

Differing Amygdala Responses to Facial Expressions in Children and Adults With Bipolar Disorder

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Objective: Child and adult bipolar patients show both behavioral deficits in face emotion processing and abnormal amygdala activation. However, amygdala function in pediatric relative to adult bipolar patients has not been compared directly. The authors used functional MRI to compare amygdala activity during a face processing task in children and adults with bipolar disorder and in healthy comparison subjects.

Method: Amygdala responses to emotional facial expressions were examined in pediatric (N=18) and adult (N=17) bipolar patients and in healthy child (N=15) and adult (N=22) volunteers. Participants performed a gender identification task while viewing fearful, angry, and neutral faces.

Results: In response to fearful faces, bipolar patients across age groups exhib-

ited right amygdala hyperactivity relative to healthy volunteers. However, when responses to all facial expressions were combined, pediatric patients exhibited greater right amygdala activation than bipolar adults and healthy children.

Conclusions: Amygdala hyperactivity in response to fearful faces is present in both youths and adults with bipolar disorder. However, compared with bipolar adults and healthy child volunteers, pediatric bipolar patients showed amygdala hyperactivity in response to a broad array of emotional faces. Thus, abnormal amygdala activation during face processing appears to be more pervasive in children than in adults with bipolar disorder. Longitudinal studies are needed to elucidate the mechanisms of this developmental difference, thus facilitating developmentally sensitive diagnosis and treatment.

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Both children and adults with bipolar disorder exhibit deficits in face emotion processing and abnormalities in amygdala structure and activity (1–3). However, to our knowledge, no study has compared bipolar children and adults in amygdala activity during face emotion processing. Such a comparative study could facilitate developmentally sensitive diagnosis and treatment for bipolar disorder (4, 5). In this cross-sectional functional MRI (fMRI) study, our goal was to begin to fill this research gap.

Studies have reported behavioral deficits during explicit emotion processing (i.e., face emotion labeling) in children with bipolar disorder (6, 7), in unaffected children at risk for bipolar disorder (8), and in adults with bipolar disorder (1, 9). Neural abnormalities during explicit emotion processing have been observed in both bipolar children and adults (10). However, the most consistent evidence of neural abnormalities in emotion processing in children and adults with bipolar disorder is that of amygdala hyperactivity during implicit emotion processing. During such implicit tasks, emotional features are reflected in aspects of a stimulus, such as the display of emotion in a face, but task instructions focus on nonemotional fea-

tures of the face, such as the gender of the person depicting the emotion. For example, using this type of implicit task, amygdala hyperactivity has been observed in bipolar children in response to fearful, angry, and happy faces (3, 11) and in bipolar adults in response to fearful, happy, and sad faces (12, 13). Thus, in the present study, we used a gender identification paradigm that involves implicit face emotion processing to test for abnormal amygdala activation in child and adult patients with bipolar disorder.

Evidence suggests that the course of bipolar disorder may be more severe in children than in adults (5, 14) and that younger patients may have greater impairment in face emotion perception than older patients (1). This in turn suggests that the neural circuitry mediating emotion information processing may be more impaired in youths than in adults with bipolar disorder. Indeed, recent meta-analyses have reported that decreased amygdala volume is observed more consistently in youths than in adults with the disorder (15, 16). However, these meta-analyses were based on separate structural studies of either youths or adults alone; studies that include both populations and employ identical procedures are needed. In fact, amyg-

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dala function in bipolar disorder has not been examined by applying identical methods to assess both adults and children. Such a study will initiate the process of identifying developmental trajectories of amygdala function in bipolar disorder to be pursued in future longitudinal work.

In this cross-sectional study, we compared amygdala activity in children and adults with bipolar disorder and in healthy comparison subjects during implicit processing of angry, fearful, and neutral facial expressions. We included only three facial expressions to ensure an adequate number of presentations of each stimulus type, thus maximizing statistical power while keeping the task brief enough to be tolerable for children. Fearful expressions were selected because they elicit amygdala hyperactivity consistently in both children and adults with bipolar disorder (3, 12). Angry and neutral expressions were included as a comparison negative emotion and a control stimulus, respectively. To compare neural activity in bipolar children and adults and comparison subjects of similar age, we conducted an amygdala region-of-interest and a whole-brain analysis.

Method

Participants

Bipolar children (ages 7–18 years) and adults (ages 19–60 years) were recruited through advertisements placed on support group websites and distributed to psychiatrists nationwide. Healthy child and adult volunteers were recruited by advertisement. No participants were biologically related.

The 72 participants included in this study were pediatric patients with bipolar disorder (N=18; age range: 9–18 years), adult patients with bipolar disorder (N=17; age range: 20–58 years), healthy child volunteers (N=15; age range: 12–17 years), and healthy adult volunteers (N=22; age range: 20–56 years). Participants enrolled in an institutional review board-approved protocol at the National Institute of Mental Health. Adult participants provided written informed consent. Parents and pediatric participants provided written informed consent and assent, respectively.

Pediatric patients were assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) (17), which was administered separately to children and parents by clinicians with established interrater reliability ($\kappa \geq 0.9$). To evaluate mood state in bipolar children, clinicians administered the Children's Depression Rating Scale (18) and the Young Mania Rating Scale (19) within 48 hours of fMRI scanning. Pediatric patients met criteria for narrow phenotype bipolar disorder (20), with at least one full-duration hypomanic episode characterized by abnormally elevated mood and at least three DSM-IV-TR criterion B symptoms for mania. Adult patients were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition (21) or the Diagnostic Interview for Genetic Studies (22) by clinicians with established interrater reliability ($\kappa \geq 0.85$). The Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (23), and Young Mania Rating Scale were used to evaluate mood state in adult patients.

Healthy volunteers were medication free and had no lifetime psychiatric diagnoses and no first-degree relatives with a mood disorder. They were assessed using the same diagnostic interviews as patients.

Inclusion criteria were an IQ >70 (as determined by the Wechsler Abbreviated Scale of Intelligence [24]) and no history of

neurological disorder, pervasive developmental disorder, chronic medical illness, or substance abuse or dependence in the past 3 months. After fMRI scanning, 28 of the 100 scanned participants were excluded as a result of scanner malfunction (N=19), excessive movement (N=1), poor image alignment (N=1), or behavioral accuracy below 65% (N=7).

Behavioral Paradigm

The behavioral paradigm we employed has been used previously (25, 26). Participants viewed gray-scale images of fearful, angry, and neutral expressions of 10 men and 10 women from the Pictures of Facial Affect series (27). For fearful and angry faces, in addition to standard (100%) expression intensity, lower (50%) and higher (150%) expression intensities were created by morphing with the neutral expression picture. This was done to enhance ecological validity, since individuals normally encounter different face expression intensity levels (25). To create neutral faces, neutral and happy faces were morphed to obtain a 25% happy expression, since studies suggest that children (28) and adults (29) perceive such expressions as neutral.

Using a two-button response box, participants indicated whether the face presented was male or female. Faces were presented for 2500 msec followed by a 500-msec fixation cross. Each of the four runs included 80 face trials (20 neutral trials and 10 trials of each intensity of fearful and angry faces) and 25 fixation trials. The trial order was randomized within each run.

Image Acquisition

Scanning was conducted using a 1.5-T General Electric scanner (General Electric, Milwaukee). Functional data were acquired using multislice gradient echo-planar sequence (31 axial slices, 4-mm thick, voxel size=3.75 mm × 3.75 mm × 4 mm, TR=3000 msec, TE=30 msec, flip angle=90°, field of view=240 mm, matrix size=64×64). Anatomical T₁-weighted three-dimensional spoiled gradient-recalled acquisition steady-state images with inversion recovery prep pulse (128 axial slices, 1.5 mm thick, TR=8.1 msec, TE=3.2 msec, flip angle=20°, field of view=240 mm, matrix size=256×256) were acquired to be coplanar with the fMRI scans for spatial registration.

Behavioral Data

We used SPSS (SPSS, Inc., Chicago) to conduct a three-way repeated-measures analysis of covariance (ANCOVA) with age group (child, adult) and diagnosis (bipolar disorder, healthy volunteer) as between-subject factors and emotion (fearful, angry, neutral) as a within-subject factor to compare accuracy and reaction time. Since there was a nearly significant difference in IQ between groups, IQ was included as a covariate. Post hoc ANCOVAs were performed using SPSS.

fMRI Data

Data preprocessing. Functional imaging data were preprocessed and analyzed using AFNI (Analysis of Functional Neuro-Images [30]). The first four images of each run were discarded to account for magnetic equilibrium. After slice time correction, images within each run were realigned to the fifth image to correct for movement. Images with motion greater than 2 mm in any direction were censored. If more than 5% of a participant's total images were censored, the participant was excluded. After motion correction, realigned functional images were coregistered to anatomical images, and functional images were anatomically normalized to Talairach space. Images were spatially smoothed with 6-mm root-mean-square deviation Gaussian blur.

At the individual participant level, general linear models were used to estimate the shape of the hemodynamic response to each event type (fearful, angry, and neutral expressions). To account for baseline drift and residual motion artifact, regressors

TABLE 1. Demographic and Clinical Characteristics of Pediatric and Adult Bipolar Disorder Patients and Healthy Child and Adult Volunteers

Characteristic	Bipolar Disorder Patients				Healthy Volunteers			
	Pediatric (N=18)		Adult (N=17)		Pediatric (N=15)		Adult (N=22)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	14.29	2.54	40.04	10.06	14.98	2.03	34.91	12.27
Wechsler Abbreviated Scale of Intelligence full-scale IQ score	107.83	13.83	114.53	12.71	108.27	15.35	118.05	15.51
Young Mania Rating Scale (YMRS) score ^a	6.83	3.73	3.77	4.55				
Children's Depression Rating Scale (CDRS) score ^b	26.53	7.41						
Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD) score			17.47	15.59				
Age at onset ^{a,c}	9.77	3.49	20.85	8.59				
Number of medications	2.83	1.89	3.00	1.06				
	N	%	N	%	N	%	N	%
Male	10	55.6	5	29.4	5	33.3	9	40.9
Bipolar type								
Type I	14	77.8	9	52.9				
Type II	4	22.2	8	47.1				
Mood state ^d								
Euthymic ^a	15	83.3	9	52.9				
Depressed ^a	2	11.1	8	47.1				
Hypomanic	1	5.6	0	0				
Manic	0	0	0	0				
Mixed	0	0	0	0				
Comorbid conditions								
Attention deficit hyperactivity disorder ^{a,e}	12	66.7	2	11.8				
Oppositional defiant disorder	3	16.7	0	0				
Anxiety disorders ^f	8	44.4	7	41.2				
Medication								
Medication free	3	16.7	0	0	15	100	22	100
Atypical antipsychotic	11	61.1	8	47.1				
Lithium	6	33.3	5	29.4				
Antiepileptic ^a	9	50.0	15	88.2				
Antidepressant	8	44.4	9	52.9				
Stimulant ^a	5	27.8	0	0				

^a Significant difference between adult and child patients with bipolar disorder.

^b Data were not available for one pediatric bipolar patient.

^c Data were not available for one pediatric bipolar patient and one adult bipolar patient.

^d Euthymia in children was defined as a CDRS score <40 and a YMRS score ≤12 and in adults as a YMRS score ≤12 and a SIGH-SAD score ≤20. Depression in children was defined as a CDRS score >40 and a YMRS score ≤12 and in adults as a SIGH-SAD score >20 and a YMRS score ≤12. Hypomania/mania in children was defined as a CDRS score ≤40 and a YMRS score >12 and in adults as a SIGH-SAD score ≤20 and a YMRS score >12. Mixed state was defined as a SIGH-SAD score >20 and a YMRS score >12.

^e Data were missing for three adult bipolar patients.

^f Diagnoses include generalized anxiety disorder, separation anxiety disorder, social phobia, panic disorder, posttraumatic stress disorder, and obsessive-compulsive disorder.

included six motion parameters obtained during coregistration and a third-order baseline drift function. Regressors were created for each event type. Regressors for fearful and angry expressions were weighted according to emotional intensity (1 for 50%, 2 for 100%, and 3 for 150%). Trials with incorrect answers were analyzed separately by including a regressor that accounted for incorrect behavioral responses. All regressors were convolved with a gamma-variate hemodynamic response function. Beta coefficients from the individual participant level were oriented to the standard Talairach-Tournoux space and then resampled to a resolution of 3 mm³.

Region-of-interest analysis. Anatomic masks of the right and left amygdala were created based on the Talairach-Tournoux Daemon. The masks were resampled to match their resolution to the fMRIs. Blood-oxygen-level-dependent (BOLD) signal change

from each event type versus the fixation was averaged across all amygdala voxels and entered in SPSS for the group-level analysis. An omnibus three-way repeated-measures ANCOVA with age group (child, adult) and diagnosis (bipolar disorder, healthy volunteer) as between-subject factors and emotion (fearful, angry, neutral) as a within-subject factor was performed for the right and left amygdala. Since reaction time differed between groups, it was included as a covariate in addition to IQ. Post hoc univariate ANCOVAs were performed in SPSS to identify differences between groups.

Whole-brain analysis. A group-level linear mixed-effects model was conducted with the 3dLME program in AFNI to examine between-group differences in response to the face emotions. The model included age group and diagnosis as between-subject factors and emotion as a within-subject factor, with IQ and reaction

TABLE 2. Behavioral Performance of Pediatric and Adult Bipolar Disorder Patients and Healthy Child and Adult Volunteers

Variable and Event Type	Bipolar Disorder Patients				Healthy Volunteers			
	Pediatric (N=18)		Adult (N=17)		Pediatric (N=15)		Adult (N=22)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Percent correct^a								
Angry expressions	86.05	10.13	95.67	3.33	90.92	8.82	96.00	3.20
Fearful expressions	86.07	9.23	98.23	1.87	91.49	9.51	97.89	2.57
Neutral expressions	87.39	11.50	98.27	1.79	93.25	7.45	98.26	1.83
Reaction time^b								
Angry expressions	933.94	110.46	788.85	127.67	843.52	152.43	749.14	86.91
Fearful expressions	932.26	112.78	780.10	127.18	830.77	161.30	749.14	87.31
Neutral expressions	935.19	119.55	760.77	121.09	827.35	154.40	739.73	91.83

^a There was a main effect of age group ($F=23.98$, $df=1$, 67 , $p<0.001$).

^b There was a main effect of age group ($F=13.63$, $df=1$, 67 , $p<0.001$) and of diagnosis ($F=5.64$, $df=1$, 67 , $p=0.02$).

time as covariates. Using the 3dClustSim program in AFNI (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html), Monte Carlo simulation (10,000 iterations, dimensions: $54 \times 64 \times 50$ mm, $3 \times 3 \times 3$ voxels, $9 \times 9 \times 8$ -mm smoothness) indicated that an initial voxel-wise threshold of $p<0.001$ and a minimum cluster size of 22 voxels yielded a corrected p value of 0.05. Post hoc univariate ANCOVAs were performed in SPSS to identify differences between groups and conditions.

Post hoc analyses. We conducted post hoc exploratory univariate ANCOVAs in SPSS to test potentially confounding effects of mood state, medication treatment, comorbid illnesses, and bipolar disorder subtype on the region-of-interest results (see the data supplement accompanying the online edition of this article). Because these exploratory analyses included relatively small subsets of bipolar patients, we have provided significant results as well as those that fell short of statistical significance ($p<0.10$).

Results

Demographic and Clinical Characteristics

Within each age group, patients and healthy volunteers did not differ in mean age (Table 1). Between groups, participants did not differ in gender distribution. There was a nearly significant difference for higher IQ among adults relative to children ($F=2.46$, $df=3$, 68 , $p=0.07$), and thus IQ was included as a covariate in all analyses.

Compared with adult patients, child patients were more likely to have an earlier age at illness onset ($t=-4.93$, $df=31$, $p<0.001$), to be euthymic ($\chi^2=3.75$, $df=1$, $p=0.05$), and to have higher Young Mania Rating Scale scores ($t=3.70$, $df=33$, $p=0.001$). Child patients had higher rates of attention deficit hyperactivity disorder (ADHD) ($\chi^2=8.78$, $df=1$, $p=0.003$) and stimulant treatment ($\chi^2=5.51$, $df=1$, $p=0.02$); they also had a higher rate of oppositional defiant disorder, although the difference fell short of statistical significance ($\chi^2=3.10$, $df=1$, $p=0.08$) (Table 1). Child patients were more likely to be medication free, although this difference also fell short of significance ($\chi^2=3.10$, $df=1$, $p=0.08$). Adult patients were more likely to be depressed ($\chi^2=5.54$, $df=1$, $p=0.02$) and to be receiving antiepileptic medication ($\chi^2=5.93$, $df=1$, $p=0.02$).

Behavioral Data

For accuracy in the faces task, no three- or two-way interaction was observed. The only main effect was that of age group ($F=23.98$, $df=1$, 67 , $p<0.001$), indicating that children were less accurate in their responses than adults (Table 2). Since only correct trials were included in the fMRI analysis, accuracy was accounted for in the analysis of fMRI data.

For reaction time, no three- or two-way interaction was observed. There were main effects of diagnosis (bipolar disorder patients were slower than healthy volunteers; $F=5.64$, $df=1$, 67 , $p=0.02$) and age group (children were slower than adults; $F=13.63$, $df=1$, 67 , $p<0.001$) (Table 2). Because of these between-group differences, reaction time was included as a covariate in the fMRI analyses.

fMRI Data

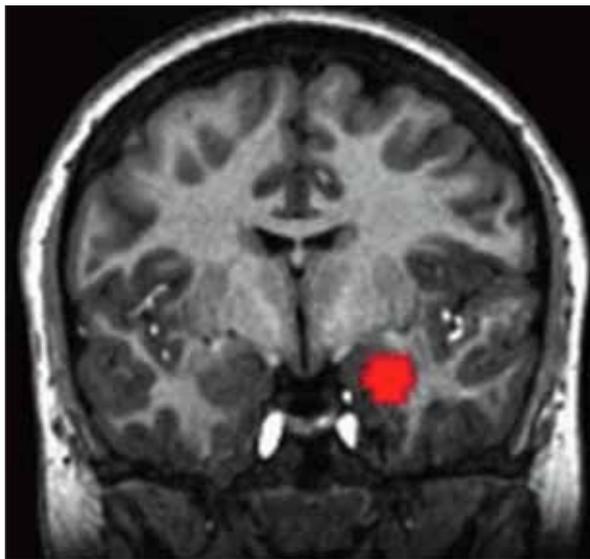
Region-of-interest analysis. In the right amygdala (Figure 1), the age group-by-diagnosis-by-emotion interaction was not significant, but both two-way interactions achieved statistical significance (age group by diagnosis [$F=4.30$, $df=1$, 64 , $p=0.04$]; diagnosis by emotion [$F=4.52$, $df=2$, 128 , $p=0.01$]).

A post hoc ANCOVA of the age group-by-diagnosis interaction revealed that across expressions, bipolar children exhibited greater amygdala activation than both bipolar adults ($F=5.66$, $df=1$, 29 , $p=0.02$) and healthy children ($F=8.99$, $df=1$, 27 , $p=0.006$), whereas no difference was observed for bipolar adults and healthy adults (Figure 2).

A post hoc ANCOVA of the emotion-by-diagnosis interaction revealed that bipolar patients had greater amygdala responses to fearful expressions than healthy volunteers ($F=12.49$, $df=1$, 68 , $p<0.001$) (Figure 3). For angry and neutral expressions, amygdala activity did not differ between patients and healthy subjects.

In the left amygdala, no significant interactions were observed. A main effect of age indicated that amygdala activation was greater among children than adults ($F=7.75$, $df=1$, 64 , $p=0.007$).

FIGURE 1. Region of Interest fMRI Results for Three- and Two-Way Interactions in the Right Amygdala in Pediatric and Adult Bipolar Patients and Healthy Child and Adult Volunteers^a



^a The age group-by-diagnosis and diagnosis-by-emotion interactions achieved statistical significance ($p=0.04$ and $p=0.01$, respectively), but the age group-by-diagnosis-by-emotion interaction did not.

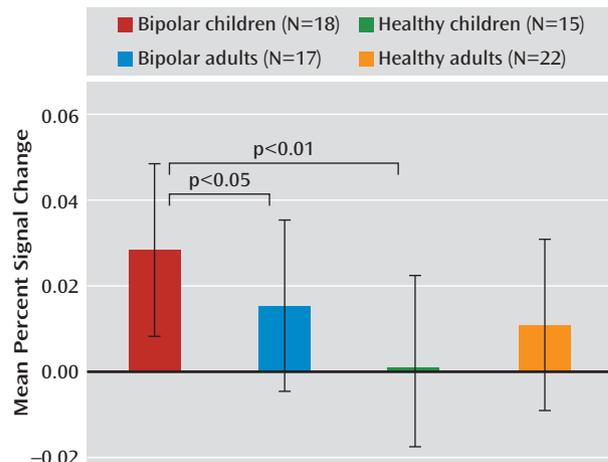
Whole-brain analysis. An age group-by-diagnosis-by-emotion interaction was observed in the left posterior cingulate cortex ($F=12.34$, $df=2$, 128; Montreal Neurological Institute coordinates: -7 , -28 , 38; 38 voxels, $p<0.05$ [corrected]). In the left posterior cingulate cortex, the age group-by-diagnosis interaction was observed only in response to angry expressions ($F=4.61$, $df=1$, 68, $p=0.04$). Specifically, bipolar children showed less activity in this region in response to angry expressions than healthy children ($F=5.81$, $df=1$, 31, $p=0.02$).

Effects of Mood State, Medication, Comorbid Illnesses, and Bipolar Subtype

Post hoc analyses examined whether the age group-by-diagnosis interaction in the right amygdala could be driven by differences between child and adult bipolar patients in mood state, in medication treatment, in comorbid illnesses, or in bipolar disorder subtype (see the online data supplement). The differences in this region between child and adult bipolar patients were either significant or fell just short of statistical significance after we controlled for most clinical differences (all p values <0.07). The exceptions were for differences in antiepileptic medication treatment and comorbid oppositional defiant disorder, for which confounding effects could not be ruled out.

Data indicate that relative to healthy volunteers, patients with anxiety disorders have amygdala hyperactivity in response to fearful faces (31). Therefore, we tested whether amygdala hyperactivity in bipolar patients in response to fearful faces, compared with healthy volunteers, could be a result of comorbid anxiety disorders. Bipolar

FIGURE 2. Age Group-by-Diagnosis Interaction in Pediatric and Adult Bipolar Patients and Healthy Child and Adult Volunteers^a



^a The graph depicts blood-oxygen-level-dependent (BOLD) responses across expressions in the right amygdala ($F=4.30$, $df=1$, 64, $p=0.04$). Error bars indicate standard deviations.

patients without comorbid anxiety disorders showed greater amygdala activity ($p=0.003$) in response to fearful expressions than healthy volunteers.

Discussion

We compared amygdala activity in children and adults with bipolar disorder and healthy volunteers of similar age while they performed an implicit face emotion processing task that included fearful, angry, and neutral faces. Compared with healthy subjects, both children and adults with bipolar disorder exhibited amygdala hyperactivity in response to fearful expressions. However, compared with bipolar adults, children with the disorder exhibited amygdala abnormalities in response to a greater array of facial expressions. The results of this cross-sectional study suggest that there are potential developmental differences in amygdala activity in patients with bipolar disorder. Longitudinal studies are needed to test the hypothesis that amygdala abnormalities persist in response to fearful, but not angry and neutral, expressions as children with bipolar disorder age.

In response to fearful faces, both children and adults with bipolar disorder had increased right amygdala activity relative to healthy volunteers of similar age. This is consistent with results from previous studies that included only children or adults (3, 10, 12). However, in our study, when amygdala response was considered across all emotions (angry, neutral, and fearful expressions), pediatric bipolar patients exhibited amygdala hyperactivity relative to both bipolar adults and healthy children. Observation of amygdala hyperactivity across expressions in pediatric bipolar patients suggests that there is a more general form of face emotion dysfunction in pediatric bipolar disorder

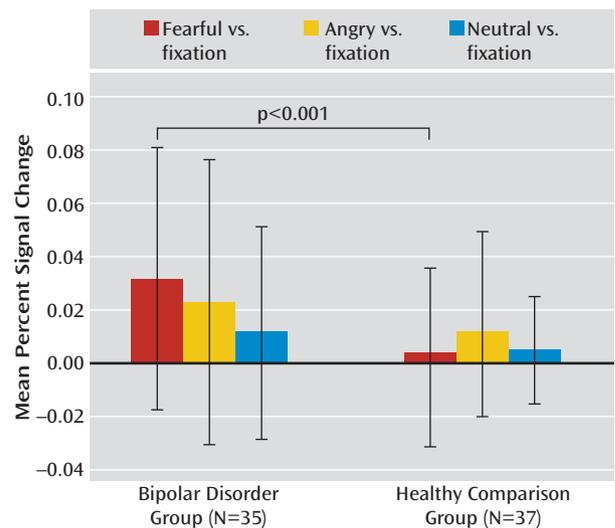
than in adult bipolar disorder. Such an observation is consistent with previous data, including behavioral results. A recent meta-analysis suggested that explicit face emotion processing deficits (i.e., deficits in face emotion labeling across expressions) are observed more consistently in youths than in adults with bipolar disorder (1). However, it is important to note that abnormalities in implicit and explicit emotion processing may not necessarily be linked (32). Thus, more fMRI studies are needed to understand the relevance of implicit processing deficits to behavioral explicit processing deficits as well as to examine brain activity during explicit emotion processing in both pediatric and adult patients with bipolar disorder.

Greater cumulative lifetime medication exposure in adult bipolar patients compared with pediatric patients may explain the amygdala activity differences between these two patient groups. In our study, the two groups did not differ on current rates of antidepressant and antipsychotic treatment. Nonetheless, cross-sectional research suggests that such medications may normalize amygdala activity in adults with bipolar disorder (33). Although to our knowledge this has not yet been tested, it is likely that cumulative exposure to medication may affect amygdala activity. In addition, the developmental differences in amygdala activity that we observed may be associated with differences in the clinical course between adults and youths with bipolar disorder. Although few studies have compared clinical course between the two groups directly, evidence suggests that pediatric bipolar patients may be more likely than adult patients to experience rapid cycling or mixed states (14). These clinical features, along with early age at onset, tend to be associated with poor longitudinal outcomes (14, 34). In our study, detailed information about mood cycling or global functioning was not available to test the hypothesis that amygdala hyperactivity across emotions may be linked with worse clinical outcome among pediatric relative to adult bipolar patients. However, this is an important issue for future research.

Our whole-brain analysis revealed that neural activity differences between pediatric and adult patients with bipolar disorder and between bipolar patients and healthy volunteers were not limited to the amygdala. Replicating a previously reported finding, children with bipolar disorder exhibited less activation in the left posterior cingulate cortex than healthy subjects in response to angry expressions (11). Studies have suggested that the posterior cingulate cortex is involved in top-down control of attention (35) and in integrating information about emotional expressions, particularly anger (36). Thus, the abnormal posterior cingulate cortex activity observed in pediatric bipolar patients may be associated with impaired attentional and information processing of angry expressions.

The limitations of this study include its cross-sectional design, since only longitudinal data can support firm conclusions about associations between development and brain activation in individuals with bipolar disorder.

FIGURE 3. Diagnosis-by-Emotion Interaction in Pediatric and Adult Bipolar Patients and Healthy Child and Adult Volunteers^a



^a The graph depicts blood-oxygen-level-dependent (BOLD) responses to fearful, angry, and neutral expressions across age groups in the right amygdala ($F=4.52$, $df=2, 128$, $p=0.01$). Error bars indicate standard deviations.

First, we cannot disambiguate two relevant hypotheses: 1) that abnormal amygdala activity in children with bipolar disorder becomes specific to fearful expressions as these children age and 2) that throughout a patient's life, pediatric-onset bipolar disorder is associated with more severe amygdala abnormalities than the adult-onset form of the disorder. While children and adults with bipolar disorder differed on some clinical characteristics, our post hoc exploratory analyses suggest that these variables largely did not account for the age-related differences we observed. Second, to ascertain whether differences in amygdala activity between bipolar patients and healthy volunteers represent dysfunction, rather than compensatory mechanisms in response to dysfunction in other brain regions, future studies should examine 1) associations among neural activity during emotional information processing, 2) behavior, and 3) clinical characteristics. For example, if amygdala hyperactivity in patients reflects amygdala dysfunction, one would expect elevated amygdala activity to be associated with behavioral deficits and poor clinical course. In contrast, if such hyperactivation is compensatory to dysfunction in other brain regions, one might expect elevated amygdala activity to predict relatively intact behavior and a relatively benign clinical course. Research examining the compensatory process ideally would follow children prospectively after acquisition of imaging data. In addition, while we were unable to identify aberrant activity in other brain regions to which amygdala hyperactivation might be compensatory, future studies examining larger samples, along with connectivity analyses, could be informative in that regard.

Our study provides the first evidence, to our knowledge, of age-related differences in amygdala activity in response to facial expressions among bipolar patients. Although bipolar disorder patients across age groups showed amygdala hyperactivity in response to fearful faces, the abnormal amygdala activation was present in response to more emotions in pediatric than in adult patients. These findings provide support and guidance for future longitudinal work examining the developmental trajectory of amygdala function, from the asymptomatic risk state through the course of the illness. Knowledge about this trajectory could help in the early detection of bipolar disorder and the development of age-appropriate treatments.

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Dr. Zarate is listed as a co-inventor on a patent application for the use of ketamine in major depression; he has assigned his rights in the patent to the U.S. government but will share a percentage of any royalties that may be received by the government. All other authors report no financial relationships with commercial interests.

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