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Intrinsic Connectivity and Family Dynamics: Striatolimbic Markers of Risk and Resilience in Youth at Familial Risk for Mood Disorders

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ABSTRACT

BACKGROUND: Few studies to date have characterized functional connectivity (FC) within emotion and reward networks in relation to family dynamics in youth at high familial risk for bipolar disorder (HR-BD) and major depressive disorder (HR-MDD) relative to low-risk youth (LR). Such characterization may advance our understanding of the neural underpinnings of mood disorders and lead to more effective interventions.

METHODS: A total of 139 youth (43 HR-BD, 46 HR-MDD, and 50 LR) aged 12.9 ± 2.7 years were longitudinally followed for 4.5 ± 2.4 years. We characterized differences in striatolimbic FC that distinguished between HR-BD, HR-MDD, and LR and between resilience and conversion to psychopathology. We then examined whether risk status moderated FC–family dynamic associations. Finally, we examined whether baseline between-group FC differences predicted resilence versus conversion to psychopathology.

RESULTS: HR-BD had greater amygdala–middle frontal gyrus and dorsal striatum–middle frontal gyrus FC relative to HR-MDD and LR, and HR-MDD had lower amygdala–fusiform gyrus and dorsal striatum–precentral gyrus FC relative to HR-BD and LR (voxel-level $p < .001$, cluster-level false discovery rate–corrected $p < .05$). Resilient youth had greater amygdala–orbitofrontal cortex and ventral striatum–dorsal anterior cingulate cortex FC relative to youth with conversion to psychopathology (voxel-level $p < .001$, cluster-level false discovery rate–corrected $p < .05$). Greater family rigidity was inversely associated with amygdala–fusiform gyrus FC across all groups (false discovery rate–corrected $p = .017$), with a moderating effect of bipolar risk status (HR-BD vs. HR-MDD $p < .001$; HR-BD vs. LR $p = .005$). Baseline FC differences did not predict resilence versus conversion to psychopathology.

CONCLUSIONS: Findings represent neural signatures of risk and resilience in emotion and reward processing networks in youth at familial risk for mood disorders that may be targets for novel interventions tailored to the family context.

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Bipolar disorder (BD) and major depressive disorder (MDD) are two of the leading causes of disability among youth and are associated with a significantly increased risk of suicide, the second leading cause of death in youth (1,2). One of the strongest risk factors for the development of psychopathology in youth is having a parent with a mood disorder (3). Risk factors for developing BD may be different from risk factors for developing MDD. Elevated risk for mood and other psychiatric disorders in these youth may be attributed to a combination of genetic liability and family system factors unique to parents with BD versus MDD. Indeed, parenting plays a significant role in the child's functioning, both individually and within the family system. Parenting characteristics that are common to parents with BD and MDD—such as critical parenting and difficulty modeling emotion regulation—may increase the risk that a child will develop psychopathology (3,4). Early and specific phenotyping is needed to inform interventions that integrate information from genetic and environmental influences for developing psychopathology in high-risk offspring (5). Characterizing neural mechanisms that underlie early pathways of risk for developing specific mood disorders is essential for identifying precise targets for preventive interventions and for learning how to promote resilience in children, particularly those at familial risk.

Significant maturation of brain circuitry subserving emotion and reward processing occurs during childhood (6,7). Appropriate connectivity and recruitment of striatolimbic circuitry is essential for adaptive emotion processing and reward functions (8,9). Mood symptoms are associated with dysregulation within reward and emotion processing networks in both BD and MDD (10–12). Further, neuroimaging studies in individuals at risk for BD and MDD suggest disorder-specific abnormalities in functional connectivity (FC) of these networks (13–17). Aberrant amygdala and striatum FC are among the most consistently reported findings among high-risk BD (HR-BD) (13,17–19) and high-risk MDD (HR-MDD) (15,20,21) samples.

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FC is of particular interest because of its potential to improve categorization and treatment selection in pediatric mood disorders; specifically, resting-state FC analysis provides a noninvasive means of investigating connectivity across multiple brain regions (22) and can detect plasticity within brain networks (23) that underlie specific diagnostic categories.

Parenting, at the core of dynamics within the family system, profoundly affects child brain development and necessitates flexibility and adaptation (24). The amygdala and striatum are key components of the parental caregiving brain network (24,25), and FC between the amygdala, striatum, and paralimbic and cortical brain regions implicated in empathy and emotion regulation (26,27) subserve parents' ability to adaptively respond to their children (28). Researchers have posited that changes in FC within this network are a mechanism by which biobehavioral synchrony develops between parents and children, forming the dynamics within a family system (24). Disruption in striatolimbic FC in parents with a mood disorder has been linked to maladaptive dynamics within the family system (29) and to increased risk for childhood-onset psychopathology in offspring (30). At present, however, we have a limited understanding of the neurobehavioral mechanisms underlying children's experience of family dynamics and its link to the development of psychopathology. Findings that resting-state networks can change with family-focused therapy in a randomized controlled setting provide the foundation for more informed neuroscience-based prevention and treatment efforts for HR youth (31). Relative to low-risk (LR) offspring, offspring of a parent with BD characterize their family dynamics as having lower cohesion, adaptability, and flexibility and greater rigidity and conflict (32–34), which were significantly associated with clinical symptom severity (34,35). Offspring of a parent with MDD experience lower levels of family cohesion and greater family discord relative to LR offspring (36), which is prospectively associated with the development of mood symptoms (37,38). Given that family function contributes to the development of emotion regulation and other mood symptoms in youth at familial risk for mood disorders (33,34,37), family function may also influence neurodevelopment of emotion and reward circuitry in HR youth. Indeed, associations between family environment and connectivity of emotion and reward networks have been demonstrated, with findings suggesting increased amygdala FC in youth exposed to negative parenting styles (39,40). However, researchers have not yet examined whether familial risk moderates the association between family function and intrinsic connectivity of emotion and reward networks. Understanding the moderating influence of having a parent with BD or MDD on the association between family dynamics and striatolimbic FC in youth at high risk for mood disorders prior to symptom onset is critical given that mood symptoms (41) and striatolimbic network connectivity (31) can be modified via family-focused psychotherapeutic approaches for HR youth. Evaluating youth prior to symptom onset and tracking mood outcome may aid in determining which youth might benefit from this and other evidenced-based interventions to personalize treatment.

Here, we assessed FC and family dynamics in 139 psychiatrically healthy youth (mean age = 12.9 years) at high or low familial risk for BD or MDD and followed up with youth approximately 4.5 years later to assess resilience versus conversion to a psychiatric diagnosis. Our primary aims were to examine 1) whether there were common or dissociable patterns of FC in the emotion and reward networks of HR-BD, HR-MDD, and LR youth and 2) whether baseline differences in amygdala and striatal network FC distinguished subsequent resilience (RES group; defined as youth with the absence of psychiatric illness at follow-up) from conversion (CVT group; defined as youth with the presence of psychiatric illness at follow-up) among HR youth. We predicted that HR youth would exhibit atypical and distinct patterns of FC, including hyperconnectivity of the amygdala in HR-BD youth and hypoconnectivity of the striatum in HR-MDD youth (13–17). Based on prior research (14,15,42,43), we hypothesized further that greater FC between the amygdala and striatum and prefrontal cortical brain regions would distinguish RES from CVT. Our secondary aim was to examine the moderating effect of risk status on the associations between child-reported family dynamics and striatolimbic FC within youth. Based on the literature demonstrating a relationship between greater amygdala FC in youth exposed to negative parenting styles (39,40), we predicted that HR-BD and HR-MDD status would have a greater moderating effect on the relationship between amygdala FC and dysfunctional family dynamics, including greater family rigidity in families with a parent with BD (32–34) and reduced family cohesion in families with a parent with MDD (36), relative to LR. Our final, exploratory aim was to test whether baseline differences in FC and family dynamic among HR-BD, HR-MDD, and LR youth predicted resilience versus conversion to psychopathology in HR youth.

METHODS AND MATERIALS

Participants

Participants were 139 youth (43 HR-BD, 46 HR-MDD, 50 LR) aged 12.9 $\pm$ 2.7 years. Youth were longitudinally followed for 4.5 $\pm$ 2.4 years. At study entry, participants had no lifetime history of psychopathology. HR-BD and HR-MDD youth had one biological parent with a confirmed diagnosis of BD or MDD, respectively. LR youth had no history of psychopathology and did not have first- or second-degree relatives with an Axis I disorder. Exclusion criteria for all participants were significant medical disorder, substance use disorder, pervasive developmental disorder or IQ $<$ 80, or magnetic resonance imaging contraindications. Participants were recruited through advertisements in the local community and clinics. Eight participants were excluded due to poor data quality. Study procedures were approved by the Stanford University Institutional Review Board. Written informed assent and consent was obtained from all youth and their parents, respectively.

Demographic, Clinical, and Family Function Data

All participants were assessed for psychiatric diagnoses by trained interviewers blinded to family history status at baseline and follow-up. Mood sections of the Washington University in St. Louis Kiddie-Schedule for Affective Disorders (44,45) were administered to assess lifetime psychiatric diagnoses. At baseline, trained interviewers administered the Structured Clinical Interview for DSM-IV (46) to both parents to assess whether a parent met criteria for BD type I or MDD for the HR

groups, and to rule out family history of psychiatric disorders in the LR group. All diagnostic interviews were confirmed by a board-certified child and adolescent psychiatrist. At follow-up (4.5 ± 2.4 years), youth who met diagnostic criteria for a psychiatric disorder were classified as CVT, and youth who did not meet any diagnostic criteria were classified as RES.

At baseline, youth completed the Wechsler Abbreviated Scale of Intelligence (47), the Young Mania Rating Scale (YMRS) (48), the Children's Depressive Rating Scale-Revised (CDRS-R) (49), the Multidimensional Anxiety Scale for Children (MASC) (50), the ADHD Rating Scale (ADHD-RS) (51), and the Children's Global Assessment Scale (CGAS) (52). Age, sex, race, ethnicity, parental education (Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version) (45), socioeconomic status (Hollingshead Four Factor Index) (53), and handedness (Crovitz Handedness Questionnaire) (54) were also assessed.

Youth and one parent completed the Family Adaptability and Cohesion Scale (FACES-IV) (55) at baseline to assess family dynamics along six subscales: cohesion, flexibility, disengaged, enmeshed, rigidity, and chaos (Table S1; psychometrics information is provided in the Supplement). We used the child-reported FACES-IV scores to examine their associations with FC in emotion and reward circuitry in HR versus LR youth because we aimed to elucidate how child perceptions of family dynamics are related to the child's clinical outcomes and related to intrinsic connectivity within the child's reward and emotion regulation networks (56,57). Further, we used child (vs. parent) FACES-IV scores to avoid potential negative bias in reporting from a parent with a mood disorder (58). Previous work supports our decision to use child-reported (vs. parent-reported) FACES-IV scores to predict child-related clinical outcomes, particularly for internalizing disorders (56,57). Correlations between the parent- and child-reported FACES-IV scores are presented in the Supplement. Parent and child FACES-IV cohesion, flexibility, and chaos subscale scores were moderately and significantly associated. Parent and child FACES-IV disengagement, enmeshed, and rigidity subscales were modestly, but not significantly, associated.

Statistical analyses were conducted using R version 3.5.1. We compared HR-BD, HR-MDD, and LR groups on demographic and clinical assessments using one-way analyses of variance with post hoc Tukey tests for continuous variables and χ^2 tests for categorical variables.

Regions of Interest Selection and FC Analyses

We conducted FC analysis using SPM12 and CONN (59). Methods for the acquisition of functional magnetic resonance imaging and parameters for preprocessing and for artifact correction are described in the Supplement. We selected a whole-brain seed-to-voxel analysis approach to test a priori hypotheses involving striatolimbic neural networks subserving emotion and reward processing and to facilitate comparisons with the extant resting-state functional magnetic resonance imaging literature on pediatric BD (17,18,60) and MDD (14,15,61,62). We generated whole-brain seed-to-voxel correlation maps by extracting the residual blood oxygen level–dependent signal time course from regions of interest, including the amygdala (emotion network) and striatum (reward network). Both ventral striatum (encompassing the nucleus accumbens) and dorsal striatum (encompassing the putamen) seeds were included due to their importance in risk for pediatric mood disorders documented in previous studies (15,18,21,63). A total of six seed regions of interest were generated, each 5 mm in diameter. Region of interest spheres created were centered on peak coordinates from the literature from regions in which youth at high versus low familial risk for mood disorders differed in their blood oxygen level–dependent response (14,15,17,18,61,64,65): bilateral amygdala seeds (central coordinates: ±22, −5, +17), bilateral ventral striatum seeds (central coordinates: ±9, +9, −8), and bilateral dorsal striatum seeds (central coordinates: ±24, +4, +2).

Age, sex, and race were included as covariates. We computed Pearson's correlation coefficients between the time course of each seed and all other voxels in the brain. We converted correlation coefficients to z scores using Fisher's transformation and used them in a second-level general linear model to examine group differences between HR-BD, HR-MDD, and LR and between RES and CVT. Significance thresholding was set to voxel-level $p < .001$ and cluster-level false discovery rate (FDR)–corrected $p < .05$. Finally, we examined whether there were any significant associations between baseline FC and baseline psychiatric symptom scores on the CDRS-R, YMRS, MASC, and ADHD-RS (Supplement).

Moderating Effect of Risk Status on Family Dynamic and FC

Because family dynamics have been shown to differ in families with a parent with BD or MDD relative to families without a parent with a psychiatric diagnosis (33,36,37) and family dynamic influences FC (39), we probed how risk status influenced FC–family dynamic associations. First, we sought to characterize family dynamic–FC associations in our dataset. We tested the null hypothesis that there were no significant associations between any FACES domains (cohesion, flexibility, disengagement, enmeshment, rigidity, and chaos) and any FC variables. We constrained our analysis to baseline striatolimbic FC that distinguished HR-BD, HR-MDD, and LR. Linear regressions were conducted across all three groups between each FACES domain (independent variables) and FC (dependent variables). Significant findings were FDR-corrected at $p < .05$ for multiple comparisons (6 FACES variables × 9 FC variables = 54 tests). Compared with a multiple linear regression approach (i.e., running nine regressions with six FACES domain independent variables each), our analysis approach allowed us to directly test the null hypothesis while controlling for both type I error (via FDR correction) and type II error (due to multicollinearity between FACES domains; see the Supplement). We note, however, that this approach does not allow us to assess whether any FACES domain was associated with FC after controlling for the influence of other FACES domains. Therefore, we present such a multiple linear regression analysis in the Supplement and refer the reader there for both a description of the approach and results. Notably, findings were consistent across both approaches (running 54 simple linear regressions vs. running nine multiple linear regressions).

Next, to determine whether significant family dynamic–FC relationships were moderated by risk status, we examined whether interactions between risk status (i.e., HR-BD vs. HR-MDD vs. LR) and FACES were significantly associated with FC. Main effects of FACES subscale scores and risk status were included as independent variables, and FC was the dependent variable.

Predictive Modeling: RES Versus Psychiatric Diagnosis (CVT) at Follow-up

We used logistic regression to examine whether FC profiles that differentiated HR-BD, HR-MDD, and LR at baseline predicted RES or CVT at follow-up. To assess whether these relationships were significant over and above clinical correlates, we statistically adjusted for baseline clinical symptoms, including YMRS, CDRS-R, MASC, and ADHD-RS scores, as well as current and most severe CGAS scores. We also assessed whether family dynamics (FACES-IV subscales) and interactions between family dynamics and differentiating baseline FC were associated with RES or CVT. Time to follow-up was included as a covariate in the model.

RESULTS

Demographic, Clinical, and Family Dynamic Data

Demographic and clinical data are summarized in Table 1. Groups did not differ in age, sex, handedness, IQ, parental education, social status, YMRS scores, CDRS-R scores, MASC scores, ADHD-RS scores, or CGAS most severe scores but differed in race (p = .04). CGAS current scores were higher in the LR group (mean = 91.02, SD = 5.40) than in the HR-BD (mean = 87.85, SD = 5.88) and HR-MDD (mean = 87.55, SD = 5.68) groups. Groups did not differ in level of child-reported flexibility, engagement, enmeshment, rigidity, or chaotic FACES-IV subscales but differed in family cohesion subscale scores. A post hoc Tukey test indicated that HR-MDD (mean = 48.38, SD = 26.11) had lower cohesion than LR (mean = 67.18, SD = 26.87). A comparison of parent-reported FACES-IV scores can be found in the Supplement. At follow-up, there was a group difference in the presence of any DSM-IV diagnosis, such that more HR-BD (n = 16) and HR-MDD (n = 17) participants met criteria for a psychiatric diagnosis relative to LR (n = 7) participants (Table 1). Clinical diagnostic data at follow-up are detailed in the Supplement (Table S2).

HR-BD, HR-MDD, and LR Between-Group FC Differences

Results are summarized in Figure 1 and Table 2.

Amygdala Seeds. HR-BD had greater FC between the bilateral amygdala seeds and the left middle frontal gyrus (MFG) compared with HR-MDD and LR. HR-MDD had lower left amygdala–left fusiform gyrus FC than HR-BD and LR. Relative to LR, HR-BD and HR-MDD had greater left amygdala–left postcentral gyrus and lower left amygdala–left lingual gyrus and left amygdala–right lingual gyrus FC.

Striatum Seeds. HR-BD had greater right dorsal striatum–right MFG and lower left dorsal striatum–right lingual gyrus FC compared with HR-MDD and LR. HR-MDD had lower left dorsal striatum–left precentral gyrus FC compared with HR-BD and LR. There were no FC differences between HR-BD, HR-MDD, and LR groups in the ventral striatum seed.

CVT and RES FC Between-Group FC Differences

Results are summarized in Table 3 and Figure 2.

Amygdala Seeds. RES had greater right amygdala–right orbitofrontal cortex and right amygdala–left paracingulate gyrus FC relative to CVT.

Striatum Seeds. RES had greater left ventral striatum–dorsal anterior cingulate cortex and left dorsal striatum–left postcentral gyrus FC relative to CVT. CVT had greater left dorsal striatum–left fusiform gyrus FC relative to RES.

Moderating Effect of Risk Status on Family Dynamic and FC

Across all three groups, there was a negative association between family rigidity and left amygdala–left fusiform gyrus FC, such that high family rigidity was associated with low FC ($\beta = -0.386$, $t_{81} = -3.765$, FDR-corrected p = .017). Moderation analyses demonstrated that risk status moderated the relationship between family rigidity and amygdala–fusiform gyrus FC (Figure 3), such that the negative association between family rigidity and FC was stronger in the HR-BD group than the LR group ($\beta = -0.916$, $t_{77} = -2.913$, p = .005) and the HR-MDD group ($\beta = -0.938$, $t_{77} = -3.497$, $p < .001$). The negative association between family rigidity and FC was not different in the HR-MDD group compared with the LR group ($\beta = 0.026$, $t_{77} = 0.082$, p = .935).

Logistic Regression to Predict Psychiatric Diagnosis (CVT) Versus RES

FC profiles that differentiated HR-BD, HR-MDD, and LR did not predict RES or CVT status at follow-up. Family dynamics (i.e., FACES-IV subscales) and interactions between baseline FC profiles and family dynamics also did not predict RES or CVT at follow-up. See the Supplement for detailed results.

DISCUSSION

Few studies to date have examined the influence of family dynamics and intrinsic brain network connectivity in the context of risk for psychopathology in children with a parent with BD (HR-BD) or MDD (HR-MDD). The goal of this study was to address this gap in the literature by characterizing FC markers of risk and resilience within emotion and reward networks in relation to family dynamics. We found that FC profiles within emotion and reward processing networks distinguished HR-BD from HR-MDD and LR youth, with a moderating effect of risk status on the association between family rigidity and corticolimbic FC. Although risk status did not predict resilience or conversion to psychopathology, we identified baseline FC differences in emotion and reward processing circuitry that distinguished resilience from conversion to

Table 1. Participant Characteristics

Characteristic	LR	HR-BD	HR-MDD	Statistical Value	*p* Value
Demographic Information					
Child Age, Years, Mean (SD)	12.75 (2.78)	12.24 (2.63)	13.50 (2.50)	$F_{2,136} = 2.58$	.79
Child IQ, Mean (SD)	117.16 (14.89)	114.30 (11.40)	112.02 (14.32)	$F_{2,134} = 1.66$	.20
Sex, *n* (%)					
Female	30 (60%)	30 (69.8%)	22 (47.8%)	$\chi^2_2 = 4.46$	.11
Male	20 (40%)	13 (30.2%)	24 (52.2%)		
Handedness, *n* (%)					
Right	37 (74%)	35 (81.4%)	41 (89.1%)	$\chi^2_4 = 5.28$	.26
Left	6 (12%)	3 (7%)	4 (8.7%)		
Ambidextrous	4 (8%)	4 (9.3%)	0		
Race and Ethnicity, *n* (%)					
African American	2 (4%)	0	1 (2.2%)	$\chi^2_8 = 16.26$	.04
Asian[a]	14 (28%)	2 (4.7%)	5 (10.9%)	$\chi^2_8 = 16.26$	.04
Biracial	5 (10%)	3 (7%)	2 (4.3%)	$\chi^2_8 = 16.26$	.04
Hispanic	6 (12%)	3 (7%)	6 (13%)	$\chi^2_2 = 0.89$	.64
White[a]	22 (44%)	32 (74.4%)	29 (63%)	$\chi^2_8 = 16.26$	.04
Declined to state	7 (14%)	6 (14%)	9 (19.6%)	$\chi^2_8 = 16.26$	.04
Maternal Education, *n* (%)					
Less than high school	4 (8%)	7 (16.3%)	6 (13%)	$\chi^2_8 = 5.65$	.69
High school	1 (2%)	0	3 (6.5%)		
Associates	23 (46%)	16 (37.2%)	21 (45.7%)		
4-year college	18 (36%)	13 (30.2%)	13 (28.3%)		
More than 4-year college	2 (4%)	2 (4.7%)	2 (4.3%)		
Paternal Education, *n* (%)					
Less than high school	4 (8%)	6 (14%)	8 (17.4%)	$\chi^2_8 = 8.97$	.34
High school	1 (2%)	2 (4.7%)	1 (2.2%)		
Associates	19 (38%)	11 (25.6%)	14 (30.4%)		
4-year college	19 (38%)	16 (37.2%)	13 (28.3%)		
More than 4-year college	5 (10%)	1 (2.3%)	8 (17.4%)		
Social Status Range, *n* (%)					
Lower	0	1 (2.3%)	2 (4.3%)	$\chi^2_8 = 10.97$	.20
Lower-middle	1 (2%)	4 (9.3%)	0		
Middle	6 (12%)	3 (7%)	8 (17.4%)		
Upper-middle	10 (20%)	11 (25.6%)	9 (19.6%)		
Upper	26 (52%)	18 (41.9%)	21 (45.7%)		
Baseline Clinical Information					
YMRS, Mean (SD)	0.92 (1.30)	2.05 (3.28)	1.74 (3.55)	$F_{2,133} = 1.92$	.15
CDRS-R, Mean (SD)	19.00 (2.54)	20.93 (6.39)	20.07 (3.96)	$F_{2,128} = 2.04$	.13
MASC, Mean (SD)	37.29 (17.57)	37.08 (14.93)	41.76 (17.90)	$F_{2,97} = 0.86$	.43
ADHD-RS, Mean (SD)	2.09 (2.59)	3.72 (5.74)	4.46 (7.87)	$F_{2,83} = 1.41$	.25
CGAS Current[b,c], Mean (SD)	91.02 (5.40)	87.85 (5.88)	87.55 (5.68)	$F_{2,128} = 6.55$	.002
CGAS Most Severe, Mean (SD)	85.10 (5.40)	83.15 (5.88)	83.12 (5.68)	$F_{2,128} = 1.08$	.34
FACES-IV Child Report[d], Mean (SD)					
Cohesion[c]	67.18 (26.87)	55.25 (28.64)	48.38 (26.11)	$F_{2,80} = 3.58$	.03
Flexibility	67.96 (21.47)	54.71 (28.36)	53.52 (23.76)	$F_{2,80} = 3.02$	.05
Disengaged	28.36 (12.96)	27.00 (14.14)	32.35 (15.30)	$F_{2,80} = 1.09$	.34
Enmeshed	21.93 (7.15)	20.92 (7.97)	19.68 (9.09)	$F_{2,80} = .56$	.57
Rigid	42.79 (11.92)	36.00 (13.07)	37.32 (16.65)	$F_{2,80} = 1.74$	.18
Chaotic	23.50 (8.25)	30.13 (20.63)	27.23 (12.46)	$F_{2,80} = 1.42$	.25
FACES-IV Parent Report[d], Mean (SD)					
Cohesion[b]	81.74 (15.38)	61.22 (28.97)	69.37 (27.50)	$F_{2,95} = 5.19$	.007
Flexibility[b,c]	78.59 (14.03)	55.13 (26.58)	64.44 (20.79)	$F_{2,95} = 9.75$	<.001

Table 1. Continued

Characteristic	LR	HR-BD	HR-MDD	Statistical Value	*p* Value
Disengaged	19.44 (6.65)	24.09 (13.83)	22.20 (10.80)	$F_{2,95} = 1.45$	.24
Enmeshed	20.29 (10.79)	25.22 (13.59)	19.34 (6.99)	$F_{2,95} = 2.60$	.08
Rigid[c,e]	40.94 (12.19)	37.04 (12.30)	30.15 (8.59)	$F_{2,95} = 9.50$	<.001
Chaotic[b]	20.47 (12.35)	33.35 (21.85)	25.63 (15.84)	$F_{2,95} = 4.23$	.02
Follow-up Conversion Status[b,c], *n* (%)					
Converted	7 (14%)	16 (37.2%)	17 (37%)	$\chi^2_2 = 7.98$	.02
Resilient	42 (84%)	27 (62.8%)	29 (63%)		
Years of Follow-up[c,e], Mean (SD)	4.98 (2.64)	5.32 (2.55)	3.24 (1.07)	$F_{2,136} = 11.58$	<.001

Means and standard deviations (continuous variables) and frequencies and percentages (categorical variables) displayed for LR, HR-BD, and HR-MDD. One-way ANOVAs (continuous variables) and χ^2 tests (categorical variables) were conducted for all variables of interest.

ADHD-RS, ADHD Rating Scale; ANOVA, analysis of variance; CDRS-R, Children's Depression Rating Scale-Revised; CGAS, Children's Global Assessment Scale; FACES-IV, Family Adaptability and Cohesion Scale; HR-BD, high-risk bipolar disorder; HR-MDD, high-risk major depressive disorder; LR, low-risk; MASC, Multidimensional Anxiety Scale; YMRS, Young Mania Rating Scale.

[a]Post hoc Tukey test results indicate that HR-BD, HR-MDD, and LR are significantly different.

[b]Post hoc Tukey test results indicate that HR-BD and LR are significantly different.

[c]Post hoc Tukey test results indicate that HR-MDD and LR are significantly different.

[d]FACES-IV values indicate percentiles.

[e]Post hoc Tukey test results indicate that HR-BD and HR-MDD are significantly different.

psychopathology within the sample of HR youth. These findings have the potential to inform our understanding of the neural underpinnings of early-onset mood disorders and improve intervention approaches to mitigate risk and promote resilience in HR youth.

HR-BD and HR-MDD youth who did not have a psychiatric diagnosis at baseline differed in FC profiles within emotion and reward processing circuitry, suggesting that there are unique trait-level vulnerability profiles or compensatory processes in these youth. HR-BD had greater amygdala and dorsal striatum FC with the MFG, reduced dorsal striatum–lingual gyrus FC relative to HR-MDD and LR, and reduced amygdala–fusiform gyrus FC relative to HR-MDD. Both HR-BD and HR-MDD had reduced amygdala–postcentral gyrus and amygdala–lingual gyrus FC relative to LR. The MFG, a site of convergence of the dorsal and ventral attention networks, is involved in goal-directed and stimulus-driven attention and flexible attention modulation (66). Reduced MFG response to inhibitory errors in children has been found to predict externalizing behaviors (67,68). Indeed, deficits in response inhibition are observed in pediatric BD (69,70). A preliminary study of the functional benefits of working memory training in youth with BD also found evidence of near and far transfer of working memory improvement (71). The greater FC of striatal and limbic regions of emotion and reward networks with the MFG and other visuospatial and attention-processing regions in HR-BD youth suggests greater compensatory attention regulation and behavioral control. Thus, the relative hyperconnectivity of emotion and reward networks with cognitive control regions may serve to counteract familial vulnerability in HR youth.

While dorsal striatum FC differentiated RES from CVT HR youth, these two groups did not differ in ventral striatal FC. In this context, we previously found that HR-BD youth show significantly reduced putamen (i.e., dorsal striatal) activation and putamen–ventral anterior cingulate cortex FC during implicit emotion processing compared with HR-MDD and LR but no differences in ventral striatal FC (42). The dorsal and ventral striatum subserve different reward functions (72). For instance, selective activation of the ventral striatum is found during reward anticipation, whereas dorsal striatum activation also increases proportional to the magnitude of anticipated punishment (73). Our findings suggest that the ventral striatum has shared common origins in HR-BD and HR-MDD youth that are difficult to distinguish before symptom expression but may arise after the onset of BD or MDD. Dissociable patterns of striatal reward circuit processing and FC have been found to differentiate symptomatic patients with BD and MDD (74–77) that may represent differences in pathophysiological processes underlying BD and MDD (78). Indeed, state-dependent differences within BD (e.g., [hypo]mania vs. bipolar depression) cannot be inferred from asymptomatic risk group comparisons but point to temporal differences in neural mechanisms (79). Thus, our findings may indicate trait-level premorbid differences between HR-BD and HR-MDD youth. Future studies are needed to assess whether aberrant reward processing, particularly with respect to loss or punishment, is characteristic of HR-BD youth relative to HR-MDD and LR youth.

Risk status was found to moderate the relation between family rigidity and amygdala–fusiform gyrus FC, such that the negative association between family rigidity and FC was strongest among the HR-BD group. Thus, having a parent with BD moderates the relation between family rigidity and corticolimbic FC, providing insight about how bipolar risk and context may selectively modulate connectivity in brain networks that subserve emotion regulation in children. In particular, child-perceived family rigidity appears to distinctively characterize intrinsic amygdala FC with the fusiform gyrus in HR-BD youth. Relatedly, interaction effects between negative stressful life events and activity in the amygdala and fusiform gyrus have been previously identified in HR-BD youth during emotion processing (19). Indeed, living with a parent diagnosed with either BD or MDD has been found to contribute to a greater likelihood of experiencing repeated stressful life events and reduced parental care (19,80), and limbic networks appear to be particularly vulnerable to the effects of early adversity (81). Greater activation of the fusiform gyrus and other higher-

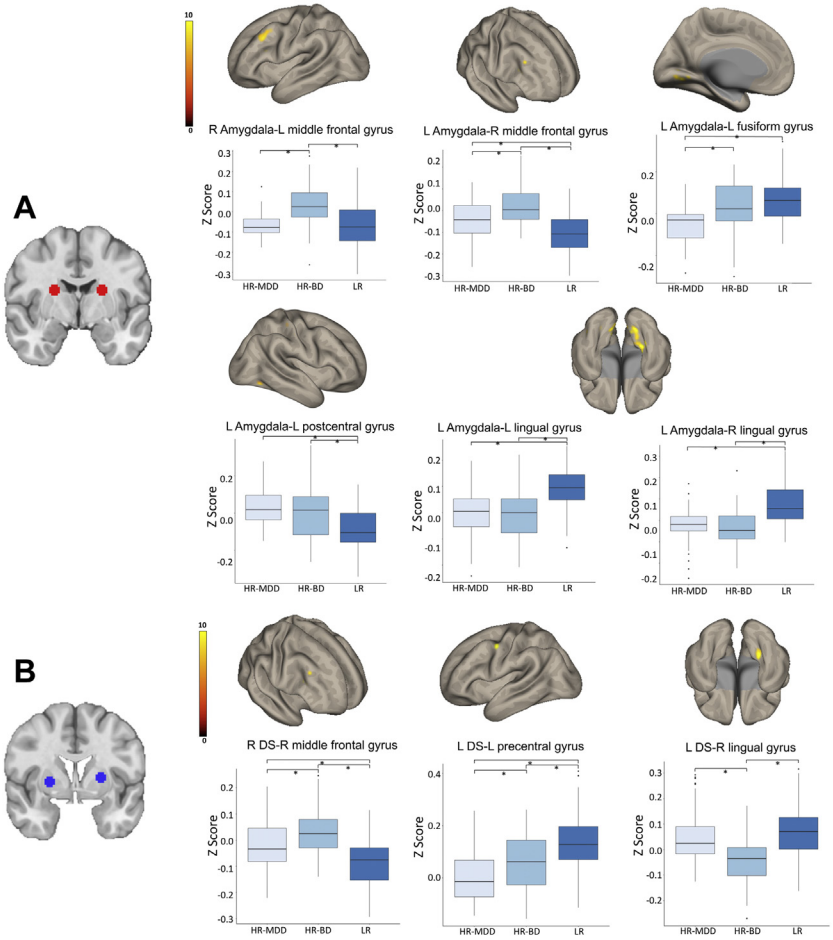

Figure 1. High-risk bipolar disorder (HR-BD), high-risk major depressive disorder (HR-MDD), and low-risk (LR) between-group functional connectivity (FC) differences. **(A)** Bilateral amygdala seeds (central x, y, z coordinates: ±22, −5, +17). HR-BD displayed greater FC between the right amygdala and the left middle frontal gyrus (peak x, y, z coordinates: −50, +20, +26) compared with HR-MDD and LR. HR-BD displayed greater FC between the left amygdala and the right middle frontal gyrus (peak x, y, z coordinates: +32, +26, +28) compared with HR-MDD and LR. HR-MDD displayed reduced FC between the left amygdala and the left fusiform gyrus (peak x, y, z coordinates: −38, −62, −12) compared with HR-BD and LR. HR-BD and HR-MDD displayed greater FC between the left amygdala and the left postcentral gyrus (peak x, y, z coordinates: −48, −36, +56) compared with LR. HR-BD and HR-MDD displayed reduced FC between the left amygdala and the left lingual gyrus (peak x, y, z coordinates: −8, −62, −8) and right lingual gyrus (peak x, y, z coordinates: + 30, −42, −14) compared with LR. **(B)** Bilateral dorsal striatum (DS) seeds (central x, y, z, coordinates: ±24, +4, +2). HR-BD displayed greater FC between the right DS and the right middle frontal gyrus (peak x, y, z coordinates: +32, +28, +30) compared with HR-MDD and LR. HR-MDD exhibited reduced FC between the left DS and the left precentral gyrus (peak x, y, z coordinates: +54, +2, +48) compared with HR-BD and LR. HR-BD displayed reduced FC between the left DS and the right lingual gyrus (peak x, y, z coordinates: +30, −44, −6) compared with HR-MDD and LR. Color bar represents *F* values from one-way analyses of variance. Significant between-group FC differences were corrected for multiple comparisons at $p < .001$ voxel-level and $p < .05$ cluster-level threshold. L, left; R, right.

order face-processing brain regions involved in social cognition and emotion processing have also been found to differentiate HR-BD from LR youth during emotion processing (16). Parenting requires flexibility in response to changing contextual demands; thus, greater rigidity within the family context could prevent adaptive plasticity within limbic circuitry that is needed to develop healthy self-regulation and emotion processing in offspring (24).

Family dynamic has been conceptualized as an environmental factor that can be modified via therapeutic interventions, such as family-focused therapy, for BD to restore family functioning and to sustain recovery from mood symptoms in youth at high risk for BD (82,83). Although our findings require replication, our results suggest that family rigidity alters the development of limbic circuitry or, conversely, that amygdala hyperconnectivity with face-processing regions contributes to greater family rigidity, thereby conferring heightened risk for emotion dysregulation among HR-BD youth (32,84,85). Indeed, changes in FC within this brain network is a mechanism by which researchers have posited that biobehavioral synchrony develops between parents and children, serving as a substrate for the evolving dynamics within a family system (24). Thus, targeting limbic-associated face emotion processing in a family context also has clinical implications, given that family functioning is a known modifiable risk factor that can be targeted in preventive interventions for HR-BD youth.

Greater baseline FC with prefrontal cortical regions distinguished reslience relative to conversion to psychopathology, including greater amygdala–orbitofrontal cortex and ventral striatum–dorsal anterior cingulate cortex FC. These brain regions are implicated in top-down modulation of emotion and reward processing (10), which are dysregulated in HR-BD (86,87) and HR-MDD (14,20) youth and posited to contribute to mood symptoms in BD and MDD (10). In a separate investigation of adolescent females at familial risk for MDD, we found that greater amygdala–orbitofrontal cortex FC (14) and greater striatum and anterior cingulate cortex activation during reward processing (15) distinguished resilient from remitted-depressed adolescents. Distinct FC profiles with the fusiform gyrus were also found to distinguish subsequent risk from resilience, a finding that has been proposed to be a candidate resilience (vs. risk) endophenotype in youth at familial risk for BD (16,88). Thus, our findings suggest that youth at high familial risk for mood disorders have compensatory, protective

Table 2. Baseline Between-Group Functional Connectivity Differences (HR-BD vs. HR-MDD vs. LR)

Group Characteristic	L/R	Cluster Size, mm^3	MNI Coordinates			Fisher *z* Scores, Mean (SD)		
			x	y	z	HR-BD	HR-MDD	LR
Right Amygdala Seed								
Middle frontal gyrus[a,b]	L	109	−50	+20	+26	0.031 (0.110)	−0.067 (0.062)	−0.072 (0.107)
Left Amygdala Seed								
Middle frontal gyrus[c]	R	172	+32	+26	+28	0.023 (0.088)	−0.046 (0.013)	−0.109 (0.091)
Lingual gyrus[b,d]	L	177	−8	−62	−8	−0.008 (0.103)	−0.007 (0.096)	0.091 (0.086)
Lingual gyrus[b,d]	R	477	+30	−42	−14	−0.035 (0.092)	−0.026 (0.086)	0.075 (0.095)
Fusiform gyrus[a,d]	L	66	−38	−62	−12	0.028 (0.122)	−0.054 (0.090)	0.063 (0.110)
Postcentral gyrus[b,d]	L	64	−48	−36	+56	−0.003 (0.131)	0.029 (0.103)	−0.084 (0.109)
Right Dorsal Striatum Seed								
Middle frontal gyrus[c]	R	129	+32	+28	+30	0.033 (0.100)	−0.022 (0.096)	−0.091 (0.094)
Left Dorsal Striatum seed								
Precentral gyrus[c]	L	100	+54	+2	+48	0.060 (0.114)	0.003 (0.100)	0.137 (0.123)
Lingual gyrus[a,b]	R	96	+30	−44	−6	−0.045 (0.092)	0.049 (0.111)	0.076 (0.108)

Significant functional connectivity differences between HR-BD, HR-MDD, and LR. All reported clusters reached significance of voxel-level $p < .001$ and FDR-corrected cluster-level $p < .05$.

FDR, false discovery rate; HR-BD, high-risk bipolar disorder; HR-MDD, high-risk major depressive disorder; L, left; LR, low-risk; MNI, Montreal Neurological Institute; R, right.

[a]Post hoc Tukey test results indicate that HR-BD and HR-MDD are significantly different.

[b]Post hoc Tukey test results indicate that HR-BD and LR are significantly different.

[c]Post hoc Tukey test results indicate that HR-BD, HR-MDD, and LR are significantly different.

[d]Post hoc Tukey test results indicate that HR-MDD and LR are significantly different.

connectivity characteristics within emotion and reward processing networks that confer resilience to psychopathology.

Finally, we investigated whether baseline FC that differentiated HR-MDD, HR-BD, and LR predicted resilience or the development of psychopathology at follow-up. Differences in baseline striatolimbic FC among these groups did not predict resilience versus conversion to psychopathology. One possible explanation for this null finding is that intrinsic FC differences in limbic circuitry that differentiate HR-BD, HR-MDD, and LR are distinct from those that distinguish resilience from conversion to psychopathology to psychiatric diagnosis. Another possibility is that our follow-up time window, which is among the longest follow-up periods of healthy youth at high risk for BD and MDD (4.5 ± 2.4 years), may still not have been sufficient to capture the neurobiological impact of conversion to psychopathology within striatolimbic circuitry.

Limitations

We note four limitations of this study. First, the sample size is modest; larger samples are needed to replicate and extend our findings. Nevertheless, this is the largest study to date to directly compare FC between HR-BD, HR-MDD, and LR youth and differences in baseline FC that distinguish subsequent resilience from conversion to psychopathology. Second, neuroimaging data and measures of family dynamic were obtained at one time point; it will be informative to assess longitudinal developmental trajectories of emotion processing and reward circuitry that may distinguish HR-BD, HR-MDD, and LR youth and RES from CVT, as well as trajectories of family dynamics and parent-child relationships. Third, not all youth were followed longitudinally through the end of adolescence; thus, some youth categorized as resilient may develop psychopathology later. Finally, due to sample size, we were unable to

Table 3. Follow-up Between-Group Functional Connectivity Differences (RES vs. CVT)

Group Characteristic	L/R	Cluster Size, mm^3	MNI Coordinates			Fischer *z* Scores, Mean (SD)	
			x	y	z	CVT	RES
Right Amygdala Seed							
Paracingulate gyrus	L	81	−16	+34	−08	−0.141 (0.153)	−0.012 (0.101)
Orbitofrontal cortex	R	82	+20	+24	0	−0.078 (0.162)	0.057 (0.079)
Left Ventral Striatum Seed							
Ventral anterior cingulate cortex	L/R	337	0	+34	+24	0.053 (0.120)	0.178 (0.110)
Left Dorsal Striatum Seed							
Fusiform gyrus	L	167	−30	−12	−46	0.095 (0.098)	−0.038 (0.091)
Postcentral gyrus	L	113	−12	−44	+72	−0.022 (0.103)	0.105 (0.111)

Significant functional connectivity differences between RES and CVT. All reported clusters reached significance of voxel-level $p < .001$ and FDR-corrected cluster-level $p < .05$.

CVT, conversion; FDR, false discovery rate; L, left; MNI, Montreal Neurological Institute; R, right; RES, resilience.

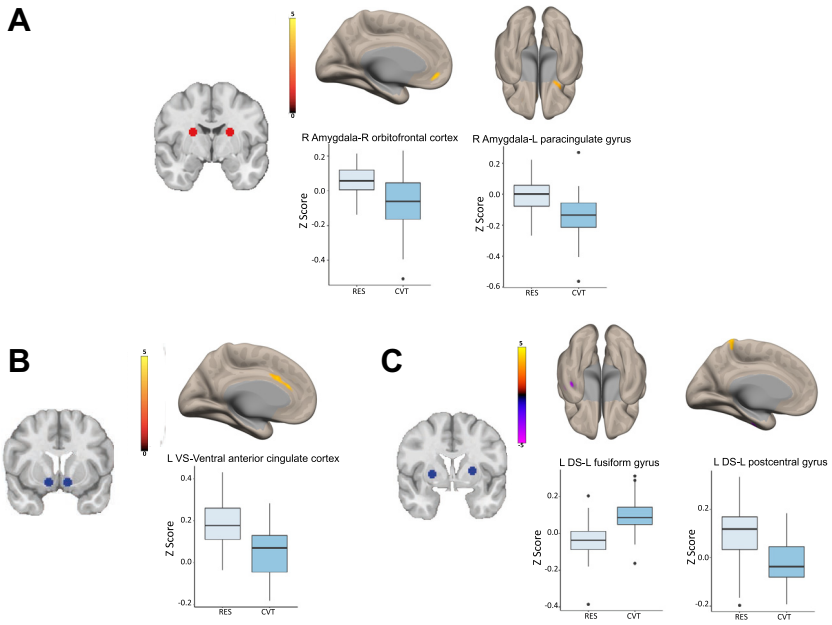

Figure 2. Resilience (RES) vs. conversion (CVT) functional connectivity (FC) differences. **(A)** Bilateral amygdala seeds (central x, y, z, coordinates: ±22, −5, +17). RES had greater FC between the right amygdala and the right orbitofrontal cortex (peak x, y, z coordinates: +20, +24, 0) and the left paracingulate gyrus (peak x, y, z coordinates: −16, +34, −8) relative to CVT. **(B)** Ventral striatum (VS) seeds (central x, y, z, coordinates: +9, +9, −8). RES had greater FC between the left VS and the ventral anterior cingulate cortex (peak x, y, z coordinates: 0, +34, +24) relative to CVT. **(C)** Dorsal striatum (DS) seeds (central x, y, z, coordinates: ±24, +4, +2). RES had decreased FC between the left DS seed and the left fusiform gyrus (peak x, y, z coordinates: −30, −12, −46) and greater FC between the left DS seed and the left postcentral gyrus (peak x, y, z coordinates: −12, −44, +72) relative to CVT. Color bar represents *t* values from the between-group paired *t* tests. Significant between-group connectivity differences were corrected for multiple comparisons at voxel-level $p < .001$ and cluster-level $p < .05$. L, left; R, right.

compare FC differences that distinguished resilience versus conversion to psychopathology within HR-BD and HR-MDD separately. Thus, we are limited in our ability to examine how the differential profiles of FC are related to resilience versus conversion to psychopathology. While longitudinal studies of larger HR samples are needed, this study highlights unique markers of resilience versus conversion to psychopathology among otherwise healthy asymptomatic youth at high risk for a mood disorder, which is a valuable contribution to the field. Indeed, BD is often misdiagnosed as MDD in the pediatric age range studied (89). Future research that follows youth into adulthood should examine whether the intrinsic FC profiles characterized here predict onset of or protect youth from developing psychopathology.

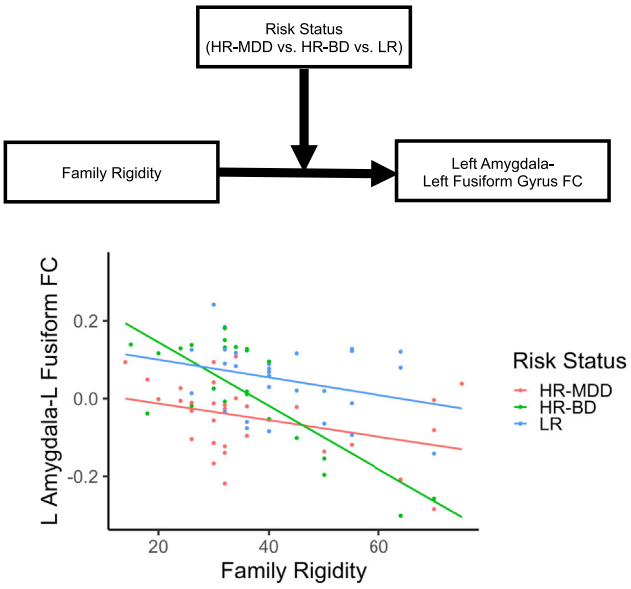

Figure 3. Risk status moderates the relationship between amygdala functional connectivity (FC) and family function. Moderation analyses demonstrated that risk status moderated the relationship between family rigidity and amygdala–fusiform gyrus FC, such that the negative association between family rigidity and FC was stronger among the high-risk bipolar disorder (HR-BD) group compared with the high-risk major depressive disorder (HR-MDD) group ($\beta = -0.938$, $t_{77} = -3.497$, $p < .001$) and the low-risk (LR) group ($\beta = -0.916$, $t_{77} = -2.913$, $p = .005$). The negative association between family rigidity and FC was not different in the HR-MDD group compared with the LR group ($\beta = 0.026$, $t_{77} = 0.082$, $p = .935$). L, left.

While preliminary, our findings identify potential targets and modifiable risk factors that might improve approaches to prevention and treatment selection for youth at familial risk for mood disorders. Specifically, our prior work has found that youth randomized to family-focused therapy (vs. standard psychoeducation) demonstrated greater connectivity between regions of the cognitive control network (i.e., ventrolateral prefrontal cortex) and the default mode network and a reduction in depression severity that inversely correlated with default mode network connectivity (31). Moreover, family communication training, problem solving, and behavioral parenting strategies have been found to facilitate symptom remission in HR offspring (83). Our findings highlight the potential clinical importance of interventions that promote less rigid and more flexible parent-child interactions in HR-BD youth who are otherwise healthy and asymptomatic, and these interventions may alter striatolimbic FC, thereby promoting family resilience and reducing the likelihood of the onset of psychopathology in youth at high familial risk for mood disorders.

Conclusions

In this study, we characterized unique profiles within emotion regulation and reward processing brain networks in youth at

high familial risk for BD and MDD relative to youth at low familial risk for psychopathology. We also demonstrated the moderating effect of familial risk status on the relationship between dynamics within the family system and limbic FC. Although larger longitudinal studies are needed, our findings offer insights into neural signatures of risk and resilience, as well as compensatory processes within emotion and reward processing networks in youth at familial risk for pediatric mood disorders that may be targets for early identification and prevention programs. Taking a social neuroscience approach to the study of child-onset mood disorders with a focus on the mechanisms underpinning the intergenerational transmission of mood disorders, we will continue to identify modifiable mediators and moderators of risk that may help prevent psychopathology and improve outcomes in HR youth.

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