
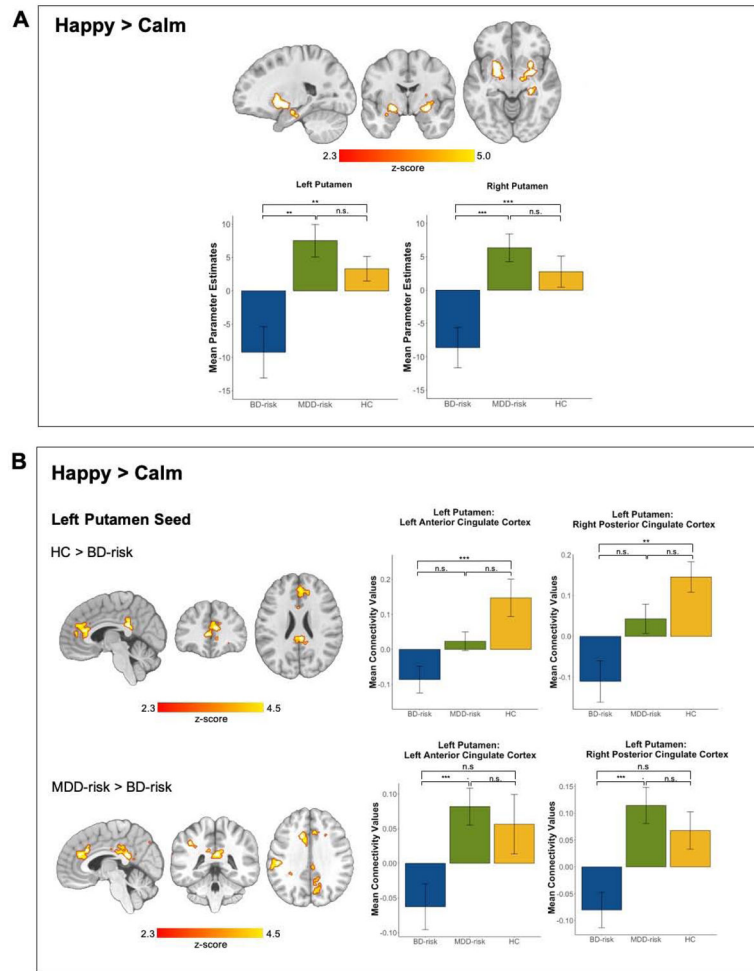
Figure 2. Significant Clusters of Activation and Functional Connectivity and Graphs Illustrating Group Differences For Each Cluster

Note: A. The BD-risk group exhibited significantly less activation in the left and right putamen compared to the MDD-risk and HC groups during Happy > Calm. **B.** The BD-risk group exhibited decreased connectivity compared to HCs between the left putamen seed and the left anterior cingulate cortex and between the left putamen seed and the right posterior cingulate cortex during Happy > Calm. Further, the BD-risk group exhibited decreased connectivity compared to the MDD-risk group between the left putamen seed and the left anterior cingulate cortex and between the left putamen seed and the right posterior cingulate cortex during Happy > Calm. Z- statistics images were thresholded (Z > 2.3) using corrected cluster significance threshold of $p < .05/2 = .025$. Legend: blue: BD-risk, green: MDD-risk; yellow: HC. Left side of image corresponds to the left hemisphere. Error bars are standard errors of the mean. n.s. = not significant.

** $p < .01$; *** $p < .001$

Table 1.

Participant Characteristics, and Motion and Task Performance Results

	BD-risk (n=29)	MDD-risk (n=44)	HC (n=28)	F or χ^2	p
Sex, female (N)	18 (62.1%)	21 (47.7%)	16 (57.1%)	.77	.47[a]
Baseline age	13.01 (2.73)	13.47 (2.43)	14.58 (2.53)	2.93	.06[b]
Age at follow-up	17.49 (4.06)	16.72 (2.85)	18.44 (3.68)	2.12	.13[b]
Length of follow-up (years)	4.31 (2.25)	3.25 (1.09)	3.85 (2.38)	2.85	.06[b]
Intellectual Quotient (IQ)	116.79 (11.86)	112.55 (14.10)	119.44 (12.42)	2.45	.09[b]
Children's Depression Rating Scale-R (CDRS)	22.75 (8.23)	20.30 (3.80)	19.00 (2.81)	3.31	**.04**[b]
Young Mania Rating Scale (YMRS)	2.71 (4.14)	2.02 (3.75)	.37 (.68)	2.53	.09[b]
Children's Global Assessment Scale (CGAS)	87.04 (4.81)	87.49 (5.47)	91.35 (4.52)	6.15	**<.01**[b]
Ethnicity, N (%)				11.72	.30[a]
White or Caucasian	21 (72%)	31(70%)	15 (54%)		
Asian	1 (3%)	2 (5%)	3 (11%)		
Black or African American	1 (3%)	1 (2%)	2 (7%)		
Hispanic or Latino	0 (0%)	3 (7%)	5 (18%)		
Native American or Pacific Islander	0 (0%)	1 (2%)	0 (0%)		
Mixed Race or Other	6 (21%)	6 (14%)	3 (11%)		

Parental Diagnosis

	Mother	Father	Mother	Father	Mother	Father
Bipolar Disorder (BD)	22	7	0	0	0	0
BD	(12)	(3)	(1)	(0)	(0)	(0)
BD + GAD	(1)	(1)	(1)	(0)	(0)	(0)
BD + panic disorder	(1)	(1)	(1)	(0)	(0)	(0)
BD + ADHD + GAD	(1)	(0)	(0)	(0)	(0)	(0)
BD + substance abuse + bulimia + GAD + PTSD	(1)	(0)	(0)	(0)	(0)	(0)
BD + OCD + bulimia	(1)	(0)	(0)	(0)	(0)	(0)
BD + specific phobia	(1)	(0)	(0)	(0)	(0)	(0)

Parental Diagnosis

	Mother	Father	Mother	Father
BD + substance abuse (alcohol) + panic disorder + social phobia + GAD	(1)	(0)	(0)	(0)
BD + MDD + GAD + alcohol dependence	(1)	(0)	(0)	(0)
BD + substance abuse + GAD	(1)	(0)	(0)	(0)
BD + past alcoholism + substance abuse	(0)	(1)	(0)	(0)
BD + substance abuse	(1)	(1)	(0)	(0)
Major Depessive Disorder (MDD)	1	3	29	18
MDD	(1)	(2)	(21)	(12)
MDD + panic disorder	(0)	(0)	(0)	(1)
MDD + GAD	(0)	(1)	(1)	(2)
MDD + PTSD	(0)	(0)	(0)	(1)
MDD + GAD + PTSD	(0)	(0)	(1)	(0)
MDD + substance use(alcohol) + alcohol dependence	(0)	(0)	(0)	(1)
MDD + social phobia	(0)	(0)	(1)	(0)
MDD + anorexia nervosa + PTSD	(0)	(0)	(1)	(0)
MDD + panic disorder + GAD	(0)	(0)	(1)	(0)
MDD + alcohol abuse + agoraphobia + GAD	(0)	(0)	(1)	(0)
MDD + bulimia + social phobia	(0)	(0)	(1)	(0)
MDD + panic disorder + agoraphobia + GAD	(0)	(0)	(0)	(1)
MDD + agoraphobia + specific phobia + OCD + anorexia	(0)	(0)	(1)	(0)

Diagnosis at F/U (N)

	Mother	Father	Mother	Father
Bipolar disorder (BD)	2	0	0	0
BD	(1)	(0)	(0)	(0)
BD + substance abuse (cannabis) + panic disorder + ADHD	(1)	(0)	(0)	(0)
Major depressive disorder (MDD)	5	12	3	3
MDD	(4)	(7)	(1)	(1)
MDD + generalized anxiety disorder (GAD)	(0)	(4)	(2)	(2)
MDD + ADHD	(1)	(0)	(0)	(0)
MDD + substance abuse (cannabis)	(0)	(1)	(0)	(0)
Unspecified depressive disorder	2	2	0	0
Generalized anxiety disorder	3	2	3	3

Diagnosis at F/U (N)

Generalized anxiety disorder (GAD)	(2)	(1)	(3)
GAD + ADHD	(0)	(0)	(0)
GAD + ADHD + panic disorder	(1)	(1)	(0)
Social Phobia	1	0	(0)

Happy Café Task Performance

	Baseline	F/U	Baseline	F/U		
Faces task accuracy (percent correct)	95.66 (7.80)	96.82 (3.02)	96.21 (8.21)	.30	.75[b]	
Faces task response time (milliseconds)	777.80 (132.00)	832.31 (185.67)	774.53 (170.52)	1.38	.26[b]	
Motion: Absolute mean displacement (mm) (mean, SD)	.41 (.45)	.32 (.33)	.26 (.28)	1.27	.28[b]	

Strengths and Difficulties Questionnaire	Baseline	F/U	Baseline	F/U	Baseline	F/U				
Prosocial scale	8.44 (1.59)	8.46 (1.69)	8.11 (2.01)	8.63 (1.57)	8.89 (1.28)	8.87 (1.60)	1.22	.38	.30[b]	.69[b]
Emotional problems scale	1.81 (1.68)	2.38 (2.63)	2.26 (2.33)	2.29 (2.07)	1.78 (1.35)	.95 (1.05)	.50	3.49	.61[b]	.04[b]
Peer problems scale	1.00 (1.16)	1.00 (1.18)	1.26 (1.27)	1.67 (1.69)	.89 (.96)	95 (.84)	.71	2.34	.49[b]	.10[b]
Conduct problems scale	1.06 (1.39)	.92 (1.10)	1.05 (1.39)	.93 (1.14)	1.22 (1.48)	26 (.69)	.09	3.41	.91[b]	.04[b]
Hyperactivity	2.94 (2.52)	3.38 (1.79)	4.24 (2.95)	3.18 (1.82)	2.61 (2.77)	2.91 (1.9)	2.51	.38	.09[b]	.69[b]

Note. Values indicate the Mean (SD) unless otherwise noted. ADHD = attention-deficit/hyperactivity disorder; BD = bipolar disorder; BD-risk = youth at risk for bipolar disorder; F/U = follow-up; GAD = generalized anxiety disorder; HC = healthy control youth; MDD = major depressive disorder ; MDD-risk = youth at risk for a depressive disorder; mm = millimeter; OCD = obsessive-compulsive disorder ; PTSD = posttraumatic stress disorder.

[a] Statistic computed using χ^2 test.

[b] Statistic computed using ANOVA.

Table 2.

Significant Clusters of Whole Brain Activation and Connectivity For Happy > Calm

	Contrast	Peak Brain Region	Side	BA	Cluster Size	Peak Z-score	p	Peak MNI Coordinates		
								x	y	z
F test (BD-risk vs. MDD-risk vs. HC)	Happy > Calm	Putamen	L	34	638	4.39	.003	−22	−4	−8
F test (BD-risk vs. MDD-risk vs. HC)	Happy > Calm	Putamen	R	34	856	4.56	<.001	28	−2	−8
HC > BD-risk	L Putamen seed Happy > Calm	Anterior Cingulate Cortex	L	24	1062	3.64	<.0001	−6	38	6
HC > BD-risk	L Putamen seed Happy > Calm	Posterior Cingulate Cortex	R	23	440	4.04	<.01	6	−36	26
MDD-risk> BD-risk	L Putamen seed Happy > Calm	Anterior Cingulate Cortex	L	24	826	4.04	<.0001	−14	18	34
MDD-risk > BD-risk	L Putamen seed Happy > Calm	Posterior Cingulate Cortex	R	23	979	4.04	<.0001	4	−40	22

Note. Coordinates are reported in Montreal Neurological Institute (MNI) space. BA= Brodmann area; BD-risk = youth at risk for bipolar disorder; HC = healthy control youth; L = left; MDD-risk = youth at risk for major depressive disorder; R = right.

Table 3.

Association Between Baseline Emotion Processing, Strength and Difficulties, and Diagnoses at Follow-up

		BD-risk					MDD-risk				
		B	SE	R^2	t	p	B	SE	R^2	t	p
Emotional Problems	Age	-.22	.52		-.42	.70	-.12	.22		-.55	.59
	Gender[a]	3.66	3.03		1.21	.31	.84	.85		.99	.34
	Right Putamen	.86	.32		2.66	.08	-.04	.06		-.70	.43
	Left Putamen	-.61	.26		-2.33	.10	.05	.06		.87	.40
	Left Putamen- Left ACC	-3.86	7.3		-.53	.63	-1.53	2.27		-.67	.51
	Left Putamen- Right PCC	1.7			.30	.78	-1.36	1.68		-.81	.43
	Baseline Emotional Problems	-.02	.72		-.03	.98	.25	.17		1.48	.16
				.77					.28		
Conduct Problems	Age	-.02	.19		-.10	.93	-.12	.11		-1.1	.29
	Gender[a]	-1.22	1.21		-1.01	.39	.18	.46		.39	.70
	Right Putamen	.05	.10		.44	.69	-.02	.03		-.69	.50
	Left Putamen	-.05	.09		-.510	.65	.02	.03		.76	.46
	Left Putamen- Left ACC	1.83	3.6		.50	.65	-1.34	1.18		-1.13	.27
	Left Putamen- Right PCC	-.02	1.93		-.01	.99	-1.06	.87		-1.2	.24
	Baseline Conduct Problems	.51	.39		1.33	.28	.1	.14		.69	.50
				.60					.32		
Hyperactivity	Age	-.15	.21		-.72	.52	-.13	.15		-.85	.41
	Gender[a]	-.93	1.41		-.66	.56	.86	.65		1.32	.20
	Right Putamen	.16	.15		1.06	.37	.03	.04		.68	.50
	Left Putamen	-.09	.12		-.74	.51	.005	.04		.11	.92
	Left Putamen- Left ACC	.93	.38		.27	.81	3.64	1.68		2.17	.05
	Left Putamen- Right PCC	.38	.31		.15	.89	-.73	1.26		.68	.57
	Baseline Hyperactivity	.31	.19		1.60	.21	.27	.11		2.54	**.02**
				.73					.45		
Peer Problems	Age	.001	.08		.01	.99	-.17	.16		-1.09	.29
	Gender[a]	.44	.45		.98	.38	-.10	.63		-.15	.88

		BD-risk					MDD-risk				
Outcome	Predictor	B	SE	R²	t	p	B	SE	R²	t	p
	Right Putamen	-.02	.05		-.41	.70	-.05	.04		-1.26	.22
	Left Putamen	.07	.04		1.84	.14	.08	.04		1.74	.11
	Left Putamen- Left ACC	-2.87	1.56		-1.84	.06	-.72	1.65		-.43	.67
	Left Putamen- Right PCC	-2.90	.60		-4.85	**<.01**	-3.64	1.23		-2.30	**<.01**
	Baseline Peer Problems	-.37	.28	.90	-1.31	.14	.42	.25	.52	1.68	.11
	Age	.05	.1		.48	.66	.01	.15		.05	.96
	Gender[a]	-1.21	.54		-2.22	.09	.14	.79		.18	.86
Prosocial	Right Putamen	.02	.05		.36	.73	-.01	.04		-.27	.79
	Left Putamen	.05	.03		1.54	.18	.01	.04		.21	.83
	Left Putamen- Left ACC	-1.11	1.46		-.76	.48	1.57	1.66		.95	.36
	Left Putamen- Right PCC	-.77	1.07		-.72	.50	4.26	1.4		3.03	**<.01**
	Baseline Prosocial	.64	.21	.65	3.00	**.02**	.14	.21	.46	.66	.52
	Age	.29	.20		--	.15	.13	.14		--	.38
	Gender[a]	1.71	1.0		--	.09	-.83	.74		--	.26
Conversion to Mood or Anxiety Disorder	Right Putamen	-.09	.05	.27	--	**<.05**	-.005	.02	.03	--	.85
	Left Putamen	-.07	.03	.27	--	**.04**	-.01	.02	.04	--	.62
	Left Putamen- Left ACC	-2.60	2.10	.14	--	.07	-.02	1.82	.03	--	.99
	Left Putamen- Right PCC	-1.62	1.53	.12	--	.20	-2.81	1.49	.12	--	.06

		BD-risk		MDD-risk	
Outcome	Predictor	Hazard Ratio (95%)	p	Hazard Ratio (95%)	p
	Age	.79 (.54, 1.15)	.22	1.00 (.83, 1.20)	.99
	Gender[a]	10.72 (.98, 117.67)	.05	.54 (.17, 1.66)	.28
Rate of Conversion to Mood or Anxiety Disorder	Right Putamen	.44 (.04, 4.56)	.49	1.35 (.42, 4.39)	.61
	Left Putamen[b]	3.29 (.54, 19.84)	.19	.76 (.25, 2.33)	.63
	Left Putamen- Left ACC[b]	.44 (.13, 1.47)	.18	.69 (.30, 1.57)	.37
	Left Putamen- Right PCC[b]	8.28 (1.67, 41.08)	**<.01**	2.31 (1.14, 4.68)	**.02**

Note. B = unstandardized beta; BD-risk = youth at risk for bipolar disorder; MDD-risk = youth at risk for major depressive disorder; SE = standard error. R^2 for logistic regressions refers to Cox and Snell's *R*.

[a]B and hazard ratio refers to female.

[b]Per one standard deviation (SD) unit decrease.