Parametric Modulation of Neural Activity by Emotion in Youth With Bipolar Disorder, Youth With Severe Mood Dysregulation, and Healthy Volunteers

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Context: Youth with bipolar disorder (BD) and those with severe, nonepisodic irritability (severe mood dysregulation [SMD]) exhibit amygdala dysfunction during facial emotion processing. However, studies have not compared such patients with each other and with comparison individuals in neural responsiveness to subtle changes in facial emotion; the ability to process such changes is important for social cognition. To evaluate this, we used a novel, parametrically designed faces paradigm.

Objective: To compare activation in the amygdala and across the brain in BD patients, SMD patients, and healthy volunteers (HV).

Design: Case-control study.

Setting: Government research institute.

Participants: Fifty-seven youths (19 BD, 15 SMD, and 23 HV).

Main Outcome Measure: Blood oxygenation level–dependent data. Neutral faces were morphed with angry and happy faces in 25% intervals; static facial stimuli appeared for 3000 milliseconds. Participants performed hostility or nonemotional facial feature (ie, nose width) ratings. The slope of blood oxygenation level–dependent activity was calculated across neutral-to-angry and neutral-to-happy facial stimuli.

Results: In HVs, but not BD or SMD participants, there was a positive association between left amygdala activity and anger on the face. In the neutral-to-happy whole-brain analysis, BD and SMD participants modulated parietal, temporal, and medial-frontal areas differently from each other and from that in HVs; with increasing facial happiness, SMD patients demonstrated increased, and BD patients decreased, activity in the parietal, temporal, and frontal regions.

Conclusions: Youth with BD or SMD differ from HVs in modulation of amygdala activity in response to small changes in facial anger displays. In contrast, individuals with BD or SMD show distinct perturbations in regions mediating attention and face processing in association with changes in the emotional intensity of facial happiness displays. These findings demonstrate similarities and differences in the neural correlates of facial emotion processing in BD and SMD, suggesting that these distinct clinical presentations may reflect differing dysfunctions along a mood disorders spectrum.


Pediatric bipolar disorder (BD) is diagnosed with increasing frequency, perhaps because some suggest that it presents as either severe nonepisodic irritability or episodic mania. This suggestion raises questions about clinical and pathophysiologic differences between these 2 presentations. To evaluate this, the phenotype of severe, nonepisodic irritability was operationalized as severe mood dysregulation (SMD). Family history and longitudinal data suggest that BD and SMD are dissociable phenotypes, whereas behavioral data find similarities in facial information processing. Imaging studies can elucidate similarities and differences in neural mediators of such information-processing findings. In this study, we compared blood oxygenation level–dependent (BOLD) activation patterns during the presentation of parametrically morphed emotional faces in patients with BD or SMD and healthy volunteers (HV).

Emotional faces are salient nonverbal social cues. Appropriate identification of and responses to such cues are necessary for proper learning and behavior in social situations. Children with BD or SMD, but not those with other forms of psychopathologic disorders, show perturbed fa-
Given our interest in amygdala dysfunction, we conducted a region of interest (ROI) analysis in addition to a whole-brain analysis. On the basis of behavioral findings noted in the previous paragraphs, we hypothesized that both SMD and BD youth would differ from HVs in amygdala responsiveness to subtle changes in emotional expression. However, the directionality of expected differences was unclear, given inconsistencies in prior findings. Finally, given the observed differences in the clinical presentation, longitudinal course, and pathophysiologic characteristics of SMD and BD, we expected diagnosis-specific neural correlates in other brain regions, including the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex, which have been shown to be less active in youth with BD compared with HVs in emotional face tasks.14,15,17,22

METHODS

PARTICIPANTS

Usable functional magnetic resonance imaging data were acquired from 57 individuals, including those with BD (n=19) or SMD (n=15) and HVs (n=23) (Table 1). Data from 2 HVs, 2 BD patients, and 3 SMD patients were excluded for excessive motion. All participants, aged 8 to 18 years, were enrolled in an institutional review board–approved study at the National Institute of Mental Health. Parents and youths gave written informed consent or assent. Patients and HVs were recruited and assessed using methods described previously.10 Participants were assessed using the Schedule for Affective Disorders and Schizophrenia for School-age Children–Present and Lifetime Version, including a module to ascertain SMD.23 Interviewers were master’s degree and doctoral degree clinicians, with excellent interrater reliability (κ > 0.9 for all diagnoses, including differentiating BD from SMD). Diagnoses were based on best-estimate procedures generated in a consensus conference led by a psychiatrist (one of whom was E.L.). Bipolar disorder patients were “narrow phenotype,” with at least 1 full-duration hypomanic or manic episode characterized by abnormally elevated mood and at least 3 DSM-IV B manic symptoms.2 The SMD youth had nonepisodic irritability, overreactivity to negative emotional stimuli at least 3 times per week, and hyperarousal symptoms. Symptoms had to begin before age 12 years, be present for at least 1 year with no symptom-free periods exceeding 2 months, and cause severe impairment in at least 1 setting (ie, home, school, or peers) and mild impairment in another. Euphoric mood or distinct hypomanic or manic episodes lasting more than 1 day were exclusionary.2 The HVs had no lifetime psychiatric diagnoses and, as ascertained by parent interview, no first-degree relatives with a mood disorder.

Exclusion criteria for all participants were Wechsler Abbreviated Scale of Intelligence IQ lower than 70 and history of head trauma, neurologic disorder, pervasive developmental disorder, unstable medical illness, or substance abuse or dependence. The HVs were receiving no medication; most BD and SMD youths were receiving medication.

BEHAVIORAL PARADIGM

Photographs of faces used for testing were obtained from the Ekman pictures of facial affect24 and were morphed between a 100% angry face and a neutral face (Figure 1). Face morphs were created using methods from LaBar et al25 with commercial software.
Five female faces and 5 male faces were included. The morphs were made at 25% increments, resulting in 9 facial emotions (100% angry [hereinafter called A100], 75%/25% angry/neutral [A75], 50%/50% angry/neutral [A50], 25%/75% angry/neutral [A25], 100% neutral [Neut], 25%/75% happy/neutral [H25], 50%/50% happy/neutral [H50], 75%/25% happy/neutral [H75], and 100% happy [H100]). To have adequate statistical power while keeping the paradigm brief enough to be well tolerated by children with severe psychopathologic disorders, we focused on only 2 emotions: 1 positive (happy) and 1 negative (angry). We chose these emotions because previous neuroimaging work has shown differences in neural activity between youths with BD and HVs while processing them.

There were 2 behavior conditions: nose width and hostility ratings. Ratings were on a 5-point scale, from 1 (least wide/least hostile) to 5 (most wide/most hostile). In each trial, faces appeared for 3000 milliseconds, during which the participants made ratings. The intertrial interval varied from 750 to 1250 milliseconds (average, 1000 milliseconds) (Figure 2).

### Table 1. Demographic Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BD</th>
<th>SMD</th>
<th>HV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 19)</td>
<td>(n = 15)</td>
<td>(n = 23)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>15.33 (2.13)</td>
<td>14.53 (2.24)</td>
<td>14.92 (1.99)</td>
</tr>
<tr>
<td>WASI IQ, mean (SD)</td>
<td>103.63 (15.34)</td>
<td>109.00 (12.04)</td>
<td>108.35 (13.53)</td>
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<tr>
<td>YMRS score, mean (SD)</td>
<td>6.58 (5.22)</td>
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<td>NA</td>
</tr>
<tr>
<td>CDRS score, mean (SD)</td>
<td>28.63 (7.70)</td>
<td>22.50 (6.42)</td>
<td>25.90 (6.11)</td>
</tr>
<tr>
<td>CGAS score, mean (SD)</td>
<td>52.11 (8.93)</td>
<td>45.36 (18.61)</td>
<td>50.14 (15.54)</td>
</tr>
<tr>
<td>No. of medications, mean (SD)</td>
<td>3.16 (1.64)</td>
<td>1.53 (1.55)</td>
<td>1.53 (1.55)</td>
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<tr>
<td>Male sex, No. (%)</td>
<td>7 (37)</td>
<td>11 (73)</td>
<td>12 (52)</td>
</tr>
<tr>
<td>Bipolar I, No. (%)</td>
<td>16 (84)</td>
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<td>NA</td>
</tr>
<tr>
<td>Bipolar II, No. (%)</td>
<td>3 (16)</td>
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<td>NA</td>
</tr>
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<td>Mood state, No. (%)</td>
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<tr>
<td>Euthymic</td>
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<td>15 (100)</td>
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<tr>
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<tr>
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<td>NA</td>
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<td>Comorbid conditions, No. (%)</td>
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<td></td>
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<tr>
<td>ADHD</td>
<td>10 (53)</td>
<td>13 (87)</td>
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</tr>
<tr>
<td>ODD or CD</td>
<td>5 (26)</td>
<td>12 (80)</td>
<td></td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>GAD</td>
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<td>4 (27)</td>
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<tr>
<td>SAD</td>
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<td>2 (13)</td>
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<tr>
<td>Social phobia</td>
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<tr>
<td>Medication, No. (%)</td>
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<tr>
<td>None</td>
<td>2 (11)</td>
<td>6 (40)</td>
<td>23 (100)</td>
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<td>Antidepressant</td>
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<td>3 (20)</td>
<td></td>
</tr>
<tr>
<td>Stimulant</td>
<td>7 (37)</td>
<td>7 (47)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention deficit/hyperactivity disorder; BD, bipolar disorder; CD, conduct disorder; CDRS, Children’s Depression Rating Scale; CGAS, Children’s Global Assessment Scale; GAD, generalized anxiety disorder; HV, healthy volunteer; NA, not applicable; ODD, oppositional defiant disorder; SAD, social anxiety disorder; SMD, severe mood dysregulation; WASI, Wechsler Abbreviated Scale of Intelligence; YMRS, Young Mania Rating Scale.

a Differences among the groups were not significant.
b Data were missing from 1 SMD patient; *P* = .02.
c Data from the past 6 months; data were missing from 1 SMD patient.
d Number of medications at the time of the scan; *P* = .006.
e Mood state was indicated by CDRS, Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders; and YMRS scores.

Figure 1. Example of a male identity used for creating the 9 morphs in the current experiment. 100% angry, 75%/25% angry/neutral, 50%/50% angry/neutral, 25%/75% angry/neutral, neutral, 25%/75% happy/neutral, 50%/50% happy/neutral, 75%/25% happy/neutral, and 100% happy.

(Stoik MorphMan 2000; Stoik Imaging). Five female faces and 5 male faces were included.

The morphs were made at 25% increments, resulting in 9 facial emotions (100% angry [hereinafter called A100], 75%/25% angry/neutral [A75], 50%/50% angry/neutral [A50], 25%/75% angry/neutral [A25], 100% neutral [Neut], 25%/75% happy/neutral [H25], 50%/50% happy/neutral [H50], 75%/25% happy/neutral [H75], and 100% happy [H100]). To have adequate statistical power while keeping the paradigm brief enough to be well tolerated by children with severe psychopathologic disorders, we focused on only 2 emotions: 1 positive (happy) and 1 negative (angry). We chose these emotions because previous neuroimaging work has shown differences in neural activity between youths with BD and HVs while processing them.

There were 2 behavior conditions: nose width and hostility ratings. Ratings were on a 5-point scale, from 1 (least wide/least hostile) to 5 (most wide/most hostile). In each trial, faces appeared for 3000 milliseconds, during which the participants made ratings. The intertrial interval varied from 750 to 1250 milliseconds (average, 1000 milliseconds) (Figure 2).
There were 4 blocks, each including 41 nose-width rating trials, 41 hostility rating trials, and 12 fixation trials to add jitter and provide a baseline. Stimuli and behavior conditions were presented randomly within each block. Since we were especially interested in neural activation while participants viewed the morphs containing ambiguous emotion (i.e., A50, A25, Neut, H25, and H50), these had more replicates than emotionally unambiguous faces (i.e., A100, A75, H75, and H100). For the heavily weighted morphs, there were 6 trials per morph in each condition of each block (24 total) except that Neut had 5 trials per condition per block (20 total). For the less-weighted morphs, there were 3 trials per morph in each condition of each block (12 total). Each block contained 94 trials at an average of 4000 milliseconds per trial and was approximately 6.3 minutes long, yielding a 25-minute experiment.

**IMAGE ACQUISITION**

Data were acquired on a scanner (3T; General Electric). Structural images used T1-weighted axial acquisition (3-dimensional spoiled gradient-recall acquisition in the steady state with inversion-recovery preparation pulse; 256 × 192 matrix; one hundred twenty-four 1.2-mm axial sections; 22-cm field of view) to allow normalization to standard space. Functional imaging was performed axially using a multisection gradient echo-planar sequence (24-cm field of view, 96 × 96 matrix, 38 contiguous 2.6-mm sections; repetition time, 2300 milliseconds; echo time, 25 milliseconds).

**BEHAVIORAL DATA ANALYSIS**

Ratings and reaction time (RT) were compared in separate repeated-measures 3 (group: SMD, BD, HV) × 2 (behavior: hostility, nose-width ratings) analyses of variance (ANOVAs) on linear trend values that describe the data. We divided the analysis into neutral to 100% angry (N→A) and neutral to 100% happy (N→H). Tukey-corrected post hoc analyses were conducted as needed.

**IMAGING ANALYSIS**

Functional magnetic resonance imaging data were analyzed with the Analysis of Functional NeuroImages program, using preprocessing methods described previously, with 6-mm root-mean-square blur. Data were scaled to a percentage of the voxelwise mean, subject to a limit of 200 to avoid truncation artifacts. We censored multiple movement spikes greater than 1.5 mm and excluded participants with more than 5% censored times to repetition. Regressors for each morph in each behavior condition were created by convolving stimulus times with a γ-variate hemodynamic response function. Linear regression modeling was performed per voxel with 18 regressors, 1 for each stimulus condition (9 morphs × 2 behavior states), a third-order polynomial modeling the baseline drift, and 6 motion parameters. Blank fixation trials provided a baseline. Individual β-coefficient maps were warped into standard space with a high-resolution anatomic image that had been manually normalized by identifying the anterior-posterior commissures, midsagittal plane, and outer boundary. To model neural activity to the faces morphing from N→A and N→H at the individual participant level, 2 trend analyses were performed for the parametrically modeled stimulus classes, 1 each for N→A and N→H. The regressors were analyzed for linear trends between BOLD signal and facial stimulus intensity.

For the amygdala ROI, we extracted average BOLD linear trend magnitudes for N→A and N→H in the right and left amygdala based on the Talairach-Tournoux Daemon. For
each amygdala ROI, a repeated-measures group (BD, SMD, HV) × behavior (hostility, nose-width) ANOVA was conducted on the linear trend magnitudes. If there was a main effect of group, we used commercial software (PASW 18.0.1; SPSS Inc) to evaluate whether the slope value for each group differed significantly from zero using a within-group, 1-sample t test with a single group against a test value of zero, and we conducted Tukey-corrected between-group post hoc analyses.

At the whole-brain level, we examined linear trends for both N→A and N→H in a group × behavior ANOVA. We used the AlphaSim Monte Carlo simulation in the Analysis of Functional NeuroImages program to calculate the cluster size associated with a mapwise (entire brain mask), whole-brain, false-positive probability of P < .05. This threshold was applied to data initially passing a P < .005 threshold, yielding a smoothness of 8 to 9 mm. With these features, k ≥168 at a resolution of 2×2×2 emerged as the significance threshold. For clusters meeting this threshold, average signal was extracted and post hoc ANOVAs and Tukey-corrected analyses were performed in commercial software (PASW 18.0.1). Anatomic locations were labeled using the Talairach-Tournoux Daemon.

Exploratory post hoc ANOVAs were conducted to examine the impact of potentially confounding variables. For mood state, analyses were conducted in euthymic patients only and in HVs. To test the effect of comorbid anxiety disorder, ANOVAs were used to compare nonanxious SMD patients, nonanxious BD patients, and HVs. For medication, we conducted an ANOVA on BD and SMD participants separately with medication status (with vs without) as the between-group variable. We additionally covaried medication status in the clusters where BD and SMD differed and explored the potential impact of age, sex, and pubertal status (Tanner score), as well as Child Depression Rating Scale scores (eText; available at http://www.archgenpsychiatry.com).

RESULTS

DEMOGRAPHICS

The BD, SMD, and HV participants did not differ significantly in age, sex, Wechsler Abbreviated Scale of Intelligence IQ, or Children’s Global Assessment Scale score. Participants with BD had higher Child Depression Rating Scale scores than those with SMD ($F_{1,31} = 5.86, P = .02$) (Table 1).

BEHAVIOR

Neutral→Angry

For the linear trends of angry morph ratings, there was no group × behavior interaction or group main effect. There was a main effect of behavior, with hostile ratings showing a steeper positive slope than nose-width ratings ($F_{2,54} = 117.68, P < .001$). This indicates that participants used a broader range of the 1 to 5 scale for hostility ratings than for nose-width ratings.

Linear trend analyses on RT values showed no group × behavior interactions for angry morphs. To assess absolute RT differences between groups, we also conducted a group × behavior × morph ANOVA, and no significant group differences emerged.

Neutral→Happy

For the linear trends of happy ratings, the group × behavior interaction was significant ($F_{2,54} = 4.36, P = .02$). Follow-up ANOVAs demonstrated a group difference for hostile, but not nose-width, ratings of happy morphs ($F_{2,54} = 7.76, P < .001$). Two Tukey honestly significant difference–corrected post hoc analyses of the hostile ratings showed that the linear trend for BD patients differed from that of both SMD patients ($P = .04$) and HVs ($P < .001$), with BD patients modulating their ratings less than the SMD and HV youth.

Linear trend analyses on RT values showed no group × behavior interactions for happy morphs. To assess absolute RT differences between groups we also conducted a group × behavior × morph ANOVA. No significant group differences emerged.

IMAGING

ROI Analysis

Neutral→Angry. Separate group × behavior ANOVAs were conducted for right and left amygdala on the linear trend magnitudes for N→A. In the left amygdala for N→A, there was no group × behavior interaction and no main effect of behavior. However, there was a main effect of group ($F_{2,54} = 3.69, P = .03$).Collapsed across the 2 task conditions, mean (SD) linear trend values for the groups were BD, 0.003 (0.021); SMD, 0.001 (0.023); and HV, 0.069 (0.019), indicating stronger modulation by facial emotion features in HVs than in either patient group. Between-group Tukey-corrected post hoc analyses revealed a trend, with HVs differing from BD ($P = .06$) and SMD ($P = .07$) patients. In addition, within-group contrasts were conducted with 1-sample t tests. Only HVs had a significant slope across N→A ($t_{12} = 3.3, P = .003$) (Figure 3), with an increase in amygdala BOLD activity with increasing anger in the face. For BD and SMD participants, the slope did not differ from zero. In the right amygdala, there was no group × behavior interaction, and there were no main effects.

Neutral→Happy. Separate group × behavior ANOVAs were conducted for right and left amygdala on the linear trend magnitudes for N→H. There was no group × behavior interaction, and there were no main effects in either amygdala.

Whole-Brain Analysis

Neutral→Angry. At the whole-brain level, no clusters showed a group × behavior interaction for N→A. Left posterior cingulate showed a main effect of group ($F_{2,54} = 11.50, P < .001$) (Table 2). Three Tukey-corrected post hoc analyses showed that HVs had a more positive slope than BD ($P < .001$) and SMD ($P = .02$) participants.

Neutral→Happy. At the whole-brain level, no clusters showed a group × behavior interaction for N→H.
However, 4 clusters showed a main effect of group (Table 2): right inferior parietal lobule (Brodmann area [BA]40/7), left middle occipital gyrus and fusiform gyrus (BA37), right middle occipital gyrus and cuneus (BA18/19), and left middle/superior frontal gyrus (BA6/8) (overall $F_{11,022} = 9.3$, $P < .001$ for all comparisons). In each region, Tukey-corrected post hoc analyses showed that the between-group difference was driven by BD having a more negative slope than SMD ($P < .001$ for all comparisons) and by SMD having a more positive slope than HV ($P < .05$ for all comparisons) (Figure 4).

Effect of Potential Confounding Variables

Effects of Mood State. A post hoc analysis in the left amygdala was conducted including only euthymic BD (n = 16) and SMD (n = 15) participants. There remained a group effect ($F_{1,013} = 3.29$, $P = .03$), with Tukey-corrected post hoc analyses showing HVs differing from BD (trend, $P = .06$) and SMD ($P = .03$) patients for $N \rightarrow A$. A similar analysis in the whole-
brain clusters found significant between-group differences. Thus, these analyses revealed no effect of current mood state on our findings.

Effects of Comorbid/Co-occurring Illness. An ANOVA comparing nonanxious SMD (n = 8), nonanxious BD (n = 11), and HV participants on the left amygdala N→A showed a group effect (F2,39 = 3.46, P = .04). Tukey-corrected post hoc analyses showed a significant difference between nonanxious BD patients and HVs (P = .04); nonanxious SMD patients did not differ significantly from either group.

In an ANOVA comparing nonanxious SMD, nonanxious BD, and HV participants for N→A in the posterior cingulate and in the clusters identified in the whole-brain N→H, most of the group differences remained (see eText). Thus, excluding BD and SMD participants with comorbid anxiety disorder lessened some of the group differences, but this effect may be the result of loss of statistical power.

Effects of Medication. The ANOVAs assessed medication effects on left amygdala N→A linear trends. For SMD, an ANOVA comparing unmedicated SMD (n = 6) with medicated SMD patients (n = 8) found no significant difference (P = .47). Only 2 BD participants were not receiving medication. However, correlations between the number of medications and activation in all BD patients on the amygdala and each whole-brain cluster were not significant. We also found no significant differences between SMD patients with vs without medication in any of the whole-brain clusters (P > .16 for all comparisons).

Research shows that both SMD and BD youth have facial emotion–processing deficits6-9 and amygdala dysfunction on face-viewing tasks.10 However, studies have not explored amygdala modulation in response to varying facial emotion intensity.13-17 Moreover, because only 1 prior brain-imaging study compared these 2 patient groups directly,10 questions remain regarding similarities and differences of face-elicited amygdala dysfunction in BD vs SMD patients. In the present study, we used a novel parametric design to compare BOLD activity in BD, SMD, and HV participants while they made implicit or explicit ratings of emotional faces. We examined modulation of activity with changes in the degree of emotion across faces whose expressions ranged from neutral to 100% angry (N→A) or 100% happy (N→H), in 25% increments.

During implicit and explicit ratings of the N→A morphs, only HVs showed increasing amygdala activity with increasing anger intensity, as has been found using fear faces in healthy adults.29 The fact that neither BD nor SMD youth exhibited this relationship suggests similar amygdala dysfunction in these groups. Of note, amygdala dysfunction was present during hostility and nose-
width ratings combined, consistent with studies in BD demonstrating abnormalities during both implicit and explicit facial emotion-processing conditions.13,15,17,20,22 These data suggest that, in youth with SMD or BD vs HVs, there is diminished amygdala responsiveness to changes in facial emotion across several attentional conditions. This decreased amygdala responsiveness is consistent with behavioral data demonstrating that, compared with HVs, SMD and BD patients perform poorly on facial emotion-labeling tasks,6 requiring more intense emotional information before identifying facial emotions.11

The BD and SMD patients differed from each other, and from HVs, in behavioral and neural responses to neutral faces as they morphed toward happy. The HV youth, but not those with BD or SMD, exhibited increasing amygdala activation in response to increasing facial emotion intensity. Also, compared with HVs and SMD patients, BD patients perceived these faces to have a narrower range of hostility. A failure to interpret facial stimuli as having a broad range of hostility may have resulted in the lack of relationship between amygdala response and facial emotion intensity. Alternatively, amygdala and perceived hostility ratings may be driven by an unknown third variable. Although youths with SMD also exhibited a lack of amygdala modulation, they did not display a restricted range of hostility ratings. This may indicate different pathophysiologic mechanisms between the 2 patient groups, warranting additional study.

In this parametric task, we varied the level of emotion depicted in facial stimuli and examined between-group differences in the linear slope describing activation in response to each of the face morphs; this differs from more typical analyses that compare mean activation between groups. Because parametric designs model linear changes along a continuum, they may be more sensitive to subtle between-group differences in activation patterns. Our design, which includes different gradations of emotional expressions, may be particularly useful in research on amygdala function, since the amygdala habituates rapidly to repeated presentations of identical stimuli. However, our results cannot be compared directly with those from studies that report amygdala hyperactivation5,15 or hypoactivation16 in response to faces displaying 100% emotion or in response to a limited number of morphs. Nonetheless, our results are, broadly speaking, consistent with prior studies in youth and adults with BD that find amygdala dysfunction during facial emotion processing.10,14,17,22,30-36 as well as with a prior study in SMD youth.10 Additionally, our data need to be interpreted in light of the tasks used—ratings of hostility and nose width—not with emotion labeling.

At the whole-brain level for N→A, only 1 cluster differentiated groups, that is, in the left posterior cingulate (BA29/30). The positive slope in HVs indicates increased posterior cingulate activation in association with increased anger on the face, perhaps suggesting more effortless processing. In contrast, the negative slopes in BD and SMD suggest that increasing anger in a face is associated with relative disengagement. The posterior cingulate is activated by emotional stimuli17, given its connections with amygdala, insula, orbitofrontal cortex, and parahippocampal regions, it is well placed to modulate motivation and spatial attention.30 Data suggest posterior cingulate dysfunction in adult BD while viewing sad and happy faces.41 To our knowledge, this is the first study in pediatric BD to report dysfunction in posterior cingulate activity while viewing emotional faces. As in adult BD, such dysfunction in youth could be related to the emotional and attention dysregulation that is central to both BD and SMD.

For N→A morphs, BD and SMD patients demonstrated similar dysfunction relative to HVs in the amygdala ROI and whole-brain analyses. In contrast, for N→H across both implicit and explicit conditions, there were activation differences between BD and SMD in 4 regions important for attention and visual processing: right inferior parietal lobule, left middle occipital/fusiform gyrus, right middle occipital gyrus, and left middle/superior frontal gyrus. These findings are interesting given research demonstrating BD neural dysfunction elicited by happy facial stimuli.33,42,44 As neutral faces morphed toward happy, each group showed a characteristic and unique pattern of activity across regions; specifically, BD decreased in activity (negative slope), SMD increased in activity (positive slope), and HV did not modulate activity. Mood states fluctuate in patients with BD, and SMD is characterized by a persistent negative mood state; therefore, we speculate that the processing of positive stimuli may be particularly demanding in patients with chronic, severe irritability; that is, those with SMD.

As with the posterior cingulate findings, these results should be viewed with both caution and interest. Caution is warranted given the lack of consistent prior face-viewing imaging work implicating these regions in SMD or BD. Interest is also warranted given evidence implicating these structures in processes relevant to SMD and BD.10 Specifically, in healthy individuals, both inferior parietal lobule and middle occipital/fusiform gyrus are key in face processing.45-47 Additionally, the superior frontal gyrus is active during social emotion processing,48,49 and the inferior parietal lobule mediates attention.50,51

Depression in adult BD has been associated with dysfunction in anatomic and functional connectivity between the amygdala and frontal areas52 and between frontal areas.26 In the present study, depression scores were higher in BD vs SMD youth, and BD and SMD patients showed opposite patterns of frontal activity on N→H with increasing amounts of happiness. Although the between-group differences remained in post hoc analyses covarying Child Depression Rating Scale scores (see eText), the effect of mood state on these findings merits further research.

Mood state, comorbidity, and medication complicate research on BD and SMD. Most BD patients (84%) were euthymic, and results were unchanged when the analysis included only euthymic patients. When only non-anxious BD (n = 11) and SMD (n = 8) patients were included, the differences between BD and HV participants remained but, perhaps because of type II error, SMD patients did not differ from the other 2 groups. This demonstrates the need for a larger sample of non-anxious SMD patients. Because most patients were receiving medication, we cannot rule out the possibility.
that medication influenced the blunted amygdala response in N→A seen for the BD and SMD patients. The 6 unmedicated vs 8 medicated SMD patients did not differ significantly in amygdala or whole-brain cluster slope values, although this could be the result of insufficient power. When medication status was covaried from the 4 N→H clusters where BD and SMD differed, the groups remained significantly distinct from each other. Given the post hoc nature of this analysis and the small sample sizes, replication in a larger sample is needed. Although it would be ideal to study patients not receiving medication, it is neither ethical nor feasible to test all patients in the medication-free state. Because our paradigm included only angry and happy morphs, we cannot generalize beyond these 2 emotions, eg, to fear or sadness. In addition, prior behavioral studies demonstrated facial emotion–labeling deficits in BD and SMD; however, facial emotion labeling was not assessed directly here. An additional limitation is that we did not systematically assess handedness.

In this novel parametric face paradigm with 2 attention conditions, we found that BD and SMD have similarities (amygdala) and differences (parietal and medial frontal areas) in BOLD activity dysfunction vs HVs. These data suggest that amygdala activity in both groups does not change in response to increasing amounts of anger. In contrast, in response to increasing amounts of happiness, BD and SMD patients have differing directions of dysfunction in frontal and parietal regions. The current work adds to data demonstrating that BD and SMD have clinical, neuropsychological, and pathophysiologic similarities as well as differences, suggesting that SMD and BD may be manifestations of differing abnormalities along a mood disorders spectrum. Further work is needed to examine the role of these neural correlates as they relate to differences in clinical outcomes.

The data established in this study cannot be used for diagnostic purposes, but they support the growing need to compare pediatric BD with SMD. Both are severe mood disorders, but SMD patients differ with those in BD that in only BD patients experience manic episodes (presenting instead with nonepisodic irritability) and, longitudinally, SMD patients develop depressive and anxiety disorders. Further work can aid in distinguishing BD from SMD pathophysiologically, which has important diagnostic and treatment implications for children receiving care in community clinics for severe irritability and emotional dysregulation.

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