Abnormal Amygdala and Prefrontal Cortex Activation to Facial Expressions in Pediatric Bipolar Disorder

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Objective: Previous functional magnetic resonance imaging (fMRI) studies in pediatric bipolar disorder (BD) have reported greater amygdala and less dorsolateral prefrontal cortex (DLPFC) activation to facial expressions compared to healthy controls. The current study investigates whether these differences are associated with the early or late phase of activation, suggesting different temporal characteristics of brain responses. **Method:** A total of 20 euthymic adolescents with familial BD (14 male) and 21 healthy control subjects (13 male) underwent fMRI scanning during presentation of happy, sad, and neutral facial expressions. Whole-brain voxelwise analyses were conducted in SPM5, using a three-way analysis of variance (ANOVA) with factors group (BD and healthy control [HC]), facial expression (happy, sad, and neutral versus scrambled), and phase (early and late, corresponding to the first and second half of each block of faces). **Results:** There were no significant group differences in task performance, age, gender, or IQ. Significant activation from the main effect of group included greater DLPFC activation in the HC group, and greater amygdala/hippocampal activation in the BD group. The interaction of Group × Phase identified clusters in the superior temporal sulcus/insula and visual cortex, where activation increased from the early to late phase of the block for the BD but not the HC group. **Conclusions:** These findings are consistent with previous studies that suggest deficient prefrontal cortex regulation of heightened amygdala response to emotional stimuli in pediatric BD. Increasing activation over time in superior temporal and visual cortices suggests difficulty processing or disengaging attention from emotional faces in BD. *J. Am. Acad. Child Adolesc. Psychiatry,* 2012;51(8): 821–831. **Key Words:** bipolar, fMRI, pediatric, amygdala

R etrospective studies of adults with bipolar disorder (BD) suggest that the first episode of this disorder begins in childhood or adolescence in about 50% to 67% of cases.[1,2] Compared with adult-onset illness, pediatric on-set BD has a more adverse course.[3] Early-onset BD can negatively influence emotional, cognitive, and social development, thus, early identification and treatment is important for reducing its neg-ative impact.[4] Neuroimaging investigation of pe-diatric BD may expand our understanding of neural abnormalities that could be targeted by treatment.

Patients with BD exhibit emotion processing deficits, including difficulty labeling facial ex-pressions.[5] Important components of the brain networks that process facial expressions include the amygdala and prefrontal cortex.[6-8] Several recent fMRI studies of adult patients with BD report prefrontal cortex abnormalities during face processing, particularly the dorsolateral pre-frontal cortex (DLPFC),[9] the ventrolateral pre-frontal cortex (VLPFC),[10-12] and the orbitofrontal cortex (OFC),[13,14] although the direction of the findings varies. Amygdala hyperactivation has been reported by several,[15-18] but not all,[9,10,19,20] groups. Meta-analyses of functional magnetic res-onance imaging (fMRI) studies of adult patients with BD also highlight these regions, reporting less ventrolateral prefrontal and greater limbic

(parahippocampal, hippocampal, amygdala, basal ganglia) activation during emotional tasks[21] and specifically during facial emotion processing tasks.[22] In the meta-analysis comparison focused specifically on patients in a euthymic mood state performing facial affect tasks, hypoactivation in the DLPFC and hyperactivation in the amygdala, hippocampus, superior temporal gyrus, and insula was found compared to controls.[23] However, these patterns are not always unique to the euthymic mood state. The meta-analysis by Houenou et al.[24] found increased parahippocampal/amygdala activation in both manic and euthymic patients compared to healthy control (HC), but decreased VLPFC activation in manic patients only. Different findings according to mood state were also reported by Hulvershorn et al.,[25] who found that amygdala hyperactivation in response to negative faces characterized euthymic and depressed BD patients, but not manic patients, while only manic patients showed increased DLPFC activation compared with all other groups. Taken together, these studies show somewhat consistent findings in terms of abnormalities in prefrontal and limbic regions, but are complicated by several patient factors, such as mood state, illness duration, medication exposure, and variations in task and task demands.

Studies of pediatric patients can provide important information about interactions between BD and brain development, and are less likely to be confounded by medication exposure, substance use, and the long-term effects of mood symptoms, compared with adult samples. In addition, if different brain abnormalities are found in child versus adult samples, this could suggest that the illness may manifest differently depending on developmental stage. So far, however, results from pediatric fMRI studies of pediatric patients with BD viewing facial expressions are mostly consistent with the adult BD literature, including a pattern of abnormal dorsolateral, ventrolateral, and/or orbital prefrontal activation in both euthymic patients[26,27] and a mixed group of mood states.[28] Amygdala hyperactivation also has been reported in both euthymic patients[29,30] and patients from a mixed group of mood states.[31] Interestingly, elevated amygdala activation in manic/hypomanic pediatric patients persists after treatment with lamotrigine, whereas VLPFC activation normalizes.[32]

For both adult and pediatric samples, fMRI data have been interpreted as showing that amygdala responses to emotional stimuli are poorly inhibited by prefrontal regions. Functional connectivity analyses in children support this hypothesis.[33] However, more neuroimaging studies of youth with BD are needed to understand the contributions of mood state and brain development to patterns of activation.

A potentially fruitful method for examining the relevance of amygdala/DLPFC abnormalities to pediatric BD is to examine the temporal characteristics of abnormal activation in these regions. Temporal characteristics of activation can be assessed by examining decreases (habituation) or increases (sensitization) in the magnitude of activation over time. Habituation and sensitization of amygdala activation have been reported in healthy adults,[34-36] and may reflect the ability of prefrontal brain regions to modulate responses of the amygdala over time. In BD, poor emotion regulation may be seen as abnormal habituation of amygdala activation over a block of faces, accompanied by lack of sensitization in prefrontal activation. This idea is supported by the only previous neuroimaging study that examined early and late phases of activation in adults with BD while viewing fearful faces.[37] In that study, activation in regulatory regions, including the OFC, anterior cingulate, and striatum, increased during the late versus early phase of the task in the healthy control group but not in the BD group, suggesting lack of regulatory control in BD. Temporal patterns of brain activation have not been studied in children and adolescents with BD. In the current study, we hypothesized that youth with BD will demonstrate abnormal amygdala activation during the late phase of the block of faces, and abnormal prefrontal activation during the early phase. Our study focuses on euthymic youth with BD, to build on previous studies of euthymic patients and to contrast with those in manic and depressed states.

METHOD

Subjects

The study was approved by the Stanford University Administrative Panel of Medical Research in Human Subjects. Written informed consent and assent were obtained from parents and children, and subjects were paid for participation. Participants included 32 children and adolescents with familial BD participating in an NIMH-sponsored study of offspring of adult patients with BD (MH64460-01). Participants were re-

cruited from advertisements and clinician contacts in the Stanford University Adult Bipolar Disorders Clinic and Pediatric Mood Disorders Clinic, and from San Francisco Bay Area communities. A total of 27 healthy control subjects were recruited from the same community by advertisement.

For both groups, subjects were required to be 9 through 17 years old. Exclusion criteria were pervasive developmental disorder, neurological conditions, substance use disorder, IQ <80, braces, and MRI contraindications (e.g., metal in the body). For all subjects, Full-Scale IQ was measured using the Wechsler Abbreviated Scale of Intelligence (WASI, Psychological Corporation; San Antonio, TX).

Inclusion in the BD group required a diagnosis of bipolar I or bipolar II disorder and at least one parent meeting diagnostic criteria for bipolar I or II disorder by the Structured Clinical Interview for *DSM-IV* (SCID).[38] All children were assessed using the mood disorders module of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS[39]) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime (K-SADS-PL),[40] as reported in a previous publication.[41] Subjects were deemed euthymic in that they were not experiencing a current manic, mixed, or depressive episode. However, there was variation in degree of subthreshold symptoms as indicated by Young Mania Rating Scale (YMRS) and Childhood Depression Rating Scale (CDRS) scores. On the day of the scan, current symptoms of depression within the past 2 weeks were assessed using the CDRS,[42] and current symptoms of mania within the past week were assessed using the YMRS.[43,44]

Inclusion in the healthy control group required that the subject have no current or past *DSM-IV* psychiatric diagnosis, as confirmed by K-SADS-PL interview. A SCID interview confirmed that both parents had no psychiatric diagnosis. The Family History Research Diagnostic Criteria[45] confirmed that first- and second-degree relatives did not have BD.

Emotional Facial Expressions Stimuli and Task
Validation of the affective faces stimuli has been reported in a previous publication.[46] Briefly, 96 pictures were taken from several sources.[47,48] Pictures were edited to be monochromatic and of the same size. The faces displayed a happy, sad, or neutral expression of moderate intensity. Half of the pictures showed male models, and half showed female models. Pictures were matched (across facial expression) for intensity of emotion and gender of model. Stimuli were rated by an independent group of subjects and verified to be perceived as intended by the investigators (happy, sad, or neutral). Scrambled pictures were created by randomly rearranging the voxels from these pictures into an unrecognizable pattern.

Emotional facial expressions were presented in a block design. Four (nonrepeated) blocks of each facial expression were shown (happy, sad, neutral, scrambled). Each block contained eight pictures, each of which was shown for 3 seconds with no interstimulus interval; therefore each block lasted 24 seconds. To reduce effects related to the order of the blocks, four different orders of blocks were presented.

The task used implicit emotion perception, as subjects were instructed to judge the gender of the model in each picture and to press button 1 with the right index finger to indicate female and button 2 with the right second digit to indicate male pictures. During scrambled blocks, subjects alternated pushing buttons 1 and 2. Correct and incorrect responses and response times were recorded by the task presentation software Psyscope (http://psyscope.psy.cmu.edu/). Group differences in accuracy and response time were assessed using t tests in SPSS (SPSS Inc., Chicago, IL).

Onset of scanner and task were synchronized using a transistor–transistor logic (TTL) pulse delivered to the scanner timing microprocessor. Stimuli were projected from the foot of the scanner onto a screen attached to the headcoil. The subject viewed the stimuli by looking directly up at a mirror reflecting the stimuli shown on the screen. Before the scan, all subjects underwent a training session in an MRI simulator in which they practiced performing the task, learned to lie motionless for up to 10 to 15 continuous minutes, and acclimated to the sounds and confines of the scanner. Subjects were allowed to continue current medications, except psychostimulants, which were temporarily discontinued 24 to 48 hours before the scan.

Functional Data Acquisition
Images were acquired on a 3T GE Signa scanner using a standard GE whole head coil (General Electric, Milwaukee, WI). The following spiral pulse sequence parameters were used: field of view (FOV) = 20 cm, repetition time (TR) = 2000 msec, time to echo (TE) = 30 msec, flip angle = 89° and one interleave.[49] A total of 28 axial slices were acquired (4 mm thick, 0.5 mm skip). An individually calculated, automated, high-order shimming method based on spiral acquisitions was used to reduce B0 inhomogeneities. To localize functional activation, a three-dimensional, high-resolution, T1 weighted, spoiled grass gradient recalled (SPGR) image was collected (124 coronal slices, 256 × 192 matrix; slices = 1.5 mm thick, no skip, 240 mm FOV; TR = 35 msec; TE = 6 msec; and flip angle = 45°; acquired resolution = 1.50 × 0.94 × 1.25 mm).

SPM Functional Image Analysis
Functional images were reconstructed by inverse Fourier transform for each of the 216 time points into 64 × 64 × 28 matrices (voxel size: 3.12 × 3.12 × 4.5 mm) and

analyzed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). Images were spatially realigned and motion repaired using the ArtRepair toolbox (cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm), and normalized into an age-appropriate, $2 \times 2 \times 2$ mm stereotactic template (irc.cchmc.org/software/pedbrain.php), smoothed with a 7-mm Gaussian filter and were high-pass filtered.

The general linear model and the theory of Gaussian random fields implemented in SPM5 were used for voxelwise whole-brain statistical analyses.[50] A fixed-effects model was used to identify activation associated with each facial expression compared to scrambled images. Affective facial expressions were compared to scrambled images to investigate responses to faces as emotional and social stimuli. Neutral faces were not used as the comparison condition, because neutral faces can be interpreted as having (nonneutral) affective characteristics by children and adolescents, as evidenced by activation of emotion-related brain circuitry in children.[51]

Each block of faces was divided into an early and late phase, so that the first 12 seconds of the faces block was modeled as the early phase, and the last 12 seconds was modeled as the late phase. The early phase of each facial expression block was contrasted with the early phase of the scrambled images block, and the late phase was contrasted with the late phase of the scrambled block. Voxelwise t statistics were normalized to Z scores.

Individual contrast images were combined into a random-effects analysis[52] in SPM5 using a multivariate analysis of variance (ANOVA). The ANOVA included the factors group (BD and HC), and face (happy, sad, neutral) and phase (early and late). Our primary hypothesis was tested by identifying activation associated with the interaction of group × phase. To provide consistency with previous studies in this population using this paradigm, we also investigated activation associated with the main effect of group. Finally, although we have no hypotheses about specific facial expressions, exploratory analyses tested for activation associated with group × phase × face, main effect of phase, and main effect of face. For all contrasts, significant clusters of activation were determined using the joint expected probability of height ($p = .01$) and extent ($p = .01$) of Z scores, yielding a clusterwise significance level of $p = .01$, corrected for multiple comparisons.[53] Cluster extent to reach this threshold was determined using the 3DclustSim/AlphaSim program (afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html). MNI coordinates were converted to Talairach coordinates using procedures described by Brett (1999; www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). Activation foci were superimposed on high-resolution T1-weighted images and localized with reference to the stereotaxic atlas of Talairach and Tournoux.[54] For significant

group × phase interactions, post-hoc t tests were conducted using SPSS software and using activation extracted by the MARSBAR program (http://marsbar.sourceforge.net/).

RESULTS

Subjects

All subjects tolerated the scanning session without difficulty. Twelve subjects from the BD group and six subjects from the HC group were removed from the analysis because of excessive head motion during the scan, leaving 20 subjects in the BD group and 21 subjects in the HC group for all analyses. For these remaining subjects, the number of head motion artifacts repaired during image processing did not differ between the BD (mean = 14 of 216 timepoints) and HC groups (mean = 9 of 216 timepoints) ($p = .12$).

Table 1 lists subject characteristics per group. The control and BD groups did not differ in Full-Scale IQ ($p = .28$), age ($p = .71$), or gender ($p = .59$).

Task Performance

Descriptive statistics for task performance data per group are given in Table 1. There were no significant group differences in task performance. There was a trend for lower accuracy of the BD subjects when identifying the gender of the happy ($p = .08$) and sad ($p = .09$) faces.

Whole-Brain Voxelwise Functional MRI Results

Group × Phase Interaction. Significant activation associated with the interaction of group × phase is given in Table 2. Only two clusters were significant: one spanned the left superior temporal sulcus (STS) and part of the posterior insula. The other cluster included the right visual cortex and posterior cingulate cortex. These clusters are shown and graphed in Figure 1. For both regions, activation increases from the early to late phase in the BD group, but not in the HC group.

Main Effect of Group. Significant activation associated with the Main Effect of Group is given in Table 3. When the one subject with bipolar II disorder was excluded, all ANOVA results remained unchanged. Clusters greater in BD than HC included the right amygdala and hippocampus, right and left OFC, bilateral parietal cortex, and anterior cingulate cortex. Clusters

TABLE 1 Subject Characteristics

Characteristic	BD Group (n = 20)	HC Group (n = 21)	p
Sex	6 female, 14 male	8 female, 13 male	.59
Left-handed, n	1	1	
Age, y, mean (SD)	15.63 (2.10)	15.35 (2.68)	.71
Full-Scale IQ, mean (SD)	110.72 (8.59)	113.62 (7.87)	.28
CDRS score, mean (SD)	36.6 (13.1)		
YMRS score, mean (SD)	16.3 (8.7)		
Diagnosis, % (n)			
Bipolar disorder I	95 (19)		
Bipolar disorder II	5 (1)		
ADHD	85 (17)		
ODD	40 (8)		
Conduct disorder	5 (1)		
Anxiety disorder[a]	75 (15)		
Medication, % (n)			
Anticonvulsant	60 (12)		
Valproate	45 (9)		
Atypical antipsychotic	30 (6)		
Lithium	35 (7)		
Atypical antidepressant	35 (7)		
SSRI	5 (1)		
Task performance			
Correct happy, % (SD)	82.97 (10.6)	88.69 (9.45)	.08
Correct sad, % (SD)	82.81 (11.1)	87.80 (6.16)	.09
Correct neutral, % (SD)	83.75 (8.6)	87.80 (9.68)	.17
RT happy, mean (SD)	822.31 (172.70)	906.45 (187.55)	.14
RT sad, mean (SD)	876.69 (213.73)	920.86 (205.24)	.50
RT neutral, mean (SD)	909.77 (208.85)	903.20 (179.40)	.91

Note: ADHD = attention-deficit/hyperactivity disorder; BD = bipolar disorder; CDRS = Children's Depression Rating Scale; HC = healthy control; ODD = oppositional defiant disorder; RT = response time; SSRI = selective serotonin reuptake inhibitor; y = years; YMRS = Young Mania Rating Scale.
[a] Anxiety Disorders include the following: generalized anxiety disorder (n = 7); separation anxiety disorder (n = 2); obsessive-compulsive disorder (n = 3); panic disorder (n = 1); specific phobia (n = 1); posttraumatic stress disorder (n = 1).

greater in HC versus BD included the DLPFC and bilateral visual cortex. These clusters are shown in Figure 2.
Exploratory Interactions. There were no significant clusters for the main effect of phase, the

TABLE 2 Interaction, Group × Phase

Brain Region	BA	k	Peak Z	x,y,z
L STS/insula	13	1474	3.04	−34,−32,20
L MTG	19		2.99	−53,−63,14
L visual cortex	17			
R PCC	23	416	2.88	16,−54,17
R visual cortex	17			

Note: Significant clusters: p = .01 corrected for multiple comparisons. BA = Brodmann area; L = left; MTG = middle temporal gyrus; PCC = posterior cingulate cortex; R = right; STS = superior temporal sulcus.

main effect of valence, or the interaction of group × phase × valence.
Post-hoc Follow-up t Tests for Group × Phase Interaction. Significantly activated clusters from the interaction of group × phase (e.g., those listed in Table 2) were further evaluated by extracting mean activation in each cluster using the MARS-BAR program (http://marsbar.sourceforge.net/). Extracted clusters were analyzed using SPSS software and a repeated-measures t test, which tested for significant changes in activation (indicating habituation or sensitization) from the early to late phase of the block within each group, collapsed across facial expression. We found that changes within each group were not significant: visual cortex: for HC: t < 1, for BD: t = −1.9, p = .07 (trend); for the STS/insula: for HC: t = 1.01, p = .33; for BD: t = −1.75, p = .096 (trend). Between-group t tests

FIGURE 1 Significant clusters for group × phase: superior temporal sulcus (top) and visual cortex (bottom). Note: Graphs show that activation increases over time in the bipolar disorder (BD) group, but not in the healthy control (HC) group.
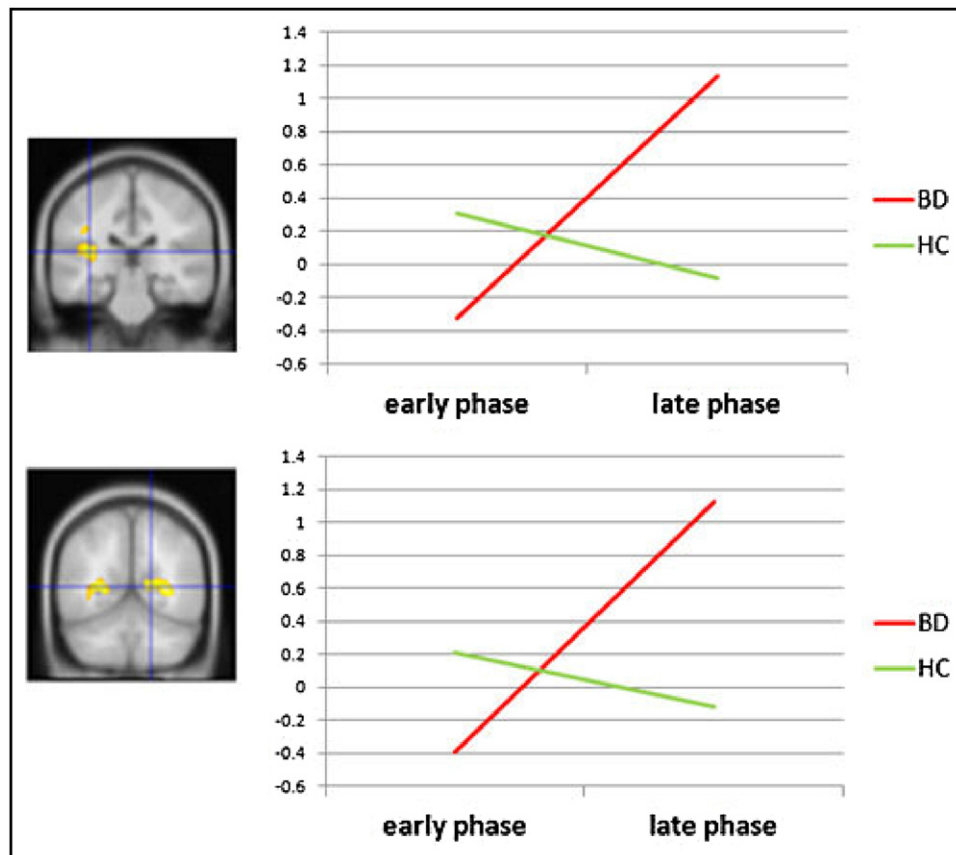
were used to compare BD and HC groups at each phase, collapsed across facial expression. There were no group differences at either phase: visual cortex: early phase: t = 1.01, p = .32; late phase: t = 2.9, *p* = .097 (trend); STS/insula: early phase: t = 1.45, *p* = .24; late phase: t = 2.67, *p* = .11). In summary, although the post-hoc t tests of extracted activation do not identify a particular phase responsible for this effect, the whole brain SPM analysis shows a significant interaction of group × phase in these regions.

Effects of Medication. Many of the subjects were taking psychotropic medications including lithium, anticonvulsants, and antipsychotics, which could affect fMRI data.[55] We sought to determine whether our primary findings (main effect of group: DLPFC, amygdala, OFC; group × phase: visual cortex/posterior cingulate and STS/insula) were affected by these medications. For each region, we used extracted activation values and independent groups t tests to compare the

following: patients taking lithium (n = 7) versus those not taking lithium (n = 13); patients taking atypical antipsychotics (n = 9) versus those not taking atypical antipsychotics (n = 11); and patients taking anticonvulsants (n = 12) versus those not taking anticonvulsants (n = 8). Results showed that medication subgroups were not significantly different in activation of the amygdala, DLPFC, or orbital frontal cortex (*p* > .05). Also, medication subgroups were not significantly different in activation of the STS/insula or the visual cortex/posterior cingulate (*p* > .05).

Correlation with Symptom Severity and Age. Within the BD group, Spearman's correlation analyses were conducted using CDRS depression scores, YMRS mania scores, and extracted activation in two primary regions of interest: the amygdala and the DLPFC. None of the correlations passed the threshold of *p* = .05. We also correlated change in activation from phase 1 to phase 2 with YMRS and CDRS scores within the BD group.

TABLE 3 Main Effect of Group

Brain Region	BA	k	Peak Z	x	y	z	Direction
R superior frontal (DLPFC)	10	887	3.97	18	65	17	HC>BD
R middle frontal gyrus	46		3.59	44	38	15	
R medial prefrontal	10		4.32	12	66	4	
R middle occipital gyrus	19/18	1595	3.86	46	−81	11	HC>BD
R fusiform gyrus	19		3.66	42	−72	−12	
R inferior occipital gyrus	18		3.53	36	−93	0	
L middle occipital gyrus	19	789	5.68	−40	−85	8	HC>BD
L fusiform gyrus	19		4.59	−44	−83	6	
R amygdala		441	4.68	30	−1	−18	BD>HC
R parahippocampal gyrus	34		4.36	30	3	−17	
R superior temporal gyrus	38		4.09	32	3	−17	
R uncus	28		3.87	32	5	−19	
R globus pallidum			3.60	20	−6	−3	
L superior parietal lobe	7	536	4.96	−28	−65	57	BD>HC
L inferior parietal lobe	40		4.27	−65	−41	26	
L supramarginal gyrus	40		3.76	−63	−43	28	
L precentral gyrus	4		3.53	−51	−7	52	
L middle frontal gyrus	6/8		3.40	−50	8	46	
L caudate tail		536	4.05	−20	−32	15	BD>HC
L thalamus (pulvinar nucleus)			3.89	−18	−32	13	
R superior parietal lobe	7	2006	4.14	22	−61	62	BD>HC
R inferior parietal lobe	40		4.13	48	−33	35	
R postcentral gyrus	5		4.04	36	−42	59	
R supramarginal gyrus	40		3.82	65	−45	26	
R precentral gyrus	44/6	1761	4.34	48	2	7	BD>HC
R insula	13		4.04	44	2	5	
R anterior cingulate cortex	32	439	3.77	10	45	0	BD>HC
R superior medial frontal gyrus	10		3.67	14	45	3	
R orbital frontal	11		3.67	24	37	−5	
L orbital frontal cortex	11		3.48	−20	42	−8	
L cerebellum		652	3.55	−22	−44	−21	BD>HC
L/R brainstem and midbrain				0	−27	−26	

Note: Significant clusters: p = .01 corrected for multiple comparisons. BA = Brodmann area; BD = bipolar disorder; DLPFC = dorsolateral prefrontal cortex; HC = healthy control; L = left; R = right; STS = superior temporal sulcus.

None of these correlations was significant ($p > .05$). Finally, we correlated age with activation across both the BD and HC groups and found one significant correlation: increasing age was associated with increasing activation in the DLPFC during the late phase of the sad faces (Spearman rho = .33, $p = .037$).

DISCUSSION

Our findings are consistent with previous fMRI studies of adult and pediatric BD that demonstrate less DLPFC and greater amygdala activation during perception of facial expressions. Our data do not support our hypothesis that abnormal amygdala activation would be seen during

the late phase of the block, whereas abnormal prefrontal activation would be seen during the early phase of the block. However, our data show a significant group × phase interaction in the STS/insula and visual cortex/posterior cingulate: For the BD group, activation increases from the early to late phase of the block, whereas for the HC group, activation decreases slightly. The STS is associated with perception of faces[8] and social aspects of face processing.[56] Greater visual cortex activation may reflect greater attention to facial emotion.[57] Thus, the interaction suggests that the HC group efficiently process the faces and then decreases allocation of neural resources, whereas the BD group has a gradually increasing response to faces, possibly reflecting difficulty processing emotional facial ex-

FIGURE 2 Selected clusters of significant activation from main effect of group. Note: y-axis denotes mean activation in cluster. BD = bipolar disorder; DLPFC = dorsolateral prefrontal cortex; HC = healthy control; OFC = orbitofrontal cortex.
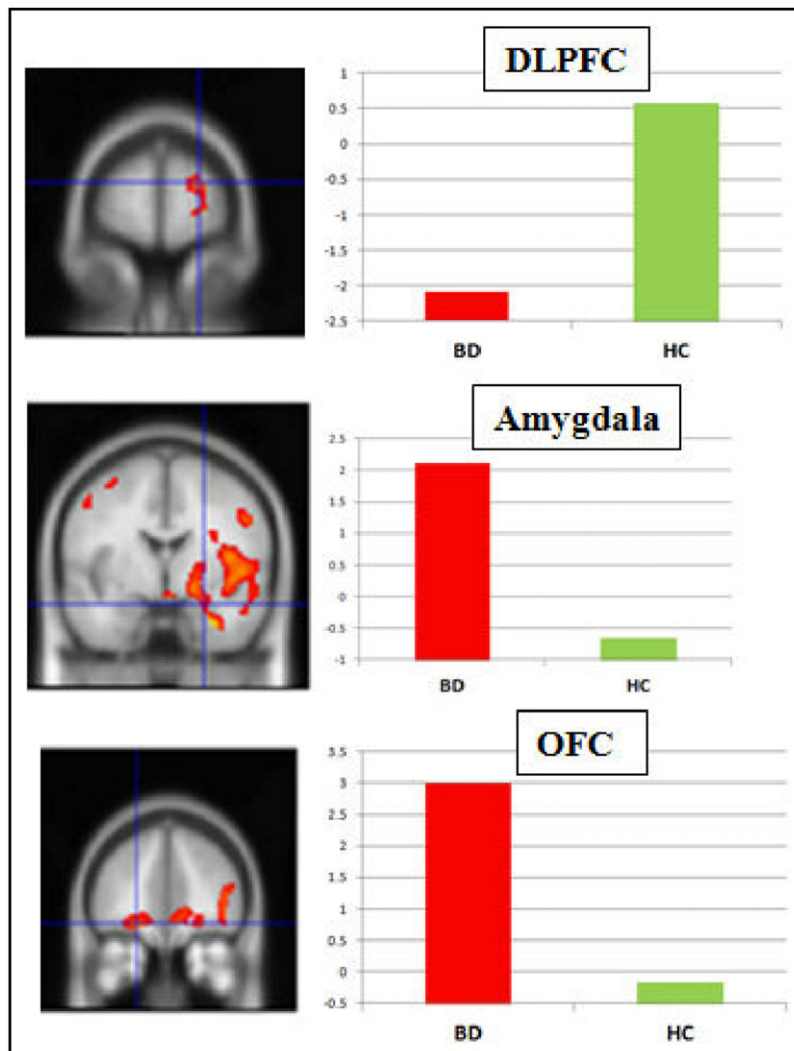
pressions, consistent with behavioral studies showing that patients with BD have difficulty identifying facial emotions.[5]

Habituation or sensitization may indicate emotion regulation processes. In previous fMRI studies of changes in activation over time in healthy adults, amygdala activation decreases with exposure to repeated presentations of fearful and neutral facial expressions.[35,36] Presumably this is an adaptive response, such that after we perceive and process the meaning of a stimulus, we reallocate resources efficiently and appropriately based on the situation. On the other hand, a series of non-repeated angry faces have been shown to elicit increasing activation over time (sensitization) in healthy adults,[34] suggesting that novel or threatening stimuli take longer to process, and/or grow in emotional significance over time. In summary, the ability to appropriately regulate responses to emotional stimuli may be reflected in gradual increases or decreases in activation over time, possibly mediated through prefrontal executive cortical regions.

In mood and anxiety disorders, including BD, abnormal increases in activation over time may reflect deficient control and/or dysregulation of emotional responses. An fMRI study of adults with BD viewing fearful faces found that activation in the OFC, anterior cingulate, and striatum increased from early to late in the task in healthy adults, but not in the BD group.[37] This study was

different from ours in defining early and late as the first versus last half of the experiment, while we used the early and late phases of each block. We did not observe habituation or sensitization per se (significant decreases or increases from early to late in the block) in either group, but rather, a significant interaction that was associated with increasing activation in the BD group, but decreasing activation in the HC group. This pattern was found in the STS and visual cortex, brain regions associated with processing faces, which may suggest that abnormalities in perception of emotional facial expressions in particular, rather than emotional responses in general, are reflected in this early/late phase analysis.

A related interpretation is that deficient control over emotion-related activation in BD may be related to an inability to disengage from negative stimuli, similar to that reported in unipolar depression.[58] Behavioral data show that increasing symptoms of depression in patients with bipolar disorder are associated with an inability to disengage attention in general, and that both euthymic and depressed patients showed a bias away from positive words.[59] In another study, children who had BD and comorbid anxiety disorders showed attention bias toward threatening facial expressions.[60] Therefore, in the current study, increasing STS and visual cortical activation in the BD group may reflect abnormal attention bias to faces, and difficulty disengaging from emotion-related stimuli.

Our study included pediatric patients with BD in a euthymic mood state, so these results may not hold for other mood states. Recent meta-analyses of adult BD studies indicate variations in profiles of abnormal activation depending on mood state.[21,23,24] Of these meta-analyses, the subanalysis most similar to the current study, euthymic patients performing facial affect tasks, found results similar to ours: lower DLPFC and greater amygdala, hippocampus, insula, and superior temporal gyrus activation.[23] Other mood states may show different findings; for example, functional connectivity between the amygdala and OFC is significantly different in adults with BD versus HC, but only for the depressed, not remitted, mood state.[61] Two published studies have used a longitudinal design to examine the effects of mood state on brain activation in adults with BD. In the first, Kaladjian et al. showed that remission from mania is associated with decreased amygdala activation during a response inhibition task.[62] The second study found greater amygdala/hippocampal activation during euthymia compared to mania, although OFC hyperactivation characterized BD versus HC across mood states.[14]

Similarly to previous fMRI studies of BD patients, we did not discontinue medications because of the high risk of mood episode relapse, and the high morbidity and mortality of untreated BD. Thus, exposure to psychotropic medications may have contributed to group differences in activation, or may have obscured abnormalities.[63] Previous studies suggest that mood stabilizer and antipsychotic medication tend to decrease amygdala activation,[55,64,65] so our findings of amygdala hyperactivation in BD were robust enough to survive this potential confound. Our analysis found that medication subgroups did not differ significantly in activation of our primary regions of interest.

The comorbid diagnoses of the subjects in this study may limit interpretations of our findings. Most of the BD subjects had a comorbid diagnosis of attention-deficit/hyperactivity disorder (ADHD), and the relatively small sample size prevented us from directly testing the effects of ADHD on brain activation in the BD group. Adler et al. showed that adolescents with BD and comorbid ADHD showed less prefrontal cortex activation than those with BD alone during performance of a simple attention task.[66] Recently, children with ADHD were found to have greater amygdala activation than children with BD while viewing neutral faces.[51] Passarotti et al. found that patients with pediatric BD, compared to those with ADHD, had greater activation in the subgenual anterior cingulate cortex (ACC) and OFC, and less activation in the DLPFC during a two-back task presenting facial expressions.[67] Together, these previous studies suggest that our results may represent abnormalities related to comorbid BD and ADHD. Future studies would benefit from including a larger number of subjects, including those with and without comorbid ADHD. This study focused on familial BD only, because this may provide a more homogeneous sample. However, our findings may not generalize beyond patients with familial BD.

In summary, our findings support models of deficient prefrontal and excessive amygdala activation in patients with BD compared with healthy controls, and add new information suggesting that youth with BD have aberrant timing of STS and visual cortical activation to facial expressions. &

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