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Abnormal deactivation of the inferior frontal gyrus during implicit emotion processing in youth with bipolar disorder: Attenuated by medication

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Highlights

- Bipolar youth show abnormal right IFG deactivation in response to emotional faces.
- IFG deactivation was most prominent in the unmedicated bipolar youth.
- IFG deactivation was not found in youth with non-bipolar psychopathology.
- Findings are not attributable to task performance or mood state.

Abstract

Previous neuroimaging studies of youth with **bipolar disorder** (BD) have identified abnormalities in emotion regulation circuitry. Using data from the Longitudinal Assessment of Manic Symptoms Cohort (a clinical sample recruited for behavioral and emotional dysregulation), we examined the impact of BD and medication on activation in these regions. **Functional neuroimaging** data were obtained from 15 youth with BD who currently were unmedicated with a mood stabilizer or **antipsychotic** (U-BD), 19 youth with medicated BD (M-BD), a non-bipolar clinical sample with high rates of disruptive behavioral disorders (non-BD, $n = 59$), and 29 healthy controls (HC) while they were shown task-irrelevant morphing emotional faces and shapes. Whole brain analysis was used to identify clusters that showed differential activation to emotion vs. shapes across group. To assess pair-wise comparisons and potential confounders, mean activation data were extracted only from clusters within regions previously implicated in emotion regulation (including **amygdala** and ventral prefrontal regions). A cluster in the right **inferior frontal gyrus** (IFG) showed group differences to emotion vs. shapes (159 voxels, corrected $p < .05$). Within this cluster, U-BD youth showed decreased activation relative to HC ($p = .007$) and non-BD ($p = .004$) youth. M-BD also showed decreased activation in this cluster relative to HC and non-BD youth, but these differences were attenuated. Results were specific to negative emotions, and not found with happy faces. IFG findings were not explained by other medications (e.g. stimulants) or diagnoses. Compared to both HC and a non-BD sample, U-BD is associated with abnormally decreased right IFG activation to negative emotions.

Keywords

Bipolar disorder; **Functional MRI (fMRI)**; Psychopharmacology; Neuroimaging; Emotion regulation

1. Objectives of the study and background

Deficits in emotion regulation are central to the clinical diagnosis of **bipolar disorder** (BD). The underlying neurobiology of these deficits is hypothesized to involve abnormally increased activation of limbic regions

coupled with decreased activation of regulatory prefrontal circuitry (Chen et al., 2011 and Womer et al., 2009). Supporting this hypothesis, BD in youth has been associated with abnormalities in amygdala and prefrontal activation during emotion processing tasks. Specifically, several groups have found amygdala hyperactivation in youth with BD during emotional processing (Garrett et al., 2012, Kim et al., 2012, Pavuluri et al., 2007 and Rich et al., 2006). Abnormalities have also been found in regions including ventrolateral prefrontal cortex (VLPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) during emotion processing, though the direction of these abnormalities differs according to task and study population (Brotman et al., 2013, Dickstein et al., 2007, Ladouceur et al., 2011 and Pavuluri et al., 2009). Limited studies with multiple patient groups have shown findings to be specific to BD, and not simply a marker of psychopathology (Passarotti et al., 2010b and Thomas et al., 2012). While medications seem to have a normalizing effect (reducing differences between activation in youth with BD versus healthy controls), few studies compare medicated and non-medicated youth (Hafeman et al., 2012 and Singh and Chang, 2012).

The current study examined the effects of diagnosis and psychotropic medication on neural activation during an emotional processing task in a subset of the Longitudinal Assessment of Manic Symptoms (LAMS) cohort, behaviorally and emotionally dysregulated youth who have been followed longitudinally (Findling et al., 2010 and Horwitz et al., 2010). Participants in the parent cohort study ($n = 707$) were recruited from 9 clinical settings at four sites (Pittsburgh, Cincinnati, Cleveland, and Columbus), preferentially selected based on an elevated score on a screen for deficits in behavior, emotion and energy regulation (Parent General Behavioral Inventory-10, PGBI-10) (Youngstrom et al., 2008). Follow-up is ongoing for over 80% of these participants, with biannual assessments of clinical symptoms, diagnoses and functional impairments. The aim of the LAMS study is to describe abnormalities in behavioral and emotional regulation and arousal over time, and ultimately to predict progression of functional impairment and disorder. As part of this aim, functional neuroimaging data were collected on a subset of youth at three sites (Pittsburgh, Cincinnati, and Cleveland) while engaging in a number of tasks, including implicit emotion processing.

Our analyses capitalized on several key attributes of this cohort. The sample was large enough to include a number of youth with BD who were currently not medicated with an antipsychotic, antidepressant or mood stabilizing drug, thus permitting comparisons between youth with unmedicated BD (U-BD), medicated bipolar youth (M-BD), and healthy controls (HC). Because recruitment was not based on diagnosis, LAMS included youth who did not meet criteria for BD (non-BD). This unique comparison group allowed us to assess the specificity of neuroimaging findings for BD, and to test whether such results could be explained by co-morbidity.

The current study tested the following hypotheses: (1) youth would activate the amygdala and prefrontal regions (as measured by BOLD signal) in response to emotional stimuli (vs. morphing shapes); (2) these activation patterns would differ across groups defined by diagnosis and medication status; and (3) differences would be most prominent in U-BD (versus HC), attenuated (but still present) in M-BD, and even less robust in non-BD. Specifically, we hypothesized that amygdala activation would be elevated in bipolar youth ($U-BD > M-BD > non-BD \geq HC$), while prefrontal activation would show the opposite pattern ($U-BD < M-BD < non-BD \leq HC$). We also assessed the degree that abnormalities differed across specific emotional stimuli, and the extent to which neuroimaging findings were related to mood state.

2. Materials and methods

2.1. Participants

A subset of the initial LAMS cohort ($n = 123$) was recruited to participate in the neuroimaging component of the LAMS follow-up study. Additionally, 32 age- and gender-matched HC were scanned for comparison. Informed consent was obtained from parents or guardians after the nature of the study had been fully explained, and youth provided written informed assent. Participants received monetary compensation and a framed structural brain image. This investigation was carried out in accordance with the latest version of the Declaration of Helsinki, and the study design was approved by the appropriate Institutional Review Boards.

Exclusion criteria included pregnancy, inability to participate in scan (claustrophobia, metal objects in the body), positive urine drug and/or salivary alcohol screen on scan day, alcohol/substance abuse in the past three months, severe systemic medical illness, neurological disorders, history of head trauma with loss of consciousness, $IQ < 70$ (Weschler, 1999), visual disturbance ($<20/40$ Snellen visual acuity), inability to complete questionnaires in English, history of physical/sexual abuse, or autistic spectrum disorders/developmental delays.

Data from 30 LAMS youth and three HC were excluded due to data loss and/or excessive head movement (>4 mm, as used in previous studies (Bebko et al., 2013)), yielding usable scans from 93 LAMS participants and 29 healthy controls. Compared to included youth, those excluded were younger ($p = .03$) and had lower IQs ($p = .0001$); they were more likely to have disruptive behavior disorders (DBD) ($p = .03$) and unmedicated ADHD ($p = .004$), but did not differ according to group (U-BD, M-BD, N-BD, and HC) ($p = .15$). (Table S1).

2.2. Assessment

Baseline assessments gathered demographic data including age, sex, IQ and parents' education. The Family History Screen (Weissman et al., 2000) tracked 15 psychiatric disorders in biological parents, and included two questions to assess for lifetime parental history of mania. Diagnoses were determined at baseline and every six months using the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Life Version with WASH-U mood supplement (K-SADS-PL-W) (Kaufman et al., 1997). During these biannual assessments, parents also completed the PGBI-10M. The PGBI-10M score nearest the scanning session (within 6 months) was used. PGBI-10M scores were very stable over the year immediately preceding scan day (Bebko et al., 2013).

On scanning day, the youth and a parent/guardian completed the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale (KMRS) (Axelson et al., 2003) and Depression Rating Scale (KDRS) (Kaufman et al., 1997), to assess for hypomanic/manic and depressive symptom severity, respectively. Interviewers determined summary scores based on all available information. Additional rating scales were administered, including the Screen for Childhood Anxiety Related Disorders (SCARED) and the Moods and Feelings Questionnaire (MFQ). Psychotropic medications taken within the past 24 h were also recorded.

Participants were categorized into four groups: U-BD ($n = 15$), M-BD ($n = 19$), non-BD ($n = 59$), and HC ($n = 29$). The mean age of the participants at time of scan was $13.6(\pm 2.1)$ years, and 57% were male. Groups did not differ significantly according to age, gender, IQ, or socioeconomic status; however, sites differed on rates of HC recruitment (Tables 1 and S3). Approximately 1/3 of the clinical sample had DBD, including oppositional defiant disorder, conduct disorder, and DBD NOS, and 2/3 of the clinical sample was diagnosed with ADHD (Tables 1 and S2). Forty-seven percent (28/59) of the non-BD youth had a current or previous diagnosis of depressive disorder. Most bipolar youth were diagnosed with BD-I (21/34); the remainder fit criteria for BD-NOS, according to previously described criteria (Birmaher et al., 2006). We included youth with BD-NOS due to previous work indicating similarities in demographics, clinical features, and family history across the bipolar spectrum (Axelson et al., 2006 and Hafeman et al., 2013).

Table 1.

Basic demographic characteristics of the study population.

	U-BD ($n = 15$)	M-BD ($n = 19$)	Non-BD ($n = 59$)	HC ($n = 29$)	p -value
Demographics					
Age (years)	14.4 ± 2.1	13.6 ± 2.1	13.8 ± 1.9	13.1 ± 2.4	.17
Gender (% male)	7/15 (47%)	13/19 (68%)	37/59 (54%)	13/29 (44%)	.24
IQ	100 ± 17	106 ± 13	104 ± 17	107 ± 12	.54
Other Diagnoses					
DBD	4/15 (27%)	5/19 (26%)	23/59 (39%)	0 (0%)	.002
ADHD	6/15 (40%)	10/19 (52%)	43/59 (73%)	0 (0%)	<.0001
Medication					
Mood Stabilizers	0/15 (0%)	9/19 (79%)	0/59 (5%)	0 (0%)	<.0001
Antipsychotics	0/15 (0%)	16/19 (68%)	6/59 (7%)	0 (0%)	<.0001
Antidepressants	0/15 (0%)	6/19 (32%)	7/59 (12%)	0 (0%)	.003
Stimulants	4/15 (27%)	10/19 (53%)	26/59 (44%)	0 (0%)	<.0001
Non-stimulant	2/15 (13%)	3/19 (16%)	2/59 (3%)	0 (0%)	.06

DBD = disruptive behavioral disorders; ADHD = attention-deficit hyperactivity disorder.

Table options 

All M-BD youth were on an antipsychotic and/or mood stabilizer medication (lithium or antiepileptic agent); six were also on an antidepressant medication, and 10 were on a stimulant (Table 1). By definition, the U-BD youth were not medicated with mood-altering medication; however, six of the 15

youth took medication for ADHD (non-stimulant ($n = 2$) or stimulant ($n = 4$)). Most non-BD youth were also on at least one psychotropic medication.

Groups differed significantly on measures of depressive and manic symptoms at time of scan (PGBI-10M, KMRS, KDRS, and MFQ), but not anxiety (Table S3). U-BD vs. M-BD youth had higher KDRS scores ($p = .001$; Table S4).

2.3. Dynamic faces paradigm

A block-design emotional dynamic faces task evaluated implicit processing of emotional stimuli. Participants watched a series of faces that morphed from neutral to full expression of emotion (happy, sad, fearful, or angry) in 1 s. During control blocks, a luminance-equated shape morphed into a larger shape. Participants identified the foreground color, rendering the emotion task-irrelevant. The subject was shown three blocks for each of the four emotions (12 stimuli per block), and six control blocks (6 stimuli per block), pseudo-randomized so that a single emotion block was not repeated sequentially. This task robustly activates the amygdala and prefrontal emotion processing circuitry in adults (Herringa et al., 2013).

2.4. Neuroimaging analysis

Data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM8 <http://www.fil.ion.ucl.ac.uk/spm>). We used a whole brain analytic approach to assess task activation, which we define as the difference in BOLD signal between emotion blocks and control (shape) blocks (Hypothesis 1); we next assessed differences in task activation between groups (Hypothesis 2). Our *a priori* regions of interest were the amygdala and prefrontal regions previously implicated in emotion regulation (Phillips et al., 2008 and Strakowski et al., 2012): ACC, OFC (BA 11), and VLPFC (BA 47). Thus additional analyses (Hypothesis 3 and Supplemental) were only conducted for clusters with peak voxels in these regions.

Hypothesis 1.

Activation of Amygdala and Prefrontal Regions:

Using SPM8, we assessed whole brain activation patterns to emotions vs. shapes across the entire study population ($n = 122$), using a 1-sample t-test and collapsing across group. To adjust for multiple comparisons, we reported only clusters that were Family Wise Error (FWE)-corrected $p < .05$, at both voxel- and cluster-wise levels.

Hypothesis 2.

Differential activation of these regions across group:

We constructed multiple regression models in SPM8 to assess differences in activation to emotional faces vs. shapes between groups. Using a whole brain analysis, we identified voxels that showed significant ($p < .01$) between-group differences in both the unadjusted and covariate-adjusted (site, gender, age, and IQ) models. This conservative approach facilitated the identification of voxels that were robust to potential confounding factors. To correct for multiple comparisons, we used a cluster-wise threshold determined by Monte Carlo simulations implemented in AlphaSim, to maintain an alpha of .05; clusters were only considered significant if they were larger than the determined threshold (≥ 146 voxels). This validated technique accounts for spatial correlations between BOLD signal changes in neighboring voxels (Ward, 2002).

Hypothesis 3.

Specific Pair-Wise Comparisons:

To determine which pair-wise comparisons explained the group differences observed above, mean BOLD signal change parameter estimates were extracted from significant cluster(s) (generated from Hypothesis 2) with peak voxels in the hypothesized regions. A general linear model (PROC GLM in SAS 9.2) was used to further assess pair-wise contrasts (e.g. M-BD vs. HC), adjusting for site, age, gender, and IQ. Because we only extracted from significant clusters, reported p-values are not spatially corrected for multiple comparisons; however, we used the Tukey test to correct for six pair-wise comparisons across four groups. The impact of parental history of mania and parental education on mean cluster activation was determined by entering these variables separately into the group-adjusted emotion vs. shapes model in SAS 9.2.

2.5. Further analyses

One strength of the LAMS cohort is the heterogeneity of the youth, but this also leads to multiple

alternative explanations for the observed results. To address several possible confounds, including comorbidity, stimulant medication, type of bipolar diagnosis, task performance, and clinical state, we conducted the following analyses in SAS 9.2 on extracted regions from Hypothesis #2. First, we entered each variable into a multivariable model, adjusting for group and demographics, to establish whether (1) the variable significantly predicted cluster activation and (2) group was still significant after adjustment. Second, when possible, we assessed the impact of group in a subset of the population not affected by the potential confound, to determine whether results were driven by this variable. To address the impact of task performance, we re-ran models (in SAS 9.2) on the subset of youth with accuracy >80%.

To determine individual emotion effects, emotion-specific activation data were extracted from the significant cluster(s) identified in Hypothesis 2. General linear models were then constructed in SAS 9.2 to assess between-group differences for each emotion. Results of these supplemental analyses are discussed briefly in the text, and detailed results are given in the [Supplemental Appendix](#).

A number of measures were utilized to address biases that may arise in multisite neuroimaging studies. As recommended by the Biomedical Informatics Research Network (BIRN; <http://www.nbirn.net>), a BIRN phantom was utilized monthly at all three sites to ensure longitudinal scanner signal stability. In addition, scan site was used as a covariate in the SPM8 analysis (Hypothesis 2) and the GLM in SAS 9.2 (Hypothesis 3). We also conducted sensitivity analyses to determine whether observed patterns of between-group differences in activity were driven by a particular site, by sequentially removing each site and rerunning primary analyses in SAS 9.2.

3. Results

Hypothesis 1.

As predicted, the task (emotions vs. shapes) diffusely activated multiple brain regions, most prominently the right fusiform gyrus, bilateral amygdala, and bilateral inferior frontal gyrus (IFG) (FWE-corrected $p < .05$) ([Fig. 1](#), [Table 2](#)). Significant activation was also observed in bilateral middle and superior temporal regions, as well as the left parahippocampal gyrus.

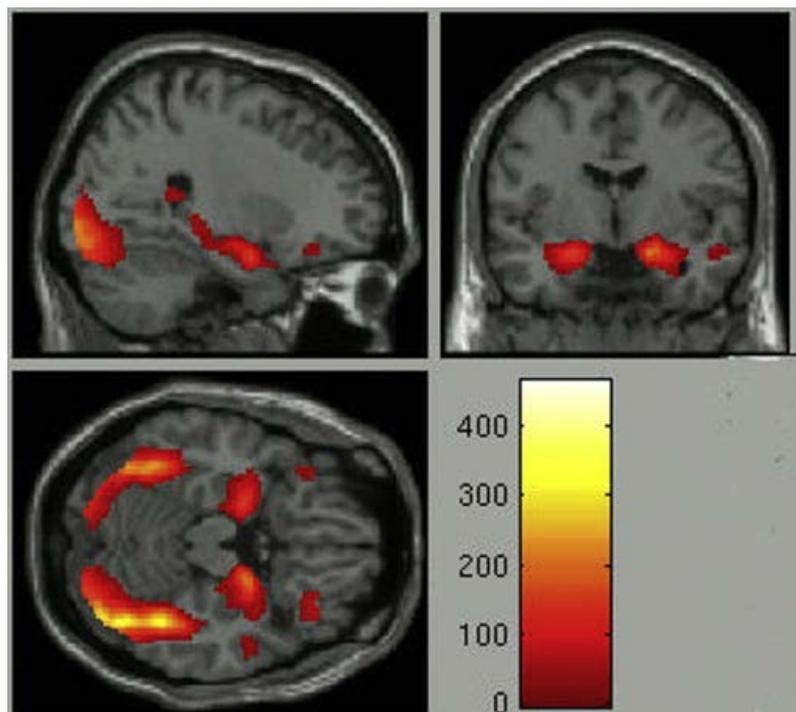


Fig. 1.
Task activation patterns to all emotions vs. shapes across the entire study sample (whole brain, FWE-corrected $p < .05$). Z-scores are labeled.

Figure options

Table 2.
Regions of activation (whole brain, FWE-corrected $p < .05$). Regions $k > 50$ listed below.

Region	Peak Coordinates (MNI)	FWE-corrected p	t	k
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Fusiform gyrus(right)	40 -48 -22	<.001	21.57	8048
Amygdala(right)	18 -4 -18	<.001	14.39	1356
Amygdala(left)	-22 -4 -18	<.001	12.43	739
IFG/BA 46(right)	52 28 18	<.001	8.46	836
IFG/BA 47(right)	34 32 16	<.001	8.05	148
Middle temporal gyrus(left)	-54 -60 6	<.001	7.82	160
Parahippocampal gyrus(left)	-16 -32 -4	<.001	7.67	167
Superior temporal gyrus(right)	48 -16 -10	<.001	6.79	169
IFG/BA 47(left)	-38 26 -16	<.001	6.47	61
Superior temporal gyrus(left)	-46 16 26	<.001	6.22	220

Table options 

Hypothesis 2.

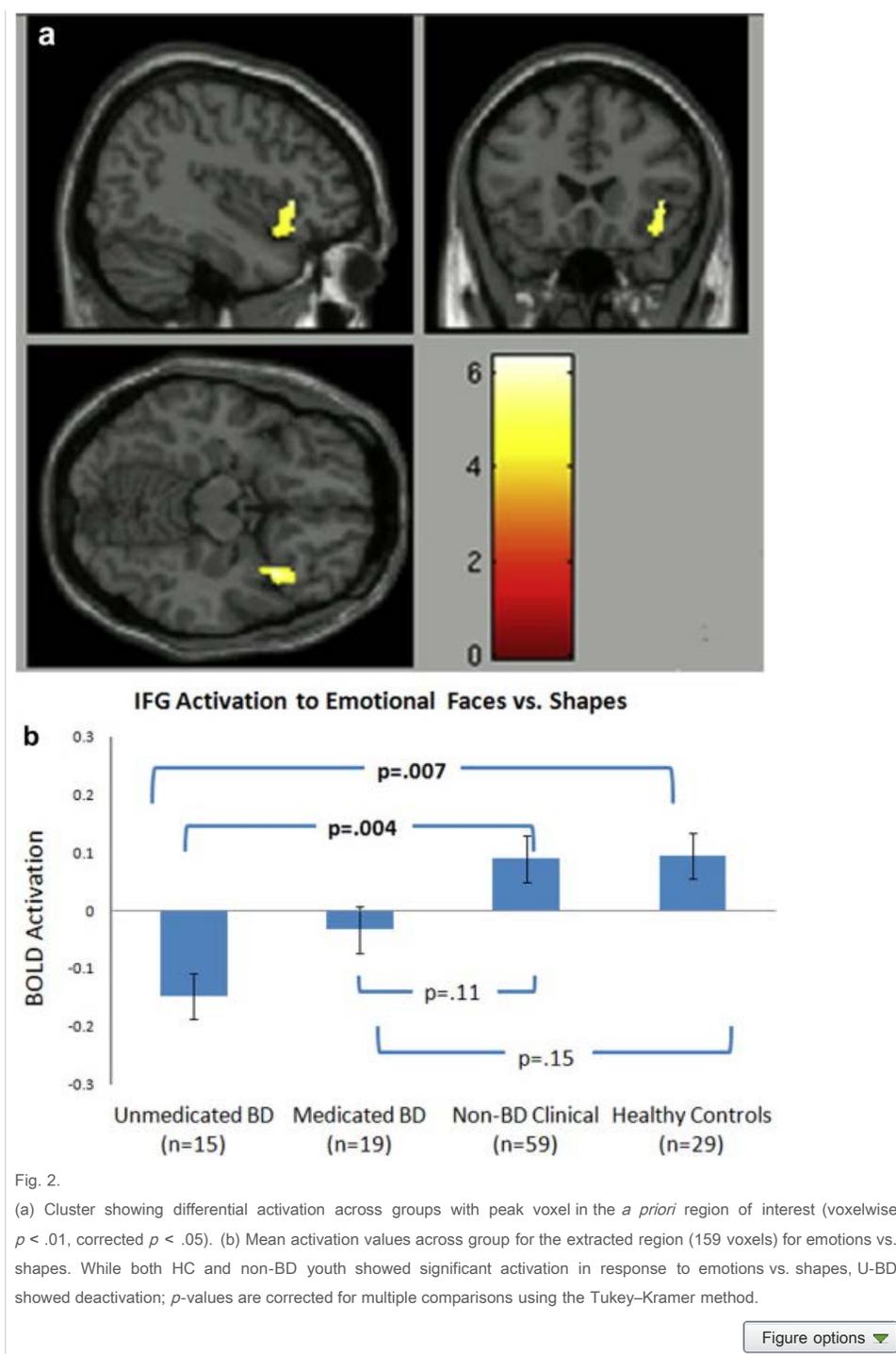
Significant group differences to emotions vs. shape were found in the right IFG (peak voxel in the VLPFC), right cuneus, right middle cingulate cortex, and left insula (voxel-wise $p < .01$, corrected $p < .05$) (Table 3). These clusters were robust to confounding, meaning that voxels were significant in both the unadjusted and covariate-adjusted models. Since the peak voxel of the IFG cluster was within an *a priori* region of interest (VLPFC), we extracted mean activation data for each participant from this cluster for further analyses (Fig. 2a).

Table 3.

Whole brain results, found in both unadjusted and covariate-adjusted models. Based on ANOVA of group differences (across emotions vs. shapes), with voxel wise threshold $p < .01$, corrected to $p < .05$ using AlphaSim threshold (146 voxels).

Region	Peak Coordinates (MNI)	F	k
Inferior Frontal Gyrus(right)	38 16 -16	6.35	159
Cuneus(right)	14 -84 14	8.18	441
Insula(left)	-46 -24 18	6.76	155
Middle cingulate gyrus(right)	2 -36 38	6.48	162

Table options 



Hypothesis 3.

While both the HC and non-BD youth showed mean activation in the extracted right IFG cluster during emotions vs. shapes ($p < .05$), the U-BD group showed deactivation in response to emotional stimuli ($p < .05$). Relative to both HC and non-BD youth, the U-BD showed decreased mean activation which was significant after correcting for multiple comparisons (corrected $p < .01$). As predicted, activation in the M-BD youth was intermediate between U-BD and non-BD. No significant differences were observed between HC and non-BD groups. Covariate-adjusted results are shown in Fig. 2b. Group effects remained significant after further adjustment for parental education and parental history of mania.

3.1. Further analyses

Group effects remained significant following sequential adjustment for co-morbidity (ADHD, DBD, depression, and anxiety), stimulant usage, and type of bipolar disorder; additionally, none of these variables independently predicted cluster activation. Results from Hypothesis 3 were replicated in (1) the subgroup without co-morbidity and (2) the subgroup of youth not on a stimulant medication, indicating

that these factors did not drive observed findings. Additionally, results from Hypothesis 3 were replicated in youth with BD-I (excluding BD-NOS), indicating that sub-syndromal BD was not driving observed results. A sensitivity analyses to determine whether results were driven by a particular site indicated that group differences remained significant in each two-site subgroup (all $p < .05$).

3.2. Effect of individual emotions

Supplementary analysis assessing the activation to each emotion indicated that there were group effects to fearful ($F = 4.08, p = .009$), angry ($F = 2.48, p = .06$), and sad faces ($F = 6.06, p = .0007$), but not happy faces ($F = 0.72, p = .54$). Thus results for emotions vs. shapes appear to be driven by neural responses to negative emotions ([Figure S1](#)).

3.3. Effect of clinical state

To determine whether the abnormality in the extracted IFG cluster correlated with current mood state, we sequentially entered both log-transformed clinician-derived (KMRS and KDRS) and self-report scales (MFQ and SCARED) into the Hypothesis 3 emotions vs. shapes model in SAS 9.2. Adjustment for these variables did not significantly impact the effect of group, indicating that between-group differences were not explained by clinical state. However, KDRS scores were positively correlated with IFG cluster activation ($t = 2.52, p = .01$). While KMRS and PGBI-10 scores did not predict activation in the entire population, both were negatively correlated with IFG cluster activation in the bipolar sample (KMRS: $t = -2.23, p = .03$, PGBI-10: $t = -2.55, p = .02$). Thus exploratory results indicate that deficits in positive affect regulation were associated with decreased right IFG activation (in the bipolar sample), while depressive symptoms were associated with increased activation. Other scales (MFQ, SCARED) did not significantly predict cluster activation, and adjustment for these variables did not appreciably change the effect of group.

3.4. Effect of task performance

There were a significant number of participants with accuracy less than 80% on this task ($n = 49$); these youth were more likely to be in the clinical sample (vs. HC) ($p < .0001$), although bipolar diagnosis (and medication status) did not significantly affect performance ([Table S3](#)). Much of the poor performance was due to missed trials. Three of the participants did not have any response data recorded, and $n = 7$ had no response data for the majority of the trials (likely due to an error in ePrime). Further analyses determined that accuracy, reaction time, or response rate did not significantly impact IFG cluster activation, and adjustment for these variables did not appreciably change the effect of group. To ensure that results were not attributable to youth with poor accuracy, results from Hypothesis 3 were replicated in the sub-population of youth ($n = 75$) who had accuracy >80% ([Supplemental Appendix](#)).

4. Discussion

We found deactivation of the right IFG (peak voxel in the VLPFC) during processing of emotional faces versus shapes in youth with U-BD, as compared to activation in HC and non-BD youth. Qualitatively similar differences were observed in youth with M-BD versus HC and non-BD youth, but these differences were attenuated. Observed IFG activation was negatively correlated with PGBI-10 and KMRS scores, and positively correlated with KDRS scores, pointing to a possible relationship between IFG deactivation and manic state. Given the role of the VLPFC in emotion regulation ([Phillips et al., 2008](#)), these results support the hypothesis that youth with BD show abnormalities in emotion regulation circuitry.

The VLPFC is emerging as a region that, given its role in emotion regulation, is potentially important for the pathophysiology of BD ([Foland-Ross et al., 2012](#) and [Strakowski et al., 2011](#)). Two recent meta-analyses found that BD in adults was associated with decreased VLPFC activation relative to healthy controls ([Chen et al., 2011](#)) and adults with major depressive disorder ([Delvecchio et al., 2012](#)). Additionally, decreased VLPFC activation correlated with manic symptomatology ([Chen et al., 2011](#)), and normalized with treatment in youth with BD during a response inhibition task ([Pavuluri et al., 2010](#)).

Current findings build on this previous work in several important ways. Our results extend conclusions of previous meta-analyses from predominately adult populations to a sample of bipolar youth, indicating that the VLPFC might have an important role in the early pathophysiology of BD. The findings that this abnormality is correlated with manic symptoms and attenuated by medication indicates that VLPFC activation during this emotion processing task might be an important marker of treatment and/or clinical state; this builds on work by [Pavuluri et al. \(2010\)](#) that showed a similar finding during a response inhibition task (albeit in the left VLPFC). In addition, our sample provides the unique opportunity to compare bipolar youth to a non-BD clinical sample; this allows us to conclude that our observed results

are specific to BD, and not simply attributable to co-morbidity of the sample. Of note, previous work has also implicated the VLPFC in response inhibition (Aron et al., 2004), and has shown decreased VLPFC activation in youth with ADHD, which is ameliorated by stimulant medication (Rubia et al., 2011). In our sample, diagnosis of ADHD and stimulant medication did not predict VLPFC activation, likely due to the nature of the task (emotional faces vs. response inhibition).

Contrary to expectations, while our task led to robust activation of the amygdala across groups, no between-group difference was observed in the amygdala. One possible explanation for this is the likely attenuation of amygdala BOLD signal during each block via repetition suppression (associated with repeated exposures to the same face stimuli), which might have obscured between-group differences (Phillips et al., 2001). Thus it is possible that BD youth initially had a greater magnitude of amygdala activation, but due to attenuation within and across blocks, these differences were not observed. While most studies have shown abnormalities in amygdala activation in bipolar youth during emotion processing, there are certainly exceptions (Brotman et al., 2010 and Passarotti et al., 2010a). A recent study found that BD is associated with a decreased ability of the amygdala to modulate in response to increasing intensity of emotional faces (Deveney et al., 2014). Given the dynamic nature of the current task, it is possible that amygdala modulation differed across groups, while mean signal did not.

Differences across groups were driven by the hemodynamic response to negative emotions, and were not evident in response to happy faces vs. shapes. This is possibly due to the greater salience of the negative emotions (relative to happy faces) in the task. Previous work also indicates that the VLPFC is particularly responsive to negative stimuli (Viinikainen et al., 2010), and involved in reappraisal of negative emotions (Wager et al., 2008). Additional regions of differential activation were observed in the right cuneus, right middle cingulate gyrus, and left insula. These findings are consistent with an analysis from a subset of this study population that focused on more posterior regions, and found that BD youth (relative to HC) showed decreased activation in primary visual cortex (Perlman et al., 2013).

This study had a number of strengths, facilitating these novel analyses. First, the large sample size, recruited selectively for deficits in behavioral and emotional regulation, included enough youths with U-BD and M-BD to assess the impact of both diagnosis and medication. Second, the non-BD clinical sample allowed us to test whether the IFG finding was specific to BD, or a general marker for psychopathology in youth. Third, the sample is well-characterized, both at time of scan and historically. Multiple diagnostic interviews have been conducted, improving diagnostic quality and covariate assessment. Thus potential confounders of the relationship between group and IFG activation, such as demographics, parental history of mania, and additional diagnoses, could be adequately tested.

This study also has a number of limitations. First, the U-BD youth were not currently medicated for BD, but they were not necessarily medication naïve, and several were on medication for ADHD. However, results were not driven by this potential confound: when youth on stimulants were excluded, the IFG activation differences between U-BD and HC were even more pronounced. Second, this multisite study used three different scanners, leading to increased noise. Results were not driven by a particular site, and adjustment for site did not appreciably change findings. Although site effects might have obscured more subtle findings, they were not responsible for the primary observed results. Third, task accuracy rates were fairly low: $\approx 2/3$ of the sample had accuracy $>80\%$. Because youth were exposed to the same emotional stimuli regardless of task accuracy, we did not exclude those with accuracy $<80\%$ from initial analysis. However, we used the conservative approach of re-running analyses after excluding these youth and results remained robust. Also, adjustment for accuracy and reaction time did not appreciably alter findings. Fourth, a significant proportion of youth were excluded due to excessive movement (33/155). While these youth differed significantly in terms of IQ and proportion with unmedicated ADHD, they did not differ according to group; thus it is unlikely that exclusion due to motion appreciably impacted our findings. Fifth, observational studies comparing unmedicated and medicated youth must be interpreted with some caution, since medications are not randomly assigned, and medication is likely correlated with severity of disorder. However, this confound would not explain the current pattern of results, since the most pronounced abnormalities are found in the unmedicated BD youth (who would likely be less severe than their medicated counterparts). Sixth, the sample size in the BD groups was fairly modest, which might have limited our power to appreciate certain between-group differences; additionally, this limitation made it impossible to assess the effects of individual medications on observed results.

In conclusion, BD was associated with abnormal IFG deactivation in response to negative emotional stimuli. The finding was ameliorated by medication and not found in a non-bipolar clinical sample. Research increasingly implicates the deactivation of the VLPFC in BD in adults, particularly in manic states. VLPFC deactivation to negative emotional stimuli might represent a potential biomarker to predict the development and trajectory of BD. Further work will assess longitudinal relationships between VLPFC activation and symptomatology in youth.

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Contributors

Drs. Birmaher, Axelson, Horwitz, Arnold, Fristad, Frazier, Youngstrom, Kowatch, Findling, Phillips, and Ms. Gill were instrumental in designing and implementing the parent LAMS study. Drs. Phillips, Travis, Diwadkar, Sunshine, Holland, and Ms. Bonar were involved in the design and implementation of the neuroimaging portion of the LAMS study. Drs. Hafeman, Phillips, and Drevets were involved in designing the analytic strategy for the current study. Drs. Hafeman, Bebko, Bertocci, Perlman, and Fournier were involved in the analysis of the neuroimaging data. Dr. Hafeman wrote the initial draft of the manuscript. Critical feedback was provided by all authors, and all authors contributed to and have approved the final manuscript.

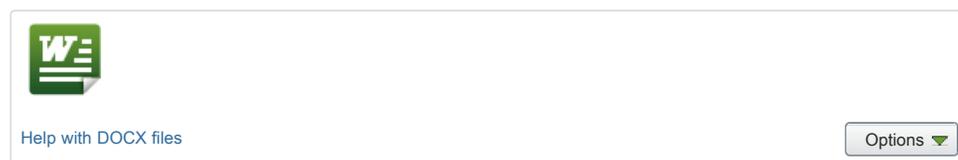
Conflict of interest

Dr. Arnold received research funding from CureMark, Forest, Lilly, and Shire, advisory board honoraria from Biomarin, Novartis, Noven, Roche, Seaside Therapeutics, and Shire, consulting fees from Tris Pharma, and travel support from Noven. Dr. Frazier received federal funding or research support from, acted as a consultant to, received travel support from, and/or received a speaker's honorarium from the Simons Foundation, Ingalls Foundation, Forest Laboratories, Ecoeos, IntegraGen, Shire Development, Bristol-Myers Squibb, National Institutes of Health, and the Brain and Behavior Research Foundation. Dr. Findling has received research support, acted as a consultant and/or served on a speaker's bureau for Alexza Pharmaceuticals, American Psychiatric Press, AstraZeneca, Bracket, Bristol-Myers Squibb, Clinsys, Cognition Group, Forest, GlaxoSmithKline, Guilford Press, Johns Hopkins University Press, Johnson & Johnson, KemPharm, Lilly, Lundbeck, Merck, NIH, Novartis, Noven, Otsuka, Oxford University Press, Pfizer, Physicians Postgraduate Press, Rhodes Pharmaceuticals, Roche, Sage, Seaside Pharmaceuticals, Shire, Stanley Medical Research Institute, Sunovion, Supernus Pharmaceuticals, Transcept Pharmaceuticals, Validus, and WebMD. Dr. Drevets is a full-time employee of Janssen Pharmaceuticals Research & Development, of Johnson & Johnson, Inc. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data



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