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Activity and functional connectivity in emotion processing and regulation neural circuitries in offspring at risk for bipolar disorder

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Abstract

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 relationships with symptoms, specific to youth at risk for BD.

Design—Cross-sectional (August 2011-July 2017) and longitudinal (February 2013-November 2017) neuroimaging study.

Setting—Academic Medical Center: University of Pittsburgh.

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Ethical Standards

The authors assert that 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.

Conflict of Interest Disclosure

Acuff, Dr. Versace, Dr. Bertocci, Dr. Hanford, Dr. Ladouceur, Dr. Manelis, Dr. Monk, Dr. Bonar, Dr. McCaffrey, Dr. Goldstein, and Dr. Phillips have no financial interests or potential conflicts of interest.

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Participants—Referred sample of offspring of bipolar parents (OBP;n=31) and offspring of comparison parents with non-BD psychopathology (OCP;n=28) from the Bipolar Offspring Study and offspring of healthy parents (OHP;n=21) from the Longitudinal Assessment of Manic Symptoms Study.

Main Outcomes and Measures—Elastic net regressions and ANOVAs examined group differences in activity and functional connectivity (FC) during emotional face processing and n-back task performance in amygdala, dorsolateral and ventrolateral prefrontal cortices (PFC), caudal (cACC) and rostral (rACC) anterior cingulate cortices. Correlation analyses examined relationships among neuroimaging measures showing between-group differences and symptom severity (anxiety, affective lability, depression, mania). We hypothesized: elevated amygdala activity and/or lower PFC activity and abnormal amygdala-PFC FC would distinguish OBP from OCP and OHP, and magnitudes of these abnormalities would positively correlate with elevated symptom severity. We explored relationships between changes in neuroimaging and symptom measures over follow-up (mean(SD)=2.88(1.37) years) in a subset of participants (n=30).

Results—Eighty participants were included (mean(SD) age=14.17(2.06), 35 female). Twelve neuroimaging measures explained 51% of the variance in group. Of these, seven showed significant effects of group (P<.05, corrected). Of these, two showed significant relationships with symptoms. OBP had greater right rACC activity when regulating attention to happy faces versus OCP (mean(SD) difference=.744(.249), 95%CI=.134–1.354, P=.011), which positively correlated with affective lability severity (ρ=.304, P=.006, uncorrected). OBP had greater amygdala-left cACC FC when regulating attention to fearful faces versus OCP (mean(SD) difference=.493(.169), 95%CI=.079-.908, P=.014). Increases in this measure positively correlated with increases in affective lability over follow-up (r=.541, P=.003).

Conclusions and Relevance—Greater anterior cingulate cortex activity and FC 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.

Background

Bipolar Disorder (BD), a serious, recurrent illness, often emerges during adolescence[1–3]. 15–28% of adults with BD experience illness onset before age 13 years and 50–66% before age 19[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 (MDD), Attention Deficit/Hyperactive Disorder (ADHD), or Anxiety Disorders, making it difficult to diagnose BD[7,8]. It is thus important to identify objective biological markers to help differentiate BD from other disorders.

BD has a heritability of 59–87%, placing first-degree relatives at high risk for BD[9]. Compared with children of parents without psychiatric illness, offspring of bipolar parents (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, 23% of OBP developed a bipolar spectrum disorder by age 21 compared with 3.2% in

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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) 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 examined activity and functional connectivity (FC) using emotion processing and regulation tasks, separately[14,15]. No studies examined how measures of activity and FC 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), and dorsolateral (dlPFC) and ventrolateral (vlPFC) prefrontal cortex. 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-vlPFC FC[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-vlPFC FC to fearful faces during emotional regulation[15], greater amygdala activity to fearful faces during emotion processing[29], and abnormal PFC-subcortical resting state FC[30]. Comparing all three groups during emotional face processing, OBP and OCP showed greater right amygdala activity to all emotional faces versus OHP, while OBP showed lower positive right amygdala-ACC FC to all emotional faces and more positive right amygdala-left vlPFC FC 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. 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-ACC FC 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.

Given studies showing 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: elevated amygdala and/or lower PFC activity and abnormal amygdala-PFC FC 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 versus 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.

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Methods

Participants

Thirty-one OBP (mean(SD) age=13.87(2.42), 15 female) and twenty-eight OCP (mean(SD) age=14.48(2.01), 10 female) were recruited from BIOS[33], and twenty-one OHP (mean(SD) age=14.20(1.48), 10 female) from BIOS and the Longitudinal Assessment of Manic Symptoms Study (Table 1)[34,35]. Participants were matched for age, sex, IQ, and socioeconomic status (SES). Twenty-six OBP, twenty-one OCP, and nineteen OHP were included in Manelis et al., 2015[14].

OBP had at least one parent with BD; OCP had at least one parent with a non-BD disorder: MDD, ADHD, and/or an Anxiety Disorder. Exclusion criteria included: history of serious medical illness, head injury, or neurological disorder; IQ<70, assessed with Wechsler Abbreviate Scale of Intelligence[36]; BD, autism, or schizophrenia; magnetic resonance imaging (MRI) contraindication (e.g., pregnancy, metal in the body); substance abuse on the day of the scan or substance abuse disorder in the last three months; and task accuracy<70%. For OHP, additional exclusion criteria included history of DSM-5 disorder. Before participation, parents and guardians provided written informed consent, and youth provided written informed assent. Participants received monetary compensation. (Supplementary Material for recruitment and exclusion criteria).

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[37] for offspring, and the Structural Clinical Interview for DSM-IV[38] for parents. Symptom assessments included the Screen for Child Anxiety Related Disorders (SCARED)[39,40], Children's Affective Lability Sale (CALS)[41], Mood and Feelings Questionnaire (MFQ)[42], and K-SADS Mania (KMRS)[43] and Depression (KDRS)[37] 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, on average, two months after the scan.

Five OBP and six OCP took antidepressant, antipsychotic, stimulant, and/or non-stimulant medications for non-BD diagnoses. Medicated OBP had greater CALS-P severity than unmedicated OBP (mean(SD) difference=8.853(3.916), 95%CI=.845–16.862, t(29)=−2.261, P=.031, uncorrected).

Neuroimaging Data Acquisition

All scan 1 and fifteen scan 2 images (mean(SD)=2.88(1.37) year inter-scan interval) were acquired on a Siemens Magnetom TrimTrio 3T scanner. Fifteen scan 2 images were acquired on a Siemens Magnetom Prisma scanner. Participants completed an emotional face processing task, the dynamic faces task (DFT), during functional MRI (fMRI) to assess implicit emotional processing[21,44–46], 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[47]. (Supplementary Material)

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Neuroimaging Data Analyses

(Supplementary Material for preprocessing). Generalized psychophysiological interaction analyses assessed task-related connectivity between a bilateral amygdala seed and regions of interest (ROIs). Task stimulus contrasts included, separately: happy, sad, angry, and fearful faces versus shapes for DFT; fearful, happy, and neutral versus no faces, and fearful and happy versus neutral faces, for EF-0-BACK and EF-2-BACK; and EF-2-BACK versus EF-0-BACK for fearful, happy, neutral, and no faces. ROIs, 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 ROIs to main stimulus contrasts per task.

Primary Hypotheses

A single elastic net regression analysis with k=10-fold cross-validation and alpha=0.5 was used for data selection and reduction using GLMNET in R[48]. This one model contained 2 dummy-coded outcome variables: BD risk (OBP versus OCP/OHP) and general psychiatric disorders risk (OBP/OCP versus OHP), and 336 predictor variables: demographics (age, sex, IQ, SES (assessed with Hollingshead Four Factor Index of Social Status[49]), handedness, highest parental education); FC between bilateral amygdala and each ROI (left/right cACC, rACC, dlPFC, vlPFC) and activity in each ROI (left/right amygdala, cACC, rACC, dlPFC, vlPFC) for each contrast and task. (Supplementary Material)

Post-hoc pseudo r-squared analyses examined the proportion of variance in dependent variables explained by the non-zero predictor variables observed with elastic net. ANOVAs and post-hoc t-tests examined between-group differences in neuroimaging measures for all non-zero predictors and symptom measures. Correlation analyses examined relationships among neuroimaging and symptom measures.

Exploratory Analyses

In nine OBP, seven OCP, and fourteen OHP with second scans, correlation and linear regression analyses examined relationships between changes in symptoms and changes in neuroimaging measures showing between group differences in the above analyses. All analyses were repeated removing medicated youth. (Supplementary Material)

Results

Hypothesis Testing

Of the initial 336 predictors, 12 variables, together, optimized model fit (ΔAICc=1.811, λ=0.553; Figure 1). A pseudo r-squared, calculated containing 12 predictors from the model versus an intercept-only model, indicated that 51.39% of the variance in group was explained by these predictors. All predictors were neuroimaging variables (Table 2). Post-hoc t-tests, Bonferroni-corrected for three between-group parallel tests, examined all twelve neuroimaging measures that were selected as non-zero predictors of group (Figure 2). Compared with OHP, OBP had lower DFT left dlPFC activity to angry faces versus shapes (mean(SD) difference=.108(.033), 95%CI=.027-.189, P=.005). Compared with OCP, OBP

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had greater EF-2-BACK amygdala-left cACC FC to fearful (mean(SD) difference=.493(.169), 95%CI=.079-.908, P=.014), happy (mean(SD) difference=.516(.148), 95%CI=.155-.877, P=.002), and neutral (mean(SD) difference=.604(.159), 95%CI=.215-.992, P=.001) versus no faces, and greater EF-2-BACK right rACC activity to happy versus no faces (mean(SD) difference=.744(.249), 95%CI=.134–1.354, P=.011). Compared with OHP, OCP had lower EF-0-BACK left (mean(SD) difference=.802(.241), 95%CI=.212–1.391, P=.004) and right (mean(SD) difference=.691(.236), 95%CI=.113–1.269, P=.014) rACC activity to happy versus neutral faces, and OBP had lower EF-0-BACK right rACC activity to happy versus neutral faces (mean(SD) difference=.626(.231), 95%CI=.060–1.192, P=.025). No significant group differences were found for the remaining measures.

ANOVAs examined effects of group on all symptoms (Table 2). Bonferroni corrections for eight parallel tests revealed two significant findings: CALS-P ($F(2,77)=6.464$, P=.003(.024, corrected)) and KMRS ($F(2,75)=6.223$, P=.003(.024, corrected)). 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(.529), 95%CI=.43–3.02, P=.005) and OCP (mean(SD) difference=1.238(.473), 95%CI=.08–2.40, P=.032) (Figure 3A).

Bivariate correlation analyses examined relationships among all seven neuroimaging and two symptom measures showing significant group differences, above. Across all subjects, one significant relationship was found: baseline CALS-P severity positively correlated with EF-2-BACK right rACC activity to happy faces (ρ=.304, P=.006; Figure 3B). This just missed significance using Bonferroni corrections for fourteen tests (P<.004).

Exploratory Analyses

Follow-up analyses were in nine OBP (mean(SD) age=15.17(1.89)), seven OCP (mean(SD) age=16.94(1.66)), and fourteen OHP (mean(SD) age=15.78(1.34)). One OBP and two OCP took medications. Bivariate correlation analyses examined relationships among changes in all seven neuroimaging and two symptom measures showing significant group differences, above. Across all thirty subjects, one significant (Bonferroni-corrected) relationship was found: increase in CALS-P severity significantly positively correlated with increase in EF-2-BACK amygdala-left cACC FC to fearful faces (r=.541, P=.003(.042, corrected); Figure 3C). A linear regression, with covariates: age, gender, IQ, time between scans, and scanner, showed that change in CALS-P scores significantly predicted change in amygdala-left cACC FC to fearful faces (R^2=.423, $F(6,21)=2.569$, P=.050).

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=.408(.275), 95%CI=−.269–1.085, P=.432) and showed borderline significantly greater amygdala-left cACC FC to fearful faces (mean(SD) difference=.454(.188), 95%CI=−.009-.917, P=.056) versus OCP. In follow-up analyses, the relationship between change in CALS-P score and change in EF-2-BACK amygdala-left cACC FC to fearful faces remained significant (r=.597, P=.002); the linear regression model just missed significance (R^2=.442, $F(6,18)=2.378$, P=.072). No other findings changed by removing medicated youth.

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Conclusions

To identify neural markers of future BD risk in OBP, we examined measures of activity and FC in amygdala-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.

OBP 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 (e.g. amygdala)[50,51] and roles in processing emotional conflict and integrating emotion and cognition[52–56]. rACC recruitment may help resolve emotional conflict by suppressing amygdala activity, leading to reduced emotional responsivity and blunted sympathetic autonomic responses to incongruent emotional distracters[57]. 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, versus child-reported, affective lability may reflect the greater reliability of parental reports of child symptoms, as these are considered more useful than child reports in diagnosing BD in children[58].

OBP 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 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.

OBP also showed greater amygdala-left cACC FC to fearful, happy, and neutral faces during EF-2-BACK performance than OCP. Changes in amygdala-left cACC FC 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[59–63]. The cACC is part of the central executive control network and has a more specific role than the rACC in attentional task performance[64–66]. Our findings thus suggest that greater amygdala-left cACC FC to emotional face distracters, and increasing amygdala-left cACC FC 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 medicated youth reduced the significance of the differences between right rACC activity to happy faces and amygdala-left cACC FC to fearful faces during EF-2-BACK performance in OBP versus OCP, as well as the relationship between change in the latter measure and change in affective lability during follow-up. Medicated OBP had greater affective lability severity than unmedicated OBP, however, and thus reflected a particularly

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high-risk subset of OBP. Furthermore, removing medicated youth from analyses affected the significance only of neuroimaging measures showing significant relationships with affective lability severity. Additionally, medication was not a predictor of group in an additional elastic net regression model including medication and all clinical variables, as well as all neuroimaging and demographic measures, as predictors (Supplementary Material). Thus, greater right rACC activity to happy faces, and greater amygdala-left cACC FC 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 reported that OBP show greater amygdala and PFC activity during emotion processing and regulation[14,15,29]. While OBP showed greater right rACC activity to happy faces during EF-2-BACK versus OCP, OBP also showed lower left dlPFC activity to angry faces and lower right rACC activity to EF-0-BACK happy faces versus 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-PFC FC in OBP. Our findings implicate amygdala-cACC FC, while other studies focused on the vlPFC, however. Additionally, our DFT findings differ from those in BIOS showing greater amygdala activity, lower amygdala-ACC FC, and more positive amygdala-vlPFC FC in OBP versus OHP[14]. Unlike this previous study, the present study employed 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 two tasks in OBP (and OCP) versus OHP.

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 FC 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 non-linear models is significantly limited in studies with such complex designs, however[67]. While age, which significantly correlated with pubertal development (Supplementary Material), did not significantly affect neuroimaging measures, pubertal development cannot be ruled out as a contributing factor in our results. Additionally, recent studies have debated the possible inflation of predictions in neuroimaging studies in individuals with psychiatric disorders[68]. 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 relationships between medications and emotional regulation neural circuitry functioning.

This is the first study to employ both cross-sectional and longitudinal analyses of emotion processing and regulation neural circuitries in youth at risk for BD versus comparative at-risk and healthy control groups. We show that greater right rACC activity to happy faces and

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greater amygdala-left cACC FC 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 relationships with affective lability, a precursor of BD. We conclude that greater right rACC activity and greater amygdala-cACC FC 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Sakolsky serves as an editorial board member of *Child & Adolescent Psychopharmacology News* and specialty consultant for the *Prescriber's Letter*. She has received a consultant fee of $300 from L.E.K. Consulting in 2015. She currently receives research funding from NIMH and has received funding from NARSAD, the World's Leading Charity Dedicated to Mental Health Research.

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Access to Data and Data Analysis

Heather Acuff had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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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

Relative to offspring of healthy parents, offspring of bipolar parents had significantly greater right rostral anterior cingulate cortex activity when regulating attention away from happy faces. This measure was significantly positively correlated with affective lability symptom severity. Additionally, offspring of bipolar parents had significantly greater left caudal anterior cingulate cortex-amygdala functional connectivity to fearful faces relative to offspring of non-bipolar, psychiatric disorder comparison parents, and increases in this measure over follow-up (mean 2.88 years) was significantly positively correlated with increases in affective lability severity.

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.

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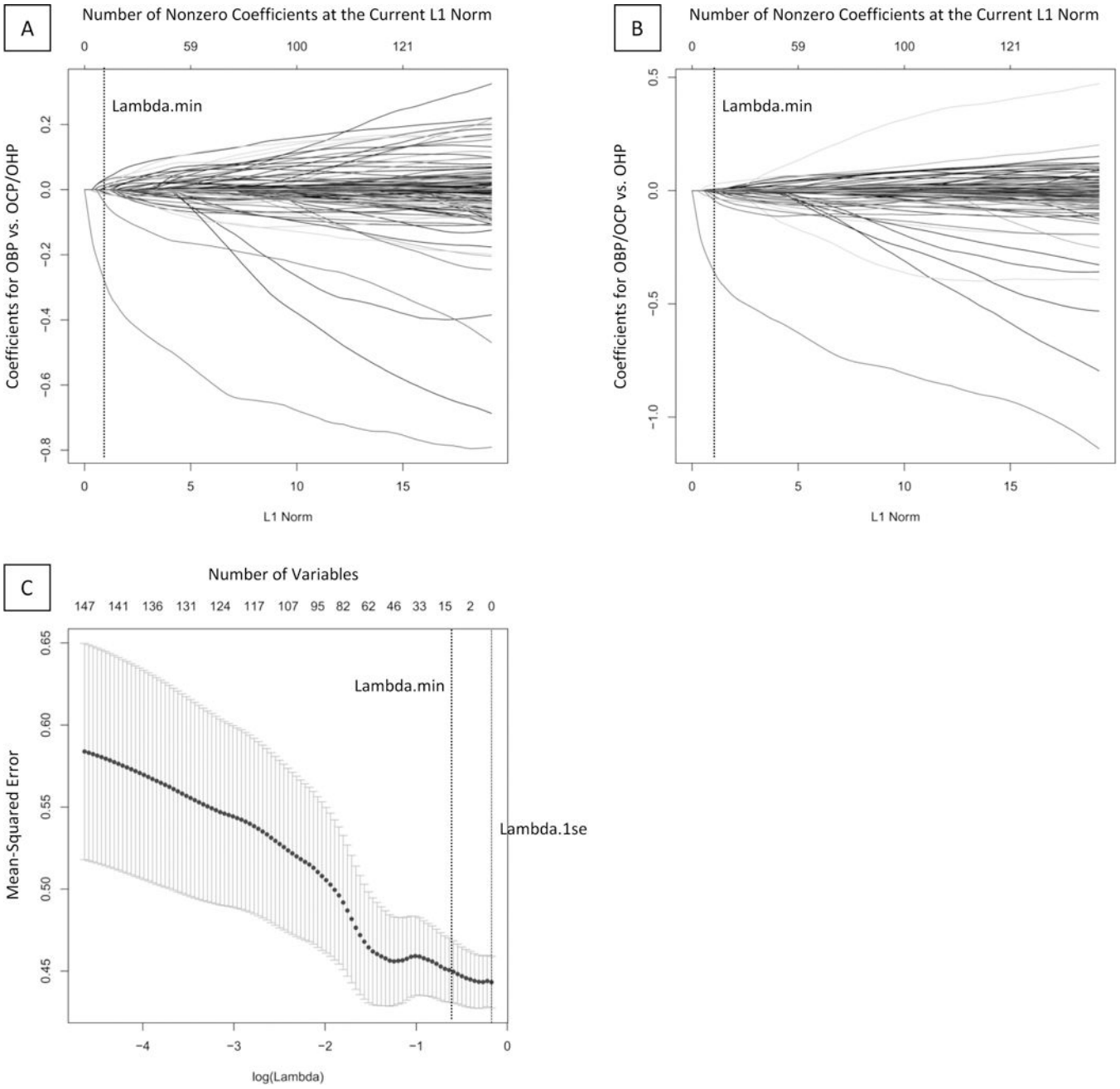

Figure 1. Elastic Net Plots Generated in GLMNET

A-B. Plots of variable fit for BD risk group (OBP versus OCP and OHP, **A**) and general risk group (OBP and OCP versus 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 which corresponds to the selected model with 12 predictor variables. **C.** Plot of non-zero variable fit after cross validation. Representation of the 10-fold cross validation performed for the elastic net regression that chooses the optimal λ. Lambda.min corresponds to the λ which minimizes mean squared error. Lambda.1se corresponds to the λ that is one standard error from the lambda.min.

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Abbreviations: Bipolar Disorder (BD); Offspring of Bipolar Parents (OBP); Offspring of Comparison Parents (OCP); Offspring of Healthy Parents (OHP).

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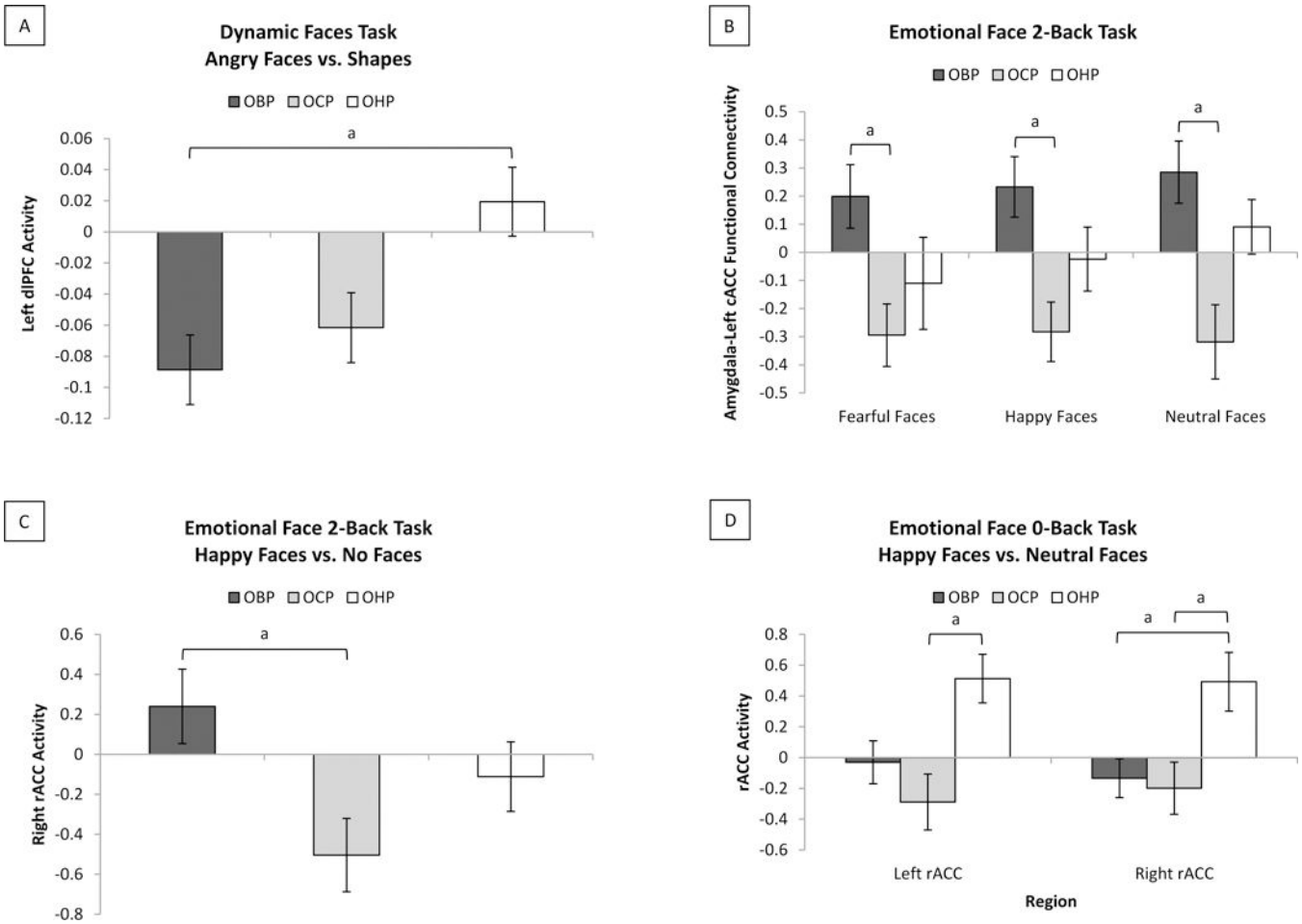

Figure 2. Group Differences in Neuroimaging Measures

Bonferroni-corrected group comparisons in non-zero predictor neuroimaging measures. **A.** For the dynamic faces task, compared with OHP, OBP had significantly lower left dlPFC activity to angry faces versus shapes (mean(SD) difference=.108(.033), 95%CI=.027-.189, P=.005). **B.** For the emotional face 2-back task, compared with OCP, OBP had significantly greater left cACC-amygdala FC to fearful (mean(SD) difference=.493(.169), 95%CI=.079-.908, P=.014), happy (mean(SD) difference=.516(.148), 95%CI=.155-.877, P=.002), and neutral (mean(SD) difference=.604(.159), 95%CI=.215-.992, P=.001) versus no faces. **C.** For the emotional face 2-back task, compared with OCP, OBP had significantly greater right rACC activity to happy versus no faces (mean(SD) difference=.744(.249), 95%CI=.134–1.354, P=.011). **D.** For the emotional face 0-back task, compared with OHP, OCP had significantly lower left (mean(SD) difference=.802(.241), 95%CI=.212–1.391, P=.004) and right (mean(SD) difference=.691(.236), 95%CI=.113–1.269, P=.014) rACC activity to happy versus neutral faces; compared with OHP, OBP had significantly lower right rACC activity to happy versus neutral faces (mean(SD) difference=.626(.231), 95%CI=.060–1.192, P=.025).

Abbreviations: [a]=significant at P=.05; Offspring of Bipolar Parents (OBP); Offspring of Comparison Parents (OCP); Offspring of Healthy Parents (OHP); Dorsolateral Prefrontal

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Cortex (dlPFC); Caudal Anterior Cingulate Cortex (cACC); Functional Connectivity (FC); Rostral Anterior Cingulate Cortex (rACC).

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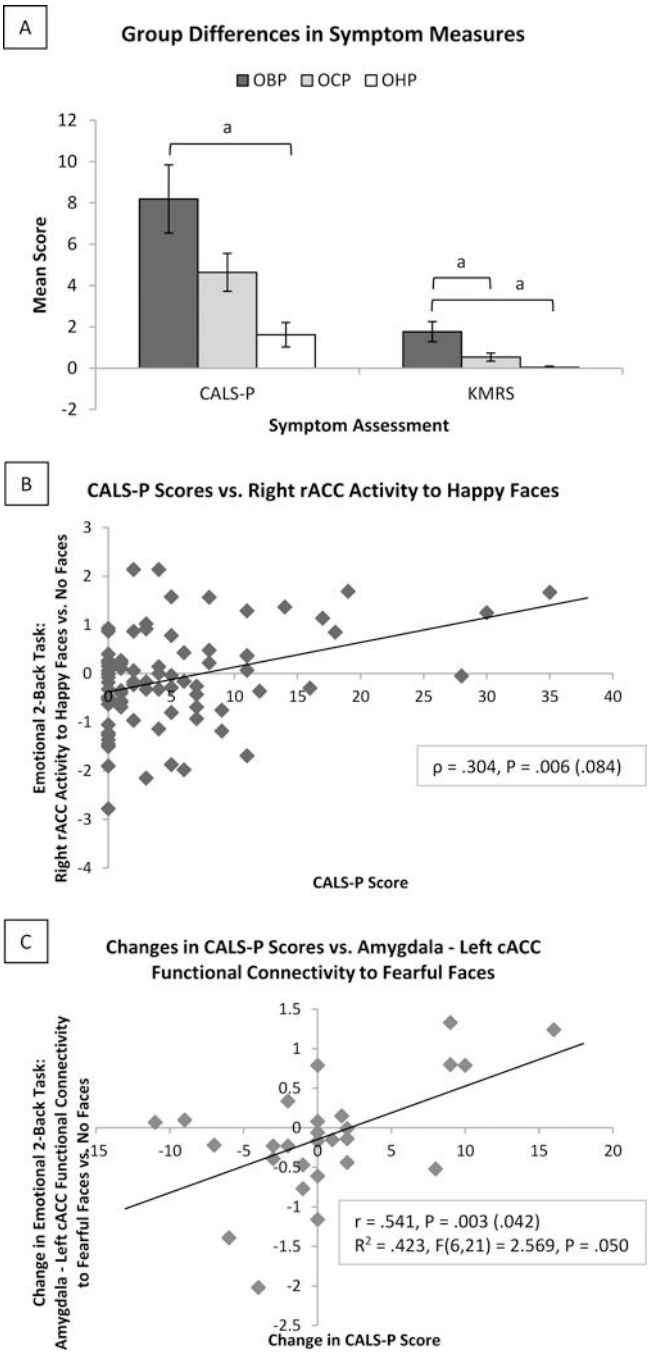

Figure 3. Relationships between Symptoms and Neuroimaging Measures

Bonferroni-corrected group comparisons in symptom measures. **A.** Bonferroni corrections for eight parallel tests revealed two significant findings: CALS-P (F(2,77)=6.464, P=.003(.024, corrected)) and KMRS (F(2,75)=6.223, P=.003(.024, corrected)). 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(.529), 95%CI=.43–3.02, P=.005) and OCP (mean(SD) difference=1.238(.473), 95%CI=.08–2.40, P=.032). **B.** Across all subjects, baseline CALS-P

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severity positively correlated with emotional face 2-back task right rACC activity to happy faces (ρ=.304, P=.006, uncorrected). **C.** Follow-up analyses comparing changes in symptom and neuroimaging measures in a subset of thirty subjects. Across all thirty subjects, changes in CALS-P scores were positively correlated with changes in emotional face 2-back task amygdala-left cACC FC to fearful faces (r=.541, P=.003(.042, corrected)). Changes in CALS-P scores, with age, gender, IQ, time between scans, and scanner, significantly predicted changes in emotional face 2-back task amygdala-left cACC FC to fearful faces (R^2=.423, F(6,21)=2.569, P=.050).

Abbreviations: [a]=significant at P=.05; Offspring of Bipolar Parents (OBP); Offspring of Comparison Parents (OCP); Offspring of Healthy Parents (OHP); Parent-Reported Children's Affective Lability Sale (CALS-P); Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale (KMRS); Rostral Anterior Cingulate Cortex (rACC); Caudal Anterior Cingulate Cortex (cACC); Functional Connectivity (FC).

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Table 1.

Comparison of OBP, OCP, and OHP.

	OBP N=31 M(SD) or Total	OCP N=28 M(SD) or Total	OHP N=21 M(SD) or Total	Statistic	P =
Demographic Information					
Age	13.87(2.42)	14.48(2.01)	14.20(1.48)	F = 0.648	.53
Sex (females)	15	10	10	χ^2 = 1.133	.57
IQ	101.13(15.55)	101.75(14.84)	105.71(12.18)	F = 0.692	.50
Socioeconomic Status					
Very Low (8–19)	7	5	1	χ^2 = 13.986	.08
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					
Right	26	26	19	χ^2 = 5.050	.28
Left	2	2	2		
Mixed	3	0	0		
Highest Parental Education					
High School Graduate or Lower	5	1	4	χ^2 = 5.960	.43
Partial College or Specialized Training	13	8	8		
Standard College or University Graduate	7	11	5		
Graduate Professional Training	6	8	4		
Clinical Measures					
Diagnosis	12	14	0	F = 8.569	**<.01**[a]
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**[a]
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					
SCARED-P	9.84(6.92)	9.50(11.14)	4.62(4.69)	F = 2.932	.06
SCARED-C	12.81(14.95)	8.00(12.16)	9.36(11.86)	F = 1.029	.36
CALS-P	8.19(9.19)	4.64(4.84)	1.62(2.71)	F = 6.464	**<.01**[a]
CALS-C	10.32(12.48)	5.32(8.76)	6.19(13.96)	F = 1.504	.23
MFQ-P	6.55(9.08)	4.48(5.00)	1.38(2.13)	F = 3.909	**.02**[a]
MFQ-C	8.41(10.87)	7.84(10.95)	5.29(11.03)	F = 0.536	.59
Assessment Closest to Scan					

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	OBP N=31 M(SD) or Total	**OCP N=28 M(SD) or Total**	**OHP N=21 M(SD) or Total**	**Statistic**	**P =**
KMRS	1.77(2.69)	0.54(1.04)	0.05(0.23)	F = 6.223	**<.01**[a]
KDRS	2.58(5.26)	2.00(3.74)	0.26(0.56)	F = 2.005	.14

[a]Abbreviations: =significant at P=.05; F=ANOVA test statistical value; χ^2=chi-squared test statistical value; OBP=Offspring of Bipolar Parents; OCP=Offspring of Comparison Parents; OHP=Offspring of Healthy Parents; IQ=Intelligence Quotient Wechsler Intelligence Test; -P=Parent Rating; -C=Child Rating; SCARED=Screen for Child Anxiety Related Emotional Disorders; CALS=Children's Affective Lability Sale; MFQ=Mood and Feelings Questionnaire; KMRS=Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale; KDRS=Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Depression Rating Scale.

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Table 2.

Between-Group Differences in Neuroimaging and Symptom Measures.

Neuroimaging Measure	ANOVA F =	ANOVA P =	Bonferroni Sig. Test for Multiple Comparisons OBP vs. OCP P =	OBP vs. OHP P =	OCP vs. OHP P =
DFT: Amygdala-Left dlPFC FC to Sad Faces vs. Shapes	3.010	.055	.768	.049	.526
DFT: Left dlPFC Activity to Angry Faces vs. Shapes	5.522	**.006**[a]	1.00	**.005**[a]	.057
EF-2-BACK: Amygdala-Left cACC FC to Fearful vs. No Faces	4.352	**.016**[a]	**.014**[a]	.289	.985
EF-2-BACK: Amygdala-Left cACC FC to Happy vs. No Faces	6.110	**.003**[a]	**.002**[a]	.337	.352
EF-2-BACK Task: Amygdala-Left cACC FC to Neutral vs. No Faces	7.413	**.001**[a]	**.001**[a]	.784	.068
EF-2-BACK: Amygdala-Right vlPFC FC to Happy vs. Neutral Faces	2.007	.141	.822	.152	1.00
EF-2-BACK: Right rACC Activity to Happy vs. No Faces	4.458	**.015**[a]	**.011**[a]	.591	.477
EF-0-BACK: Amygdala-Left dlPFC FC to Happy vs. No Faces	3.368	**.040**[a]	1.00	.100	.053
EF-0-BACK: Amygdala-Left rACC FC to Happy vs. Neutral Faces	2.254	.112	.551	.126	1.00
EF-0-BACK: Left rACC Activity to Happy vs. Neutral Faces	5.643	**.005**[a]	.716	.071	**.004**[a]
EF-0-BACK: Right rACC Activity to Happy vs. Neutral Faces	5.039	**.009**[a]	1.00	**.025**[a]	**.014**[a]
EF-2-BACK vs. EF-0-BACK: Amygdala-Left rACC FC to Happy Faces	3.247	**.044**[a]	.074	.146	1.00

Symptom Measure	ANOVA[b] F =	ANOVA[b] P =	Bonferroni Sig. Test for Multiple Comparisons OBP vs. OCP P =	OBP vs. OHP P =	OCP vs. OHP P =
SCARED-P	2.932	.059	1.00	.084	.131
SCARED-C	1.029	.362	.504	1.00	1.00
CALS-P	6.464	**.003**[a] **(.024**[a]**)**	.123	**.002**[a]	.343
CALS-C	1.504	.229	.320	.652	1.00
MFQ-P	3.909	**.024**[a] (.192)	.730	.020	.328
MFQ-C	0.536	.588	1.00	.966	1.00
KMRS	6.223	**.003**[a] **(.024**[a]**)**	**.032**[a]	**.005**[a]	1.00
KDRS	2.005	.142	1.00	.155	.451

[a]Abbreviations: =significant at P=.05;

[b]=additional Bonferroni corrections presented in parentheses; F=ANOVA test statistical value; OBP=Offspring of Bipolar Parents; OCP=Offspring of Comparison Parents; OHP=Offspring of Healthy Parents; DFT=Dynamic Faces Task; EF-2-BACK=Emotional 2-Back Task; EF-0-BACK=Emotional 0-Back Task; FC=Functional Connectivity; dlPFC=Dorsolateral Prefrontal Cortex; cACC=Caudal Anterior Cingulate Cortex; vlPFC=Ventrolateral Prefrontal Cortex; rACC=Rostral Anterior Cingulate Cortex; -P=Parent Rating; -C=Child Rating; SCARED=Screen for Child Anxiety Related Emotional Disorders; CALS=Children's Affective Lability Sale; MFQ=Mood and Feelings Questionnaire; KMRS=Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale; KDRS=Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Depression Rating Scale.