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Association of Neuroimaging Measures of Emotion Processing and Regulation Neural Circuitries With Symptoms of Bipolar Disorder in Offspring at Risk for Bipolar Disorder

Heather E. Acuff, PhD; Amelia Versace, MD; Michele A. Bertocci, PhD; Cecile D. Ladouceur, PhD; Lindsay C. Hanford, PhD; Anna Manelis, PhD; Kelly Monk, BSN, RN; Lisa Bonar, BS; Alicia McCaffrey, BS; Benjamin I. Goldstein, MD, PhD; Tina R. Goldstein, PhD; Dara Sakolsky, MD, PhD; David Axelson, MD; Boris Birmaher, MD; Mary L. Phillips, MD, MD (Cantab); for the Longitudinal Assessment of Manic Symptoms (LAMS) Consortium

IMPORTANCE Bipolar disorder (BD) is difficult to distinguish from other psychiatric disorders. Neuroimaging studies can identify objective markers of BD risk.

OBJECTIVE To identify neuroimaging measures in emotion processing and regulation neural circuitries and their associations with symptoms specific to youth at risk for BD.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional (August 1, 2011, to July 31, 2017) and longitudinal (February 1, 2013, to November 30, 2017) neuroimaging study performed at the University of Pittsburgh Medical Center compared a sample of 31 offspring of parents with BD (OBP) with 28 offspring of comparison parents with non-BD psychopathologies (OCP) and 21 offspring of healthy parents (OHP); OBP, OCP, and OHP were recruited from the Bipolar Offspring Study and the Longitudinal Assessment of Manic Symptoms Study.

MAIN OUTCOMES AND MEASURES Group differences in activity and functional connectivity during emotional face processing and n-back task performance in amygdala, dorsolateral and ventrolateral prefrontal cortices (PFC), caudal anterior cingulate cortices (cACC), and rostral anterior cingulate cortices (rACC) neuroimaging measures showing between-group differences and symptom severity (anxiety, affective lability, depression, mania). We hypothesized that elevated amygdala activity and/or lower PFC activity and abnormal amygdala to PFC functional connectivity would distinguish OBP from OCP and OHP, and magnitudes of these abnormalities would positively correlate with elevated symptom severity. We explored associations between changes in neuroimaging and symptom measures over follow-up (mean [SD], 2.9 [1.4] years) in a subset of participants (n = 30).

RESULTS Eighty participants were included (mean [SD] age, 14.2 (2.1) years; 35 female). Twelve neuroimaging measures explained 51% of the variance in the results of neuroimaging measures overall. Of the 12, 9 showed significant main associations of the group; however, after post hoc analyses and Bonferroni corrections, only 7 showed statistically significant associations between groups (corrected $P < .05$ for all). Of the 7, 2 showed significant relationships with symptoms. Offspring of parents with BD had greater right rACC activity when regulating attention to happy faces vs OCP (mean [SD] difference, 0.744 [0.249]; 95% CI, 0.134-1.354; $P = .01$), which positively correlated with affective lability severity ($\rho = 0.304$; uncorrected $P = .006$). Offspring of parents with BD had greater amygdala to left cACC functional connectivity when regulating attention to fearful faces vs OCP (mean [SD] difference, 0.493 [0.169]; 95% CI, 0.079-0.908; $P = .01$). Increases in this measure positively correlated with increases in affective lability over follow-up ($r = 0.541$; $P = .003$).

CONCLUSIONS AND RELEVANCE Greater anterior cingulate cortex activity and functional connectivity during emotion regulation tasks may be specific markers of BD risk. These findings highlight potential neural targets to aid earlier identification of and guide new treatment developments for BD.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Longitudinal Assessment of Manic Symptoms (LAMS) Consortium members are listed at the end of this article.

Corresponding Author: Heather E. Acuff, PhD, University of Pittsburgh, 121 Meyran Ave, 203 Loeffler Bldg, Pittsburgh, PA 15213 (hea19@pitt.edu).

Bipolar Disorder (BD), a serious, recurrent illness, often emerges during adolescence.[1-3] Overall, 15% to 28% of adults with BD experience illness onset younger than 13 years and 50% to 66% younger than 19 years.[4-6] Approximately 5.6% of adolescents have subthreshold manic, hypomanic, or depressive symptoms, while some symptoms of BD overlap with other disorders, such as major depressive disorder, attention-deficit/hyperactive disorder, or anxiety disorders, which makes BD difficult to diagnose.[7,8] It is thus important to identify objective biological markers to help differentiate BD from other disorders.

Bipolar disorder has a heritability of 59% to 87%, placing first-degree relatives at high risk for BD.[9] Compared with children of parents without psychiatric illness, offspring of parents with BD (OBP) are at increased risk of BD and other mood and anxiety disorders.[10] Studying OBP and comparing OBP with offspring of healthy parents (OHP) can identify early phenotypes associated with BD risk. An additional comparison group is necessary to determine whether risk markers are specific to BD or to general psychopathology, however. In a recent study,[11] 23.0% of OBP developed a bipolar spectrum disorder by age 21 years compared with 3.2% in offspring of comparison parents (OCP) with a non-BD diagnosis.[11] Including OCP can thus control for risk for non-BD psychiatric disorders and for environmental effects of living with a parent with psychiatric illness.[12] The Bipolar Offspring Study (BIOS)[13] is a longitudinal study that aims to identify objective neural markers of BD risk by comparing emotion processing and regulation neural circuitries in OBP and OCP.[13] Two previous BIOS studies[14,15] examined activity and functional connectivity using emotion processing and regulation tasks separately. That we know of, no studies have examined how measures of activity and functional connectivity in emotion processing and emotional regulation neural circuitries distinguish OBP from control groups.

Neural regions implicated in emotion processing[16] and regulation[17] include the amygdala, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC), and ventrolateral prefrontal cortex (vlPFC). Functional abnormalities in these circuitries in youth and adults with BD[18] include elevated amygdala activity to emotional stimuli,[19,20] lower prefrontal cortical (PFC) activity during emotion regulation,[16,21,22] and lower amygdala to vlPFC functional connectivity.[23-28] Cross-sectional studies of BD at-risk youth reported mixed results. Compared with OHP, OBP showed greater vlPFC activity to happy faces and reduced amygdala to vlPFC functional connectivity to fearful faces during emotional regulation,[15] greater amygdala activity to fearful faces during emotion processing,[29] and abnormal PFC-subcortical resting-state functional connectivity.[30] Comparing all 3 groups during emotional face processing, OBP and OCP showed greater right amygdala activity to all emotional faces vs OHP, while OBP showed lower positive right amygdala to ACC functional connectivity to all emotional faces and more positive right amygdala to left vlPFC functional connectivity to happy faces than OCP and OHP.[14] More studies are needed to identify abnormalities in emotion processing and regulation neural circuitries specific to OBP.

Relationships between neuroimaging measures and symptoms associated with BD risk remain relatively unexamined.

Key Points

Question Are there specific abnormalities in activity and functional connectivity in emotion processing and regulation neural circuitries in offspring at risk for bipolar disorder?

Findings In this cross-sectional study, relative to offspring of healthy parents, offspring of parents with bipolar disorder had significantly greater right rostral anterior cingulate cortex activity when regulating attention away from happy faces, which was significantly positively correlated with affective lability symptom severity. Additionally, offspring of parents with bipolar disorder had significantly greater amygdala to left caudal anterior cingulate cortex functional connectivity to fearful faces relative to offspring of parents without bipolar disorder but with other psychiatric disorders.

Meaning Greater activity and functional connectivity during emotion regulation tasks in the anterior cingulate cortex may help distinguish youth at risk for bipolar disorder from healthy youth and from youth at risk for other psychiatric disorders.

Significant symptoms of anxiety, affective lability, depression, and mania are the strongest dimensions of psychopathology associated with BD risk.[31] In emotionally dysregulated youth, worsening affective lability and depression severity correlated with increased right amygdala and left vlPFC activity, worsening anxiety with decreased right amygdala and increased left vlPFC activity, and worsening mania with increased right amygdala and decreased left vlPFC activity over time.[32] In OCP, right amygdala to ACC functional connectivity positively correlated with affective lability, depression, and anxiety severity.[14] Such studies have yet to find significant relationships between functioning in emotion processing and regulation neural circuitries and symptom severity in OBP, however. Examining these relationships can improve understanding of BD development in youth, and may enhance early identification of BD risk in, and guide novel interventions for, OBP.

Based on the literature demonstrating differences between OBP and both OCP and OHP in emotion processing and regulation neural circuitries, and the importance of relating these measures to symptoms associated with BD risk, we hypothesized that elevated amygdala and/or lower PFC activity and abnormal amygdala to PFC functional connectivity in emotion processing and regulation neural circuitries would distinguish OBP from OCP and OHP; and magnitudes of these abnormal neuroimaging measures would be positively associated with elevated anxiety, affective lability, depression, and/or mania severity in OBP vs other youth. In exploratory analyses, we examined whether changes in neuroimaging measures over time were significantly associated with changes in symptom severity in all offspring.

Methods

Participants

Thirty-one OBP (mean [SD] age, 13.9 [2.4] years; 15 female), 28 OCP (mean [SD] age, 14.5 [2.0] years; 10 female), and 21 OHP (mean [SD] age, 14.2 [1.5] years; 10 female) were recruited from

Table 1. Comparison of OBP, OCP, and OHP

Characteristic	OBP (N = 31)	OCP (N = 28)	OHP (N = 21)	Statistic[a]	*P* Value
Age, mean (SD), y	13.87 (2.42)	14.48 (2.01)	14.20 (1.48)	$F = 0.648$	.53
Female sex, No.	15	10	10	$\chi^2 = 1.133$	.57
IQ, mean (SD)[b]	101.13 (15.55)	101.75 (14.84)	105.71 (12.18)	$F = 0.692$	.50
Socioeconomic status, No.[c]				$\chi^2 = 13.986$	.08
Very low (8-19)	7	5	1		
Low (20-29)	8	1	4		
Medium (30-39)	6	4	1		
High (40-54)	7	10	9		
Very high (55-66)	3	8	6		
Handedness				$\chi^2 = 5.050$	.28
Right	26	26	19		
Left	2	2	2		
Mixed	3	0	0		
Highest parental education, No.				$\chi^2 = 5.960$	.43
High school graduate or lower	5	1	4		
Partial college or specialized training	13	8	8		
Standard college or university graduate	7	11	5		
Graduate professional training	6	8	4		
Clinical measures, No.					
Diagnosis	12	14	0	$F = 8.569$	<.001
Major depressive disorder	3	3	0	$F = 1.156$	.32
Anxiety disorder	3	5	0	$F = 2.164$	.12
Attention-deficit/ hyperactivity disorder	5	8	0	$F = 3.807$	.03
Oppositional defiant or conduct disorder	1	3	0	$F = 1.623$	.20
Obsessive-compulsive disorder	0	1	0	$F = 0.927$	.40
Eating disorder	1	0	0	$F = 0.786$	.46
Psychotropic medication use	5	6	0	$F = 2.608$	.08
Scan day assessments, mean (SD)					
SCARED parent rating	9.84 (6.92)	9.50 (11.14)	4.62 (4.69)	$F = 2.932$	.06
SCARED child rating	12.81 (14.95)	8.00 (12.16)	9.36 (11.86)	$F = 1.029$	.36
CALS parent rating	8.19 (9.19)	4.64 (4.84)	1.62 (2.71)	$F = 6.464$	<.001
CALS child rating	10.32 (12.48)	5.32 (8.76)	6.19 (13.96)	$F = 1.504$	.23
MFQ parent rating	6.55 (9.08)	4.48 (5.00)	1.38 (2.13)	$F = 3.909$	.02
MFQ child rating	8.41 (10.87)	7.84 (10.95)	5.29 (11.03)	$F = 0.536$	.59
Assessment closest to scan, mean (SD)					
KMRS	1.77 (2.69)	0.54 (1.04)	0.05 (0.23)	$F = 6.223$	<.001
KDRS	2.58 (5.26)	2.00 (3.74)	0.26 (0.56)	$F = 2.005$	.14

Abbreviations: CALS, Children's Affective Lability Scale child rating; KDRS, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Depression Rating Scale; KMRS, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale; MFQ, Mood and Feelings Questionnaire; OBP, offspring of parents with bipolar disorder; OCP, offspring of comparison parents; OHP, offspring of healthy parents; SCARED, Screen for Child Anxiety–Related Emotional Disorders.

[a] *F*, analysis of variance test.

[b] Wechsler Intelligence Test.

[c] Socioeconomic status was assessed with the Hollingshead Four Factor Index of Social Status[34]

BIOS[33] and the Longitudinal Assessment of Manic Symptoms Study (**Table 1**).[35,36] Participants were matched for age, sex, IQ, and socioeconomic status (SES). Twenty-six OBP, 21 OCP, and 19 OHP were included in a previous BIOS study by Manelis et al.[14]

Offspring of parents with BD had at least 1 parent with BD; OCP had at least 1 parent with a non-BD disorder (major depressive disorder, attention-deficit/hyperactive disorder, and/or an anxiety disorder). Exclusion criteria included history of serious medical illness, head injury, or neurological disorder; IQ less than 70 assessed with Wechsler Abbreviated Scale of Intelligence[37]; BD, autism, or schizophrenia; magnetic resonance imaging (MRI) contraindication (eg, pregnancy, metal in the body); substance abuse on the day of the scan or substance abuse disorder in the last 3 months; and task accuracy less than 70%. For OHP, additional exclusion criteria included any history of a *DSM-5* disorder. Before participation, parents and guardians provided written informed consent, and

youth provided written informed assent. Participants received monetary compensation (eAppendix in the Supplement for recruitment and exclusion criteria). This study received institutional review board approval from the University of Pittsburgh, and all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.[38]

Psychiatric diagnoses were confirmed by a licensed psychiatrist or psychologist before scanning using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS)-Present and Lifetime Version[39] for offspring, and the Structural Clinical Interview[40] for *DSM-IV* for parents. Symptom assessments included the Screen for Child Anxiety-Related Disorders (SCARED),[41,42] Children's Affective Lability Scale (CALS),[43] Mood and Feelings Questionnaire (MFQ),[44] and K-SADS Mania (KMRS)[45] and Depression (KDRS)[39] Rating Scales. Parent-reported (-P) and child-reported (-C) SCARED, CALS, and MFQ were administered on the scan day; summary KMRS and KDRS interviews, based on both parent and child information, were administered a mean 2 months after the scan.

Five OBP and 6 OCP took antidepressant, antipsychotic, stimulant, and/or nonstimulant medications for non-BD diagnoses. Medicated OBP had greater CALS-P severity than unmedicated OBP (mean [SD] difference, 8.853 [3.916]; 95% CI, 0.845-16.862; $t_{29} = -2.261$; uncorrected $P = .03$).

Neuroimaging Data Acquisition

All scan 1 and 15 scan 2 images (mean [SD], 2.9 [1.4] year interscan interval) were acquired on a Magnetom TrimTrio 3T scanner (Siemens Healthcare). Fifteen scan 2 images were acquired on a Magnetom Prisma scanner. Participants completed an emotional face processing task—the dynamic faces task (DFT)—during functional MRI to assess implicit emotional processing[21,46-48] and an emotional face n-back task, with 0-back (EF-0-BACK) and 2-back (EF-2-BACK) conditions, to examine neural regions implicated in emotional regulation during redirection of attention away from emotionally salient distracters during a working memory task[49] (eFigures 1 and 2 in the Supplement).

Neuroimaging Data Analyses

Information about preprocessing can be found in the eAppendix in the Supplement. Generalized psychophysiological interaction analyses assessed task-related connectivity between a bilateral amygdala seed and regions of interest. Task stimulus contrasts included, separately, happy, sad, angry, and fearful faces vs shapes for DFT; fearful, happy, and neutral vs no faces, and fearful and happy vs neutral faces for EF-0-BACK and EF-2-BACK; and EF-2-BACK vs EF-0-BACK for fearful, happy, neutral, and no faces. Regions of interest, anatomically defined using FreeSurfer Center for Morphometric Analysis standard labels, included bilateral amygdala, caudal ACC (cACC), rostral ACC (rACC), dlPFC, and vlPFC. Individual-level averaged blood oxygen level–dependent waveforms to the onset of each stimulus type were extracted in native space from anatomic regions of interest to main stimulus contrasts per task.

Primary Hypotheses

A single elastic net regression analysis with k = 10-fold cross-validation and α = .5 was used for data selection and reduction using GLMNET in R (R Foundation).[50] This model contained 2 dummy-coded outcome variables: BD risk (OBP vs OCP/OHP) and general psychiatric disorders risk (OBP/OCP vs OHP). The model also contained 336 predictor variables, including demographic information (age, sex, IQ, SES [assessed with Hollingshead Four Factor Index of Social Status[34]], handedness, highest parental education), functional connectivity between bilateral amygdala and each region of interst (left/right cACC, rACC, dlPFC, vlPFC), and activity in each region of interest (left/right amygdala, cACC, rACC, dlPFC, vlPFC) for each contrast and task (eAppendix in the Supplement).

Post hoc pseudo R^2 analyses examined the proportion of variance in dependent variables explained by the nonzero predictor variables observed with elastic net. Analyses of variance (ANOVAs) and post hoc *t* tests examined between-group differences in neuroimaging measures for all nonzero predictors and symptom measures. Correlation analyses examined associations between neuroimaging and symptom measures. Significance was set at 2-tailed $P < .05$.

Exploratory Analyses

In 9 OBP, 7 OCP, and 14 OHP with second scans, correlation and linear regression analyses examined associations between changes in symptoms and changes in neuroimaging measures showing between-group differences in the above analyses. All analyses were repeated removing medicated youth. Additional exploratory analyses are described in the eAppendix and eTables 1 through 6 in the Supplement.

Results

Hypothesis Testing

Of the initial 336 predictors, 12 measures (listed in **Table 2**), together, optimized model fit (λ = 0.553; **Figure 1**). The model chosen in this analysis had a ΔAICc (Akaike information criterion with correction for sample size) = 1.811 (eAppendix in the Supplement). A pseudo R^2, calculated containing 12 predictors from the model vs an intercept-only model, indicated that 51.39% of the variance in group was explained by these predictors. All predictors were neuroimaging measures (Table 2). Post hoc *t* tests, Bonferroni-corrected for 3 between-group parallel tests, examined all 12 neuroimaging measures that were selected as nonzero predictors of group (**Figure 2**). Compared with OHP, OBP had lower DFT left dlPFC activity to angry faces vs shapes (mean [SD] difference, 0.108 [0.033]; 95% CI, 0.027-0.189; $P = .01$). Compared with OCP, OBP had greater EF-2-BACK amygdala to left cACC functional connectivity to fearful faces (mean [SD] difference, 0.493 [0.169]; 95% CI, 0.079-0.908; $P = .01$), happy faces (mean [SD] difference, 0.516 [0.148]; 95% CI, 0.155-0.877; $P = .002$), and neutral faces (mean [SD] difference, 0.604 [0.159]; 95% CI, 0.215-0.992; $P = .001$) vs no faces, and greater EF-2-BACK right rACC activity to happy vs no faces (mean [SD] difference, 0.744 [0.249]; 95% CI, 0.134-1.354; $P = .01$). Compared with OHP, OCP had

Table 2. Between-Group Differences in Neuroimaging and Symptom Measures

Measure	ANOVA		Bonferroni Significance Test for Multiple Comparisons		
	F	*P* Value[a]	OBP vs OCP *P* Value	OBP vs OHP *P* Value	OCP vs OHP *P* Value
Neuroimaging Measure					
Dynamic faces task					
Amygdala to left dorsolateral prefrontal cortex FC to sad faces vs shapes	3.010	.06	.77	.049	.53
Left dorsolateral prefrontal cortex activity to angry faces vs shapes	5.522	.01	>.99	.01	.06
EF-2 BACK					
Amygdala to left cACC functional connectivity to fearful vs no faces	4.352	.02	.01	.29	.99
Amygdala to left cACC functional connectivity to happy vs no faces	6.110	.003	.002	.33	.35
Amygdala to left cACC functional connectivity to neutral vs no faces	7.413	.001	.001	.78	.07
Amygdala to right vlPFC functional connectivity to happy vs neutral faces	2.007	.14	.82	.15	>.99
Right rACC activity to happy vs no faces	4.458	.02	.01	.59	.48
EF-0-BACK					
Amygdala to left dorsolateral prefrontal cortex functional connectivity to happy vs no faces	3.368	.04	>.99	.10	.05
Amygdala to left rACC functional connectivity to happy vs neutral faces	2.254	.11	.55	.13	>.99
Left rACC activity to happy vs neutral faces	5.643	.01	.72	.07	.004
Right rACC activity to happy vs neutral faces	5.039	.01	>.99	.03	.01
EF-2-BACK vs EF-0-BACK					
Amygdala to left rACC functional connectivity to happy faces	3.247	.04	.07	.15	>.99
Symptom Measure					
SCARED parent rating	2.932	.06	>.99	.08	.13
SCARED child rating	1.029	.36	.50	>.99	>.99
CALS parent rating	6.464	.003 (.02)	.12	.002	.34
CALS child rating	1.504	.23	.32	.65	>.99
MFQ parent rating	3.909	.02 (.19)	.73	.02	.33
MFQ child rating	0.536	.60	>.99	.97	>.99
KMRS	6.223	.003 (.02)	.03	.01	>.99
KDRS	2.005	.14	>.99	.16	.45

Abbreviations: ANOVA, analysis of variance; cACC, caudal anterior cingulate cortex; CALS, Children's Affective Lability Scale; EF-0-BACK, emotional 0-back task; EF-2-BACK, emotional 2-back task; KDRS, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Depression Rating Scale; KMRS, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale; MFQ, Mood and Feelings Questionnaire; OBP, offspring of parents with bipolar disorder; OCP, offspring of comparison parents; OHP, offspring of healthy parents; rACC, rostral anterior cingulate cortex; SCARED, Screen for Child Anxiety–Related Emotional Disorders; vlPFC, ventrolateral prefrontal cortex.

[a] Additional Bonferroni corrections presented in parentheses.

lower EF-0-BACK left rACC activity (mean [SD]) difference, 0.802 [0.241]; 95% CI, 0.212-1.391; *P* = .004) and right rACC activity (mean [SD] difference, 0.691 [0.236]; 95% CI, 0.113-1.269; *P* = .01) to happy vs neutral faces, and OBP had lower EF-0-BACK right rACC activity to happy vs neutral faces (mean [SD] difference, 0.626 [0.231]; 95% CI, 0.060-1.192; *P* = .03). No significant group differences were found for the remaining measures.

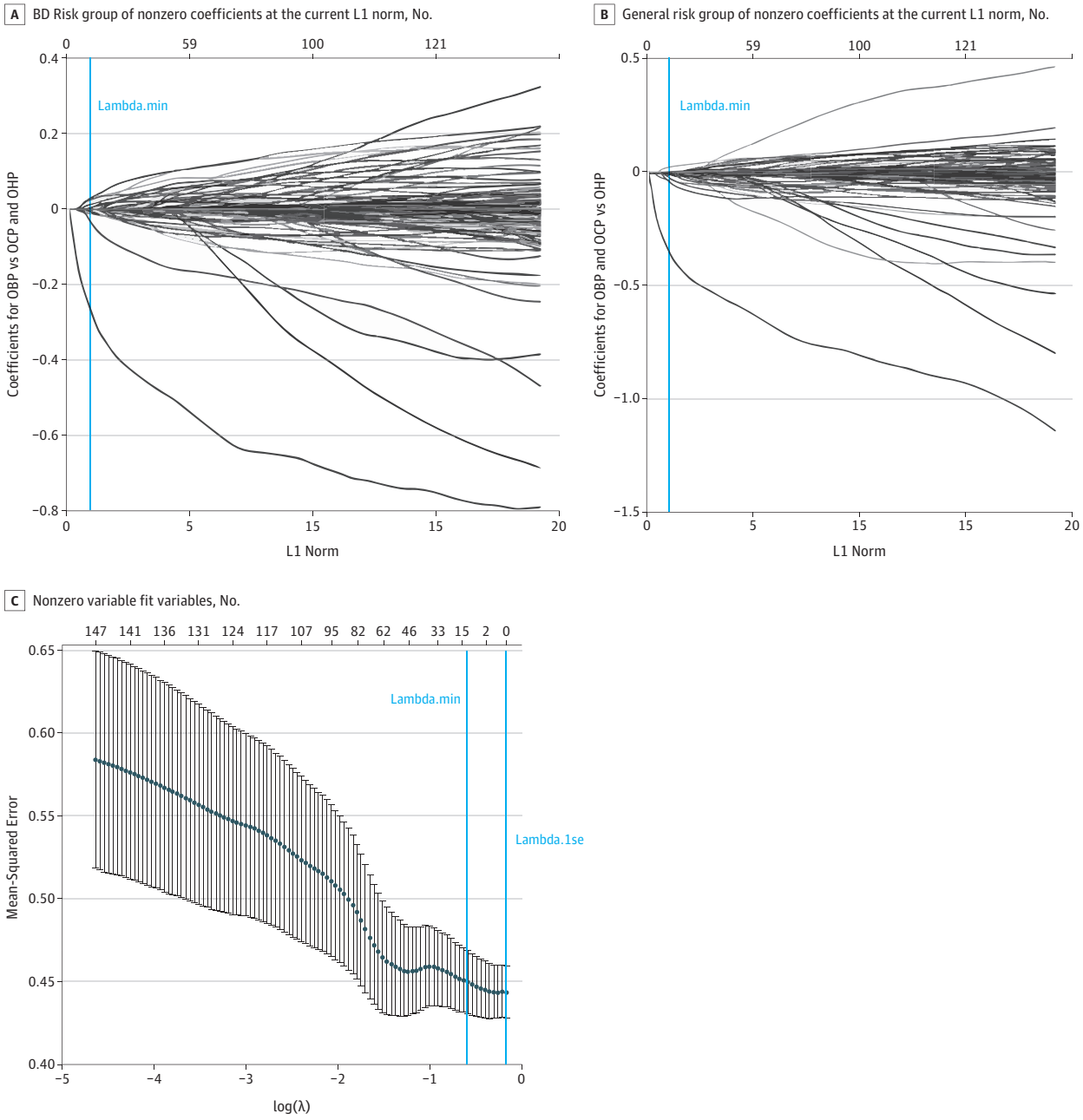
Analyses of variance examined associations between neuroimaging measures and symptoms (Table 2). Bonferroni corrections for 8 parallel tests revealed 2 statistically significant findings: CALS-P ($F_{2,77}$ = 6.464; *P* = .003; corrected *P* = .02) and KMRS ($F_{2,75}$ = 6.223; *P* = .003; corrected *P* = .02). Bonferroni-corrected post hoc *t* tests revealed that OBP had greater CALS-P severity than OHP (mean [SD] difference, 6.575 [1.853]; 95% CI, 2.04-11.11; *P* = .002), and greater KMRS severity than OHP (mean [SD] difference, 1.722 [0.529]; 95% CI, 0.43-3.02; *P* = .01) and OCP (mean [SD] difference, 1.238 [0.473]; 95% CI, 0.08-2.40; *P* = .03) (**Figure 3**A).

Bivariate correlation analyses examined associations among all 7 neuroimaging and 2 symptom measures showing statistically significant group differences. Across all participants, 1 significant association was found: baseline CALS-P severity positively correlated with EF-2-BACK right rACC activity to happy faces (ρ = 0.304; *P* = .01) (Figure 3B). This association just missed significance using Bonferroni corrections for 14 tests.

Exploratory Analyses

Follow-up analyses were in 9 OBP (mean [SD] age, 15.2 [1.90] years), 7 OCP (mean [SD] age, 16.9 [1.7] years), and 14 OHP (mean [SD] age, 15.8 [1.3] years). One OBP and 2 OCP took medications. Bivariate correlation analyses examined associations among changes in all 7 neuroimaging and 2 symptom measures showing significant group differences. Across all 30 follow-up participants, a single significant Bonferroni-corrected relationship was found: increase in CALS-P severity significantly positively correlated with increase in EF-2-BACK

Figure 1. Elastic Net Plots

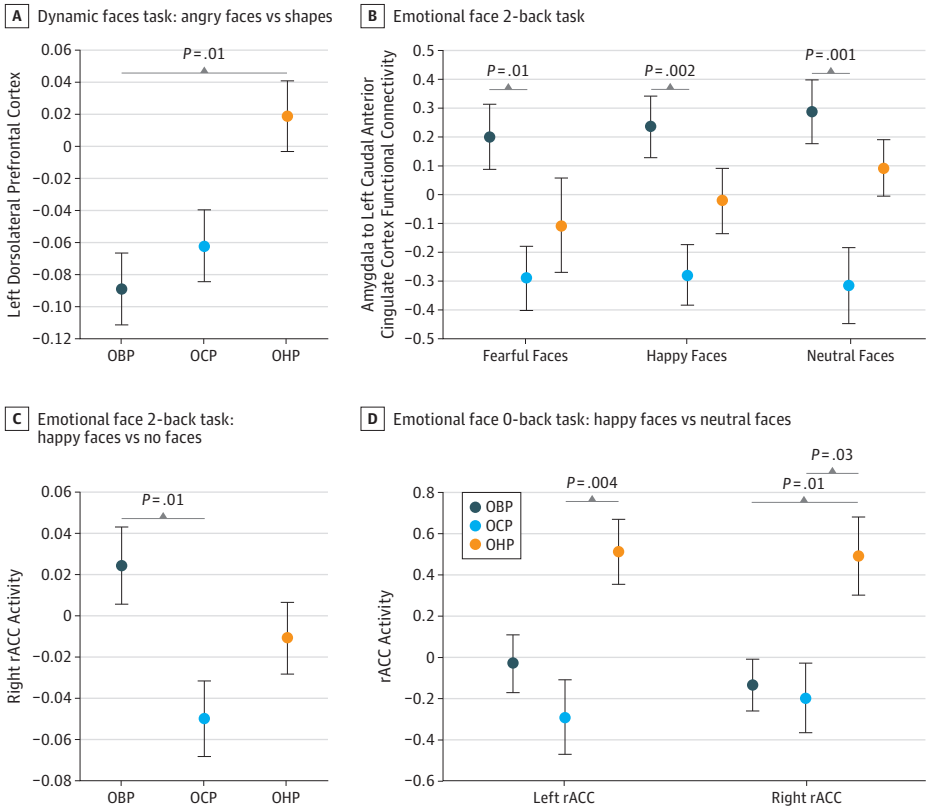


A and B, Plots of variable fit for the bipolar disorder (BD) risk group (offspring of parents with BD [OBP] vs offspring of comparison parents [OCP] and offspring of healthy parents [OHP]) (A), and the general risk group (OBP and OCP vs OHP) (B). Each curve corresponds to an independent variable in the full model prior to optimization. Curves indicate the path of each variable coefficient as λ varies. Lambda.min (λ = 0.553) corresponds to the λ that corresponds to the selected model with 12 predictor variables. C, Plot of nonzero variable fit after cross-validation shows the 10-fold cross validation performed for the elastic net regression that chooses the optimal λ. Lambda.min corresponds to the λ that minimizes mean-squared error. Lambda.1se corresponds to the λ that is 1 standard error from the lambda.min. All plots were generated in GLMNET in R[50] (R Foundation).

amygdala to left cACC functional connectivity to fearful faces (r = 0.541; P = .003; correct P = .04) (Figure 3C). A linear regression, with covariates age, sex, IQ, time between scans, and scanner, showed that change in CALS-P scores significantly predicted change in amygdala to left cACC functional connectivity to fearful faces (R^2 = 0.423; $F_{6,21}$ = 2.569; P = .05).

When analyses were repeated removing medicated youth, OBP no longer had significantly greater right rACC activity to EF-2-BACK happy faces (mean [SD] difference, 0.408 [0.275]; 95% CI, −0.269 to 1.085; P = .43) and showed borderline significantly greater amygdala to left cACC functional connectivity to fearful faces (mean [SD] difference, 0.454 [0.188]; 95%

Figure 2. Bonferroni-Corrected Group Comparisons in Nonzero Predictor Neuroimaging Measures



A, For the dynamic faces task, compared with offspring of healthy parents (OHP), offspring of parents with bipolar disorder (OBP) had significantly lower left dorsolateral prefrontal cortex activity to angry faces vs shapes (mean [SD] difference, 0.108 [0.033]; 95% CI, 0.027-0.189; P = .01). B, For the emotional face 2-back task, compared with OCP, OBP had significantly greater left caudal anterior cingulate cortex–amygdala functional connectivity to fearful faces (mean [SD] difference, 0.493 [0.169]; 95% CI, 0.079-0.908; P = .01), happy faces (mean [SD] difference, 0.516 [0.148]; 95% CI, 0.155-0.877; P = .002), and neutral faces (mean [SD] difference, 0.604 [.159]; 95% CI, 0.215-0.992; P = .001) vs no faces. C, For the emotional face 2-back task, compared with OCP, OBP had significantly greater right rostral anterior cingulate cortex (rACC) activity to happy vs no faces (mean [SD] difference, 0.744 (0.249); 95% CI, 0.134-1.354; P = .01). D. For the emotional face 0-back task, compared with OHP, OCP had significantly lower left rACC activity (mean [SD] difference = 0.802 [0.241]; 95% CI, 0.212-1.391, P = .004) and right rACC activity (mean [SD] difference, 0.691 (.236); 95% CI, 0.113-1.269; P = .01) to happy vs neutral faces; compared with OHP, OBP had significantly lower right rACC activity to happy vs neutral faces (mean [SD] difference, 0.626 [0.231]; 95% CI, 0.060-1.192; P = .03).

CI, −0.009 to 0.917; P = .06) vs OCP. In follow-up analyses, the association between change in CALS-P score and change in EF-2-BACK amygdala to left cACC functional connectivity to fearful faces remained significant (r = 0.597; P = .002); the linear regression model was not significant (R^2 = 0.442; $F_{6,18}$ = 2.378; P = .07). No other findings changed by removing participants who were taking medication.

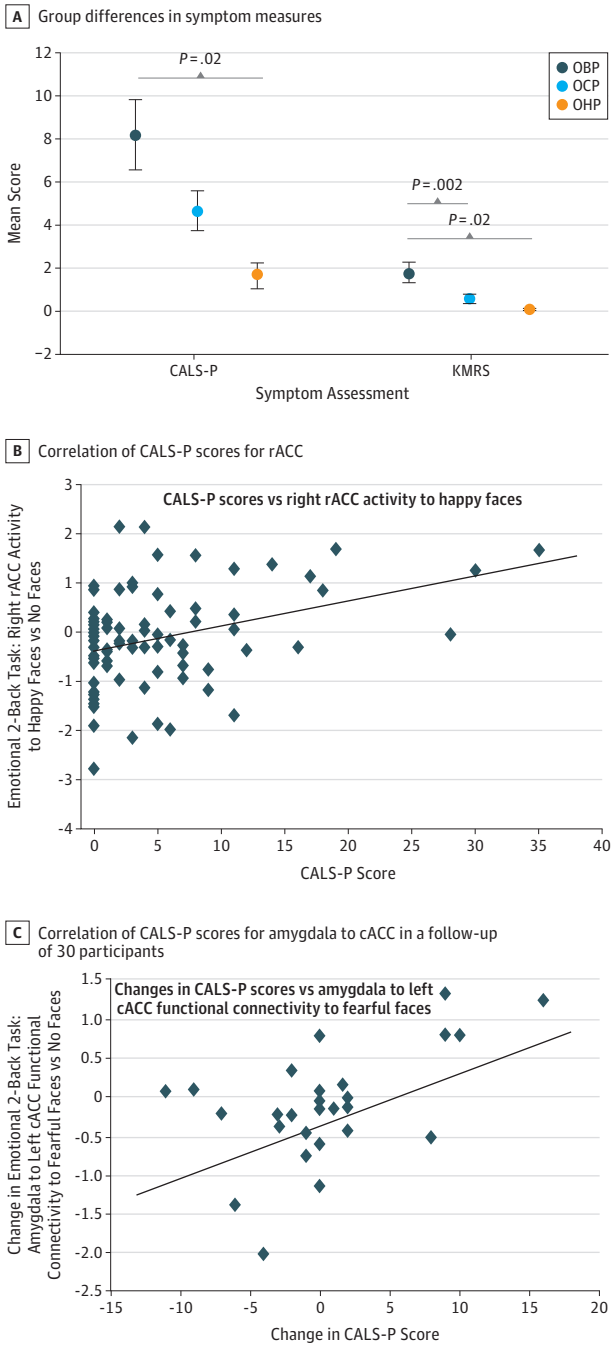
Discussion

To identify neural markers of future BD risk in OBP, we examined measures of activity and functional connectivity in amygdala to PFC circuitry during emotion processing and regulation that distinguished OBP from OCP and OHP, and the extent to which these measures were associated with symptom severity.

Offspring of parents with BD showed greater right rACC activity to happy faces during EF-2-BACK performance than OCP. The rACC is the "affective division" of the ACC with connections to affective neural regions (eg, amygdala)[51,52] and roles in processing emotional conflict and integrating emotion and cognition.[53-57] Rostral anterior cingulate cortex recruitment may help resolve emotional conflict by suppressing amygdala activity, leading to reduced emotional responsivity and blunted sympathetic autonomic responses to incongruent emotional distracters.[58] Greater right rACC activity to happy faces positively correlated with greater parent-reported affective lability severity, a precursor of BD in OBP, however,[31] and may reflect inefficient recruitment of rACC to downregulate amygdala activity, leading to affective lability, and risk for future BD in OBP. The relationship with parent-reported vs child-reported affective lability may reflect the greater reliability of parental reports of child symptoms, because these are considered more useful than child reports in diagnosing BD in children.[59]

Offspring of parents with BD and OCP showed lower rACC activity than OHP to happy faces during EF-0-BACK performance. Similarly, OBP had lower dlPFC activity than OHP to

Figure 3. Bonferroni-Corrected Group Comparisons Between Symptoms Measures and Neuroimaging Measures



A, Bonferroni corrections for 8 parallel tests revealed significant findings for the Parent-Reported Children's Affective Lability Scale (CALS-P) ($F_{2,77}$ = 6.464; P = .003; corrected P = .02) and the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale (KMRS) ($F_{2,75}$ = 6.223; P = .003; corrected P = .02). B, Across all participants, baseline CALS-P severity positively correlated with emotional face 2-back task right rostral anterior cingulate cortex (rACC) activity to happy faces. C, Across all 30 participants in follow-up analyses, changes in CALS-P scores were positively correlated with changes in emotional face 2-back task amygdala to left caudal anterior cingulate cortex (cACC) functional connectivity to fearful faces.

angry faces during the DFT, another face emotion processing task with no working memory component. These findings suggest that OBP and OCP fail to recruit, to a normal extent, PFC regions important for emotional regulation when processing or attending to emotional stimuli, while OBP recruit the rACC inefficiently when required to distract attention away from positive emotional stimuli. Differential patterns of aberrant recruitment of PFC regions to emotional stimuli in different contexts is thus a potential neural mechanism distinguishing OBP from OCP and conferring risk for BD in OBP.

Offspring of parents with BD also showed greater amygdala to left cACC functional connectivity to fearful, happy, and neutral faces during EF-2-BACK performance than OCP. Changes in amygdala to left cACC functional connectivity to fearful faces positively correlated with changes in parent-reported affective lability severity over time. Along with the rACC, the cACC is implicated in implicit emotional regulation.[60-64] The cACC is part of the central executive control network and has a more specific role than the rACC in attentional task performance.[65-67] Our findings thus suggest that greater amygdala to left cACC functional connectivity to emotional face distracters, and increasing amygdala to left cACC functional connectivity over time to fearful face distracters, may reflect a compensatory, but inefficient, neural mechanism to redirect attention away from emotional face distracters during attentional tasks, which, in turn, may predispose to increasing affective lability and BD in youth.

Removing participants taking medication reduced the significance of the differences between right rACC activity to happy faces and amygdala to left cACC functional connectivity to fearful faces during EF-2-BACK performance in OBP vs OCP, as well as the association between change in the latter measure and change in affective lability during follow-up. Offspring of parents with BD taking medication had greater affective lability severity than unmedicated OBP, however, and thus reflected a particularly high-risk subset of OBP. Furthermore, removing participants taking medication from analyses affected the significance only of neuroimaging measures showing statistically significant associations with affective lability severity. Additionally, medication was not positively associated with the overall group in an additional elastic net regression model including medication and all clinical variables, as well as all neuroimaging and demographic measures (eAppendix in the Supplement). Thus, greater right rACC activity to happy faces, and greater amygdala to left cACC functional connectivity to fearful faces during EF-2-BACK performance may represent markers of BD risk in higher-risk OBP who are more affectively labile and more likely to be medicated, but psychotropic medication in itself is not a predictor of risk for BD in youth.

Previous studies[14,15,29] reported that OBP show greater amygdala and PFC activity during emotion processing and regulation. While OBP showed greater right rACC activity to happy faces during EF-2-BACK vs OCP, OBP also showed lower left dlPFC activity to angry faces and lower right rACC activity to EF-0-BACK happy faces vs OHP. This is consistent with studies of patients with BD showing reduced activity in PFC regions supporting emotion regulation.[16,21,22] Previous studies also reported mixed results of either elevated[14] or

reduced[15,23-28] amygdala to PFC functional connectivity in OBP. Our findings show associations with amygdala to cACC functional connectivity, while other studies focused on the vlPFC, however. Additionally, our DFT findings differ from those in BIOS[14] showing greater amygdala activity, lower amygdala to ACC functional connectivity, and more positive amygdala to vlPFC functional connectivity in OBP vs OHP.[14] Unlike this previous study,[14] the present study used emotional regulation and processing tasks, with most findings pertaining to emotional regulation. Together, our findings suggest differential patterns of functional abnormalities in circuitries associated with these 2 tasks in OBP (and OCP) vs OHP.

Limitations

This study had limitations. Sample size was limited, particularly for follow-up data. Future studies should replicate and validate our findings with larger sample sizes. We focused on activity and functional connectivity in emotion processing and regulation neural circuitries; analyzing gray matter volume and cortical thickness may enhance understanding of BD risk. We assumed linear models between neuroimaging and symptom measures, while nonlinear models could be considered. Interpreting findings based on nonlinear models is limited in studies with such complex designs, however.[68] While age, which significantly correlated with pubertal development (eTable 5 in the Supplement), did not significantly affect neuroimaging measures, pubertal development cannot be ruled out as a contributing factor in our results. Additionally, recent studies[69] have debated the possible inflation of predictions in neuroimaging studies in individuals with psychiatric disorders. We used a well-validated approach that penalizes complex models using regularization, cross-validation, and sparsity enforcement in model fit. While medication impacted some findings, these effects may, in fact, reflect the medicated status of the most affectively labile and high-risk OBP. Furthermore, medication was not a predictor of group in additional elastic net regression analyses. Further study is needed to determine associations between medications and emotional regulation neural circuitry functioning.

Conclusions

To our knowledge, this is the first study to use both cross-sectional and longitudinal analyses of emotion processing and regulation neural circuitries in youth at risk for BD vs comparative at-risk and healthy control groups. We show that greater right rACC activity to happy faces and greater amygdala to left cACC functional connectivity to fearful faces during attentional task performance with high memory load conditions significantly distinguish OBP from OCP, at the group level, and these measures have significant associations with affective lability, a precursor of BD. We conclude that greater right rACC activity and greater amygdala to left cACC functional connectivity during emotional regulation are candidate objective markers of BD risk in youth. Our findings are important steps toward identifying neural markers of BD risk to aid in enhanced early identification and guide interventions for BD at-risk youth.

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Author Affiliations: Department of Neuroscience, Center for Neuroscience, University of Pittsburgh, Pittsburgh, Pennsylvania (Acuff); Department of Psychology, Center for Neuroscience, University of Pittsburgh, Pittsburgh, Pennsylvania (Acuff); Department of Psychiatry, Center for Neuroscience, University of Pittsburgh, Pittsburgh, Pennsylvania (Acuff); Medical Scientist Training Program, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Acuff); Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania (Versace, Bertocci, Ladouceur, Hanford, Manelis, Monk, Bonar, McCaffrey, T. R. Goldstein, Sakolsky, Birmaher, Phillips); Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (B. I. Goldstein); Department of Psychiatry, Nationwide Children's Hospital, The Ohio State College of Medicine, Columbus (Axelson).

Author Contributions: Dr Acuff had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Acuff, Bertocci, Ladouceur, T. Goldstein, Axelson, Birmaher, Phillips.
Acquisition, analysis, or interpretation of data: Acuff, Versace, Bertocci, Hanford, Manelis, Monk, Bonar, McCaffrey, B. Goldstein, Sakolsky, Axelson, Birmaher, Phillips.
Drafting of the manuscript: Acuff, Versace, Hanford, Phillips.
Critical revision of the manuscript for important intellectual content: Acuff, Bertocci, Ladouceur, Hanford, Manelis, Monk, Bonar, McCaffrey, B. Goldstein, T. Goldstein, Sakolsky, Axelson, Birmaher, Phillips.
Statistical analysis: Acuff, Versace, Bertocci, Hanford, Phillips.
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Supervision: Versace, Bertocci, T. Goldstein, Sakolsky, Axelson, Birmaher, Phillips.

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REFERENCES

1. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M; Child Psychiatric Workgroup on Bipolar Disorder. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2005;44(3):213-235. doi:10.1097/00004583-200503000-00006

2. Kowatch RA, Youngstrom EA, Danielyan A, Findling RL. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. *Bipolar Disord*. 2005;7(6):483-496. doi:10.1111/j.1399-5618.2005.00261.x

3. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry*. 2005;44(9):846-871. doi:10.1097/01.chi.0000170554.23422.c1

4. Leverich GS, Altshuler LL, Frye MA, et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J Clin Psychiatry*. 2003;64(5):506-515. doi:10.4088/JCP.v64n0503

5. Leverich GS, McElroy SL, Suppes T, et al. Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol Psychiatry*. 2002;51(4):288-297. doi:10.1016/S0006-3223(01)01239-2

6. Perlis RH, Miyahara S, Marangell LB, et al; STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry*. 2004;55(9):875-881. doi:10.1016/j.biopsych.2004.01.022

7. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry*. 1995;34(4):454-463. doi:10.1097/00004583-199504000-00012

8. Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Dev Psychopathol*. 2006;18(4):1023-1035. doi:10.1017/S0954579406060500

9. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. *Am J Med Genet C Semin Med Genet*. 2003;123C(1):48-58. doi:10.1002/ajmg.c.20013

10. Chang KD, Steiner H, Ketter TA. Psychiatric phenomenology of child and adolescent bipolar offspring. *J Am Acad Child Adolesc Psychiatry*. 2000;39(4):453-460. doi:10.1097/00004583-200004000-00014

11. Axelson D, Goldstein B, Goldstein T, et al. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. *Am J Psychiatry*. 2015;172(7):638-646. doi:10.1176/appi.ajp.2014.14010035

12. Goldstein TR, Birmaher B, Axelson D, et al. History of suicide attempts in pediatric bipolar disorder: factors associated with increased risk. *Bipolar Disord*. 2005;7(6):525-535. doi:10.1111/j.1399-5618.2005.00263.x

13. Birmaher B, Axelson D, Monk K, et al. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. *Arch Gen Psychiatry*. 2009;66(3):287-296. doi:10.1001/archgenpsychiatry.2008.546

14. Manelis A, Ladouceur CD, Graur S, et al. Altered amygdala-prefrontal response to facial emotion in offspring of parents with bipolar disorder. *Brain*. 2015;138(Pt 9):2777-2790. doi:10.1093/brain/awv176

15. Ladouceur CD, Diwadkar VA, White R, et al. Fronto-limbic function in unaffected offspring at familial risk for bipolar disorder during an emotional working memory paradigm. *Dev Cogn Neurosci*. 2013;5:185-196. doi:10.1016/j.dcn.2013.03.004

16. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry*. 2003;54(5):515-528. doi:10.1016/S0006-3223(03)00171-9

17. Dolcos F, Iordan AD, Dolcos S. Neural correlates of emotion-cognition interactions: a review of evidence from brain imaging investigations. *J Cogn Psychol (Hove)*. 2011;23(6):669-694. doi:10.1080/20445911.2011.594433

18. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. *Am J Psychiatry*. 2014;171(8):829-843. doi:10.1176/appi.ajp.2014.13081008

19. Lawrence NS, Williams AM, Surguladze S, et al. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biol Psychiatry*. 2004;55(6):578-587. doi:10.1016/j.biopsych.2003.11.017

20. Blumberg HP, Donegan NH, Sanislow CA, et al. Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. *Psychopharmacology (Berl)*. 2005;183(3):308-313. doi:10.1007/s00213-005-0156-7

21. Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol Psychiatry*. 2008;13(9):829, 833-857. doi:10.1038/mp.2008.82

22. Hafeman DM, Bebko G, Bertocci MA, et al. Abnormal deactivation of the inferior frontal gyrus during implicit emotion processing in youth with bipolar disorder: attenuated by medication. *J Psychiatr Res*. 2014;58:129-136. doi:10.1016/j.jpsychires.2014.07.023

23. Nusslock R, Almeida JR, Forbes EE, et al. Waiting to win: elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults. *Bipolar Disord*. 2012;14(3):249-260. doi:10.1111/j.1399-5618.2012.01012.x

24. Bermpohl F, Kahnt T, Dalanay U, et al. Altered representation of expected value in the orbitofrontal cortex in mania. *Hum Brain Mapp*. 2010;31(7):958-969. doi:10.1002/hbm.20909

25. Linke J, King AV, Rietschel M, et al. Increased medial orbitofrontal and amygdala activation: evidence for a systems-level endophenotype of bipolar I disorder. *Am J Psychiatry*. 2012;169(3):316-325. doi:10.1176/appi.ajp.2011.11050711

26. Abler B, Greenhouse I, Ongur D, Walter H, Heckers S. Abnormal reward system activation in mania. *Neuropsychopharmacology*. 2008;33(9):2217-2227. doi:10.1038/sj.npp.1301620

27. Chase HW, Nusslock R, Almeida JR, Forbes EE, LaBarbara EJ, Phillips ML. Dissociable patterns of abnormal frontal cortical activation during anticipation of an uncertain reward or loss in bipolar versus major depression. *Bipolar Disord*. 2013;15(8):839-854. doi:10.1111/bdi.12132

28. Caseras X, Lawrence NS, Murphy K, Wise RG, Phillips ML. Ventral striatum activity in response to reward: differences between bipolar I and II disorders. *Am J Psychiatry*. 2013;170(5):533-541. doi:10.1176/appi.ajp.2012.12020169

29. Olsavsky AK, Brotman MA, Rutenberg JG, et al. Amygdala hyperactivation during face emotion processing in unaffected youth at risk for bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2012;51(3):294-303. doi:10.1016/j.jaac.2011.12.008

30. Singh MK, Chang KD, Kelley RG, Saggar M, Reiss AL, Gotlib IH. Early signs of anomalous neural functional connectivity in healthy offspring of parents with bipolar disorder. *Bipolar Disord*. 2014;16(7):678-689. doi:10.1111/bdi.12221

31. Hafeman DM, Merranko J, Axelson D, et al. Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. *Am J Psychiatry*. 2016;173(7):695-704. doi:10.1176/appi.ajp.2015.15040414

32. Bertocci MA, Bebko G, Dwojak A, et al. Longitudinal relationships among activity in attention redirection neural circuitry and symptom severity in youth. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2017;2(4):336-345. doi:10.1016/j.bpsc.2016.06.009

33. Birmaher B, Axelson D, Monk K, et al. Lifetime psychiatric disorders in school-aged offspring of

parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. *Arch Gen Psychiatry*. 2009;66(3):287-296. doi:10.1001/archgenpsychiatry.2008.546

34. Hollingshead AB. *Four factor index of social status*. [unpublished manuscript] New Haven, CT: Yale University; 1975.

35. Findling RL, Youngstrom EA, Fristad MA, et al. Characteristics of children with elevated symptoms of mania: the Longitudinal Assessment of Manic Symptoms (LAMS) study. *J Clin Psychiatry*. 2010;71(12):1664-1672. doi:10.4088/JCP.09m05859yel

36. Horwitz SM, Demeter CA, Pagano ME, et al. Longitudinal Assessment of Manic Symptoms (LAMS) study: background, design, and initial screening results. *J Clin Psychiatry*. 2010;71(11):1511-1517. doi:10.4088/JCP.09m05835yel

37. Wechsler D. *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: The Psychological Corporation; 1999.

38. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053.

39. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980-988. doi:10.1097/00004583-199707000-00021

40. First MB. *SPitzer, R.L., Gibbon, M., Williams, J. Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Press; 1996.

41. Birmaher B, Khetarpal S, Brent D, et al. The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. *J Am Acad Child Adolesc Psychiatry*. 1997;36(4):545-553. doi:10.1097/00004583-199704000-00018

42. Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. *J Am Acad Child Adolesc Psychiatry*. 1999;38(10):1230-1236. doi:10.1097/00004583-199910000-00011

43. Gerson AC, Gerring JP, Freund L, et al. The Children's Affective Lability Scale: a psychometric evaluation of reliability. *Psychiatry Res*. 1996;65(3):189-198. doi:10.1016/S0165-1781(96)02851-X

44. Sund AM, Larsson B, Wichstrom L. Depressive symptoms among young Norwegian adolescents as measured by the Mood and Feelings Questionnaire (MFQ). *Eur Child Adolesc Psychiatry*. 2001;10(4):222-229. doi:10.1007/s007870170011

45. Axelson D, Birmaher BJ, Brent D, et al. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. *J Child Adolesc Psychopharmacol*. 2003;13(4):463-470. doi:10.1089/104454603322724850

46. Almeida JR, Kronhaus DM, Sibille EL, et al. Abnormal left-sided orbitomedial prefrontal cortical-amygdala connectivity during happy and fear face processing: a potential neural mechanism of female MDD. *Front Psychiatry*. 2011;2:69. doi:10.3389/fpsyt.2011.00069

47. Perlman SB, Almeida JR, Kronhaus DM, et al. Amygdala activity and prefrontal cortex-amygdala effective connectivity to emerging emotional faces distinguish remitted and depressed mood states in bipolar disorder. *Bipolar Disord*. 2012;14(2):162-174. doi:10.1111/j.1399-5618.2012.00999.x

48. Tottenham N, Tanaka JW, Leon AC, et al. The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Res*. 2009;168(3):242-249. doi:10.1016/j.psychres.2008.05.006

49. Ladouceur CD, Silk JS, Dahl RE, Ostapenko L, Kronhaus DM, Phillips ML. Fearful faces influence attentional control processes in anxious youth and adults. *Emotion*. 2009;9(6):855-864. doi:10.1037/a0017747

50. Friedman J, Hastie T, Simon N, Tibshirani R. GLMNET. https://cran.r-project.org/web/packages/glmnet/glmnet.pdf. 2014. Accessed July 19, 2018.

51. Carmichael ST, Price JL. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol*. 1995;363(4):615-641. doi:10.1002/cne.903630408

52. Van Hoesen GW, Morecraft RJ, Vogt BA. *Connections of the monkey cingulate cortex. Neurobiology of cingulate cortex and limbic thalamus*. New York, NY: Springer; 1993:249-284. doi:10.1007/978-1-4899-6704-6_9

53. Bishop S, Duncan J, Brett M, Lawrence AD. Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. *Nat Neurosci*. 2004;7(2):184-188. doi:10.1038/nn1173

54. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci*. 2000;4(6):215-222. doi:10.1016/S1364-6613(00)01483-2

55. Bissière S, Plachta N, Hoyer D, et al. The rostral anterior cingulate cortex modulates the efficiency of amygdala-dependent fear learning. *Biol Psychiatry*. 2008;63(9):821-831. doi:10.1016/j.biopsych.2007.10.022

56. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain*. 1995;118(Pt 1):279-306. doi:10.1093/brain/118.1.279

57. Vogt BA, Finch DM, Olson CR. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb Cortex*. 1992;2(6):435-443.

58. Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron*. 2006;51(6):871-882. doi:10.1016/j.neuron.2006.07.029

59. Youngstrom EA, Findling RL, Calabrese JR, et al. Comparing the diagnostic accuracy of six potential screening instruments for bipolar disorder in youths aged 5 to 17 years. *J Am Acad Child Adolesc Psychiatry*. 2004;43(7):847-858. doi:10.1097/01.chi.0000125091.35109.1e

60. Kober H, Barrett LF, Joseph J, Bliss-Moreau E, Lindquist K, Wager TD. Functional grouping and cortical-subcortical interactions in emotion: a meta-analysis of neuroimaging studies. *Neuroimage*. 2008;42(2):998-1031. doi:10.1016/j.neuroimage.2008.03.059

61. Frank DW, Dewitt M, Hudgens-Haney M, et al. Emotion regulation: quantitative meta-analysis of functional activation and deactivation. *Neurosci Biobehav Rev*. 2014;45:202-211. doi:10.1016/j.neubiorev.2014.06.010

62. Goodkind M, Gyurak A, Etkin A. *Functional neurocircuitry and neuroimaging studies of anxiety disorders. Neurobiology of Mental Illness*. New York, NY: Oxford University Press; 2013:606-620.

63. Kim MJ, Loucks RA, Palmer AL, et al. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. *Behav Brain Res*. 2011;223(2):403-410. doi:10.1016/j.bbr.2011.04.025

64. Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol Psychiatry*. 2008;13(9):829, 833-857. doi:10.1038/mp.2008.82

65. Van Veen V, Carter CS. The timing of action-monitoring processes in the anterior cingulate cortex. *J Cogn Neurosci*. 2002;14(4):593-602. doi:10.1162/08989290260045837

66. Haas BW, Omura K, Constable RT, Canli T. Interference produced by emotional conflict associated with anterior cingulate activation. *Cogn Affect Behav Neurosci*. 2006;6(2):152-156. doi:10.3758/CABN.6.2.152

67. Margulies DS, Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Mapping the functional connectivity of anterior cingulate cortex. *Neuroimage*. 2007;37(2):579-588. doi:10.1016/j.neuroimage.2007.05.019

68. Marsh L, McGlynn M, Chakraborty D. Interpreting complex nonlinear models. Paper presented at: Proceedings of SAS User's Group International1994.

69. Whelan R, Garavan H. When optimism hurts: inflated predictions in psychiatric neuroimaging. *Biol Psychiatry*. 2014;75(9):746-748. doi:10.1016/j.biopsych.2013.05.014