


## Original Investigation | META-ANALYSIS

# Developmental Meta-analyses of the Functional Neural Correlates of Bipolar Disorder

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**IMPORTANCE** Bipolar disorder (BD) is a debilitating mental illness associated with high costs to diagnosed individuals and society. Within the past 2 decades, increasing numbers of children and adolescents have been diagnosed as having BD. While functional magnetic resonance imaging (fMRI) studies have begun to investigate the neural mechanisms underlying BD, few have directly compared differences in youths with BD and adults with BD (hereafter BD-youths and BD-adults, respectively).

**OBJECTIVE** To test the hypothesis that BD-youths (<18 years old) would show greater convergence of amygdala hyperactivation and prefrontal cortical hypoactivation vs BD-adults.

**DATA SOURCES** PubMed and PsycINFO databases were searched on July 17, 2013, for original, task-related coordinate-based fMRI articles.

**STUDY SELECTION** In total, 21 pediatric studies, 73 adult studies, and 2 studies containing distinct pediatric and adult groups within the same study met inclusion criteria for our ALE analyses.

**DATA EXTRACTION AND SYNTHESIS** Coordinates of significant between-group differences were extracted from each published study. Recent improvements in GingerALE software were used to perform direct comparisons of pediatric and adult fMRI findings. We conducted activation likelihood estimation (ALE) meta-analyses directly comparing the voxelwise convergence of fMRI findings in BD-youths vs BD-adults, both relative to healthy control (HC) participants.

**RESULTS** Analyses of emotional face recognition fMRI studies showed significantly greater convergence of amygdala hyperactivation among BD-youths than BD-adults. More broadly, analyses of fMRI studies using emotional stimuli showed significantly greater convergence of hyperactivation among BD-youths than BD-adults in the inferior frontal gyrus and precuneus. In contrast, analyses of fMRI studies using nonemotional cognitive tasks and analyses aggregating emotional and nonemotional tasks showed significantly greater convergence of hypoactivation among BD-youths than BD-adults in the anterior cingulate cortex.

**CONCLUSIONS AND RELEVANCE** Our data suggest that amygdala, prefrontal, and visual system hyperactivation is important in the emotional dysfunction present in BD-youths, as well as that anterior cingulate cortex hypoactivation is relevant to the cognitive deficits in BD-youths. Future studies are required to determine if the developmental fMRI differences between BD-youths and BD-adults identified by our ALE meta-analyses are useful as brain-based diagnostic or treatment markers of BD, including either longitudinal neuroimaging studies of BD-youths as they become adults or cross-sectional imaging studies directly comparing BD-youths with BD-adults.

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**B**ipolar disorder (BD) is among the most devastating psychiatric illnesses affecting adults worldwide, with an estimated prevalence of 1% to 4%.<sup>1,2</sup> Despite our best psychopharmacologic and psychotherapeutic treatments, BD is the most expensive mental health illness; it is twice as expensive as major depressive disorder, including total health care costs and lost productivity.<sup>3,4</sup> Ultimately, greater understanding of the neural dysfunction underlying BD is required to identify biologically based targets to improve the specificity and efficacy of our diagnostic and treatment strategies for BD.

Relatedly, BD in children and adolescents (hereafter BD-youths) has received increasing attention during the past 2 decades given that 20% to 40% of adults with BD (hereafter BD-adults) report that their illness started during childhood or adolescence rather than adulthood.<sup>5,6</sup> Bipolar disorder is a burgeoning problem affecting youths, with approximately 20% of children and adolescents discharged from psychiatric hospitals in the United States in 2004 diagnosed as having BD.<sup>7</sup> Not simply a psychiatric diagnostic trend, outpatient visits to practitioners of all specialties for pediatric BD diagnoses have also increased 40-fold during the same period.<sup>8</sup> This increase is international, with inpatient BD psychiatric diagnoses in German youths rising 68.5% from 2000 to 2007, outpacing the general rise in mental illness.<sup>9</sup> Despite our best treatments, BD exacts a considerable toll on youths, including psychosocial and academic impairment<sup>10-13</sup> and high rates of psychiatric hospitalization<sup>14</sup> and suicide attempts.<sup>15</sup> Greater understanding of the underlying neural alterations in BD-youths could lead to novel biologically based diagnostic and treatment strategies.

These data raise an important question: are the neural alterations in BD-youths similar to those in BD-adults? To date, only 4 published task-related functional magnetic resonance imaging (fMRI) studies<sup>16-19</sup> have directly compared BD-youths and BD-adults in the same study. Specifically, Kim et al<sup>16</sup> found that BD-youths had greater amygdala activation during emotional face recognition than BD-adults. Weathers et al<sup>17</sup> found decreased anterior cingulate cortex (ACC) activation in BD-youths during failed response inhibition, while 1 year later Weathers et al<sup>18</sup> reported increased prefrontal cortex (PFC) activation during successful response switches. Adleman et al<sup>19</sup> found decreased fusiform activation in both BD-youths and BD-adults during successful emotional face encoding. More such studies are needed to elucidate developmentally unique brain alterations among BD-youths vs BD-adults, but multigroup and longitudinal fMRI studies are inherently costly, and the latter require time to image BD-youths as they age, a process that cannot be expedited.

More broadly, fMRI studies in either BD-youths or BD-adults have demonstrated alterations in a PFC-amygdala-striatal circuit modulating numerous domains, including emotional face recognition, response inhibition, cognitive flexibility, and working memory.<sup>20-28</sup> While important, these fMRI studies have inherent methodologic limitations, including small sample sizes that limit their generalizability and statistical power. Furthermore, variations in task design and implementation influence fMRI results even within singular psychological processes.

A novel approach to these limitations is an activation likelihood estimation (ALE) meta-analysis. ALE is a coordinate-based meta-analytic technique that uses the spatial coordinates and sample sizes from published studies to model the voxelwise convergence in activation (ie, how likely that region was truly implicated in that illness or process).<sup>29-31</sup> Leveraging large sample sizes across studies, ALE has greater power to detect the convergence of brain regions implicated in a particular disorder or psychological process, with reduced susceptibility to false positives, estimated at 10% to 20% in smaller individual fMRI studies.<sup>29,30</sup> ALE meta-analyses<sup>32-35</sup> have evaluated BD-adult fMRI data, but none have included pediatric data. Moreover, to our knowledge, none have leveraged recent improvements in ALE methods enabling direct developmental comparisons of BD-youth with BD-adult data<sup>36,37</sup> as has been done in other neuropsychiatric disorders, including autism<sup>38</sup> and attention-deficit/hyperactivity disorder.<sup>39</sup>

Therefore, we conducted the first developmental fMRI ALE meta-analysis in BD to date by directly comparing the convergence of neural alterations in BD-youths with BD-adults, while incorporating how both differed from healthy controls (HCs). Our primary analysis focused on emotional face processing, the most well-researched function in BD.<sup>16,20-22,40-42</sup> Based on a prior qualitative literature review,<sup>42</sup> we predicted greater convergence of amygdala hyperactivation in BD-youths than BD-adults. Secondary analyses followed an emotional (eg, theory of mind and reward tasks) or nonemotional (eg, N-back and Go/NoGo) dichotomy from a prior BD-adult ALE study.<sup>32</sup> This tested the hypothesis that on emotional tasks PFC hypoactivation would be more implicated in BD-youths than BD-adults,<sup>42</sup> while for nonemotional tasks we hypothesized greater convergence of ACC hypoactivation in BD-youths than BD-adults.<sup>17</sup> Tertiary analyses compared BD-youths with BD-adults across all fMRI studies.<sup>32,38,39</sup>

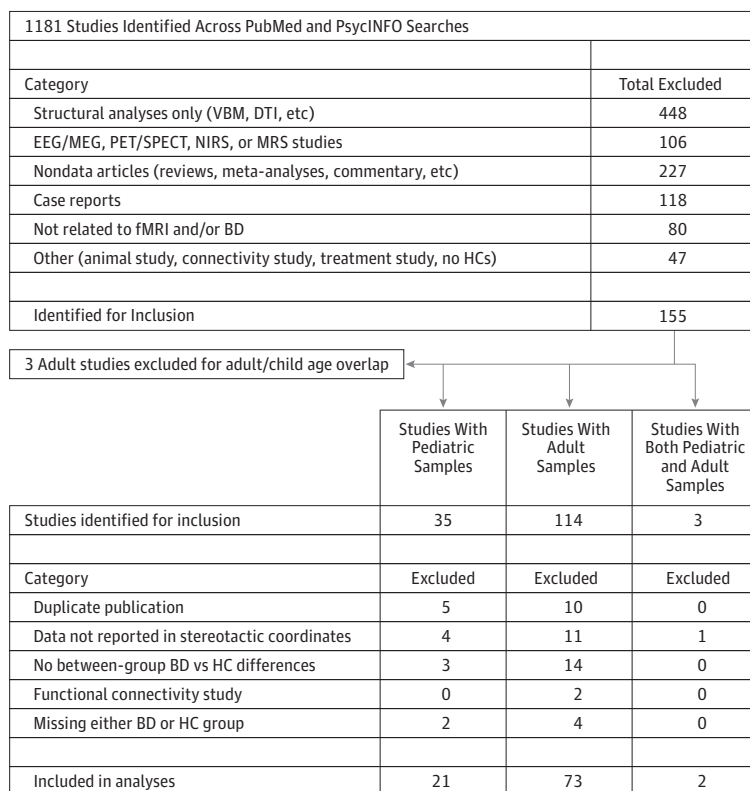
## Methods

### ALE Literature Search

This study did not use data from individuals because the data were all extracted from previously published studies and were based on group-level estimates, not individuals. Therefore, institutional review board approval and consent were not necessary. However, studies that were published previously would have already obtained institutional review board approval. As in prior developmental ALE meta-analyses,<sup>38,39</sup> we conducted literature searches first in PubMed and then in PsycINFO on the same day (July 17, 2013) using the terms *bipolar disorder* and *magnetic resonance imaging*.<sup>32,38,39,43-45</sup> Study inclusion criteria were original reports of task-related fMRI experiments and significant between-group differences between BD and HC participants reported in standard stereotactic coordinate space (Talairach or Montreal Neurological Institute).

Study exclusion criteria were applied. Excluded were duplicate samples, reviews or meta-analyses, participants whose age overlapped our pediatric and adult criteria, studies lacking between-group differences or stereotactic coordinates,

Figure 1. Flow Diagram of the Literature Search



BD indicates bipolar disorder; DTI, diffusion-tensor imaging; EEG/MEG, electroencephalography/magnetoencephalography; fMRI, functional magnetic resonance imaging; HC, healthy control; MRS, magnetic resonance spectroscopy; NIRS, near-infrared spectroscopy; PET/SPECT, positron emission tomography/single-photon emission computed tomography; and VBM, voxel-based morphometry.

studies with other magnetic resonance imaging (MRI) data (eg, structural MRI, diffusion-tensor imaging, and functional connectivity), studies with no HC group or with HCs who were relatives of BD participants (eg, discordant-twin studies), and studies in which the term *bipolar* was used for high-risk samples or an unrelated context (eg, *bipolar electrodes*).

The first-level literature search yielded 1181 unique published articles, with 155 meeting initial inclusion criteria, including 3 four-group studies<sup>16,17,19</sup> with separate BD-youth and BD-adult participant groups (Figure 1). Studies were categorized as having either pediatric (participant mean age plus 1 SD <18 years) or adult (participant mean age minus 1 SD ≥18 years) participants. This pediatric and adult cutoff is commonly used in research regulation, including institutional review boards, and has been used in prior developmental ALE meta-analyses where categorical rather than continuous comparisons of pediatric vs adult participants are required.<sup>38,39</sup>

After second-level review, 3 adult studies were excluded because their participants' ages crossed into our definition of pediatric samples (ie, in 2 studies<sup>46,47</sup> the participants' mean age minus 1 SD was less than 18 years, and in the third study<sup>48</sup> the age range of 16-50 years crossed this definition). Articles reporting results from separate tasks (eg, N-back and affective picture viewing<sup>28</sup>) and articles reporting distinct comparisons between BD and HC samples in different mood states (eg, euthymic BD vs HC and manic BD vs HC)<sup>40,41,49</sup> were entered as separate studies. Any ambiguities about whether studies met our criteria were resolved by a consensus decision between the first (E.W.)

and last (D.P.D.) authors, with consultation from coauthors. Study data (eg, coordinates and ages) were entered by the first author and were checked by the second author (G.K.C.).

Activation Likelihood Estimation

GingerALE software (version 2.3.1) from the BrainMap Project was used to conduct ALE meta-analyses of eligible studies.<sup>50</sup> As with prior ALE studies, our meta-analyses were conducted in Talairach space,<sup>31,32,35</sup> with the Lancaster transformation applied to coordinates originally reported in Montreal Neurological Institute space.<sup>50,51</sup> For uniformity, Talairach coordinates derived from the transformation by Brett et al<sup>52</sup> were converted back to Montreal Neurological Institute space and then reconverted to Talairach space with the Lancaster transformation.<sup>32,35,50</sup>

ALE is a coordinate-based meta-analysis technique that models the voxelwise spatial convergence of activation foci gleaned from published studies after they are modeled in common stereotactic space. Initial pairwise ALE analyses used random-effects methods to identify the convergence of hyperactivation in BD vs HC youths and HC adults (hereafter HC-youths and HC-adults, respectively) (ie, BD-youths > HC-youths and BD-adults > HC-adults) and the convergence of hypoactivation in BD vs HC (ie, HC-youths > BD-youths and HC-adults > BD-adults). To account for interstudy differences in sample size and preprocessing methods (eg, spatial normalization), for each pairwise ALE comparison GingerALE computed voxelwise ALE values and smoothed them with a gaussian kernel whose

full width at half maximum was set by an algorithm modeling the probability distribution of true locations based on empirical estimates of spatial uncertainty in neuroimaging experiments.<sup>37</sup> To be conservative, the smaller group size rather than the total study size (ie, BD plus HC) determined the full width at half maximum because some BD adult studies<sup>40,41,49</sup> contrasted one HC group with separate BD groups in different mood states. The Talairach Daemon determined the anatomical locations for significant ALE clusters.<sup>53</sup>

Then, developmental ALE analyses were conducted using subtraction contrasts of these pairwise analyses to directly compare BD-youths with BD-adults.<sup>36</sup> We determined the regions with (1) greater convergence of hyperactivations in BD-youths than BD-adults (BD-youths > HC-youths minus BD-adults > HC-adults), (2) greater convergence of hyperactivations in BD-adults than BD-youths (BD-adults > HC-adults minus BD-youths > HC-youths), (3) greater convergence of hypoactivations in BD-youths than BD-adults (HC-youths > BD-youths minus HC-adults > BD-adults), and (4) greater convergence of hypoactivations in BD-adults than BD-youths (HC-adults > BD-adults minus HC-youths > BD-youths). To address multiple comparisons issues, all pairwise and developmental ALE analyses were thresholded at  $P < .05$ , whole-brain corrected, with a false discovery rate algorithm<sup>54</sup> using 10 000  $P$  value permutations and a minimum cluster size of 200 mm<sup>3</sup>.

### Analytic Plan

Our primary analysis focused on emotional face perception because it is among the most well-researched neural processes in BD<sup>16,20-24,40-42</sup> (eTable 1 in the Supplement). To increase analytic power, as in prior ALE analyses with BD-adults,<sup>33,34</sup> we excluded studies with emotional faces incorporated in another task (eg, emotional Go/NoGo). Secondary ALE analyses grouped studies into either emotional or nonemotional categories.<sup>32</sup> Emotional studies were defined as those involving any emotionally valenced stimuli (eg, faces, pictures, and words), reward-based tasks (eg, reversal learning), or mood inductions. Any other studies were defined as nonemotional. Tertiary exploratory ALE analyses aggregated all studies.<sup>32,38,39,43,45</sup>

## Results

### Study Statistics

We identified 21 pediatric studies (comprising 452 BD-youths and 421 HC-youths), 73 adult studies (comprising 1495 BD-adults and 1528 HC-adults), and 2 studies containing distinct pediatric and adult groups within the same study (comprising 45 BD-youths, 55 HC-youths, 45 BD-adults, and 64 HC-adults) meeting all inclusion criteria (Figure 1). Pediatric and adult studies did not differ in sample size ( $F_{1,98} = 0.16$ ,  $P = .69$ ), percentage of female participants ( $F_{1,96} = 0.95$ ,  $P = .33$ ), or percentage of euthymic BD participants ( $t_{97} = 0.71$ ,  $P = .48$ ) (eTable 2 in the Supplement). There was a significant difference ( $t_{31.6} = 2.23$ ,  $P = .03$ ) in the mean (SD) percentage of BD participants taking medication (BD-youth 58.6% [38.3%] and BD-adult 77.4% [28.8%]), with more BD-adult studies having 100.0% of their sample taking medication (4 BD-youth and 26 BD-adult).

### Primary ALE Meta-analyses: Emotional Face Perception

ALE analyses of emotional face perception included 6 pediatric (112 coordinates) and 24 adult (203 coordinates) studies. Pairwise analyses of pediatric studies showed that BD-youths had significant convergence of hyperactivation vs HC-youths in the right amygdala and parahippocampal gyrus, left inferior frontal gyrus (IFG), and left putamen. The BD-youths had significant convergence of hypoactivation vs HC-youths in the left middle occipital gyrus and right IFG (Table 1).

Pairwise analyses of adult studies showed that BD-adults had significant convergence of hyperactivation vs HC-adults in regions that included the left amygdala, bilateral striatum, and left IFG. The BD-adults had significant convergence of hypoactivation vs HC-adults in regions that included the bilateral amygdala, bilateral IFG, and left pregenual ACC (pgACC).

Developmental ALE analyses directly comparing BD-youths with BD-adults showed greater convergence of hyperactivation in BD-youths than in BD-adults in the right amygdala (Figure 2A). No areas showed significantly greater convergence of hyperactivation in BD-adults than in BD-youths, nor were there any significant between-group differences in the convergence of hypoactivation.

### Secondary Analyses: Emotional Paradigms

Analyses of emotional paradigms included 14 pediatric (194 coordinates) and 48 adult (356 coordinates) studies. Pairwise ALE analyses showed that BD-youths had significant convergence of hyperactivation vs HC-youths in the right amygdala and parahippocampal gyrus, left IFG, right medial frontal gyrus, and precuneus. The BD-youths had significant convergence of hypoactivation vs HC-youths in the left pgACC, right IFG, and middle occipital gyrus (Table 2).

Pairwise analyses showed that BD-adults had significant convergence of hyperactivation vs HC-adults in regions that included the left IFG, parahippocampal gyrus, and caudate. The BD-adults had significant convergence of hypoactivation in regions that included the bilateral amygdala, middle frontal gyrus, putamen, and right IFG.

Developmental ALE analyses showed greater convergence of hyperactivation in BD-youths than in BD-adults in the left IFG (Figure 2B) and precuneus (Figure 2C). No areas showed significantly greater convergence of hyperactivation in BD-adults than in BD-youths, nor were there any significant between-group differences in the convergence of hypoactivation.

### Secondary Analyses: Nonemotional Paradigms

Analyses of nonemotional paradigms included 10 pediatric (47 coordinates) and 34 adult (219 coordinates) studies. Pairwise ALE analyses did not identify any regions where BD-youths had significant convergence of hyperactivation vs HC-youths. However, BD-youths had significant convergence of hypoactivation vs HC-youths in the right caudate and pgACC.

Pairwise adult analyses showed that BD-adults had significant convergence of hyperactivation vs HC-adults in the bilateral precuneus, left pgACC, and right putamen. The BD-adults also had significant convergence of hypoactivation vs

**Table 1. Activation Likelihood Estimation Meta-analyses Results for Emotional Face Perception Tasks Comparing Participants With Bipolar Disorder (BD) vs Healthy Control (HC) Participants**

Brain Side	Brain Region	Brodmann Area	Talairach Coordinate			Cluster Size, mm <sup>3</sup>	Extrema Value
			x	y	z		
<b>Pairwise Analyses</b>							
BD-youths > HC-youths							
R	Amygdala	NA	26	-4	-12	1496	0.015
L	IFG	47	-30	18	-8	824	0.016
R	Parahippocampal gyrus	35	20	-26	-14	384	0.012
L	Putamen	NA	-28	-10	-8	384	0.011
HC-youths > BD-youths							
L	Middle occipital gyrus	19	-40	-80	4	520	0.011
R	IFG	47	40	20	-4	440	0.008
BD-adults > HC-adults							
L	Amygdala	NA	-22	-4	-12	2016	0.014
R	Pallidus	NA	18	-8	-8	1616	0.027
R	Dorsal anterior cingulate cortex	32	10	28	22	776	0.012
L	IFG	46	-32	30	18	760	0.012
R	Putamen	NA	20	2	8	496	0.017
L	Caudate	NA	-16	16	19	440	0.013
HC-adults > BD-adults							
R	Middle FG	8	38	16	42	1680	0.014
R	Amygdala	NA	22	-4	-12	1360	0.018
L	Pregenual anterior cingulate cortex	24	-2	36	0	1208	0.015
R	Insula	13	32	24	10	984	0.021
L	Amygdala	NA	-22	0	-22	960	0.015
R	Superior temporal gyrus	38	32	12	-22	880	0.021
R	IFG	47	34	32	-4	680	0.013
L	IFG	47	-46	32	-8	624	0.022
R	Putamen	NA	24	4	2	616	0.013
R	Caudate	NA	8	8	-2	592	0.017
L	Middle FG	6	-30	0	44	408	0.013
R	Midcingulate	32	18	8	38	320	0.011
<b>Developmental Contrasts</b>							
BD-youths > HC-youths minus BD-adults > HC-adults							
R	Amygdala	NA	28	-6	-10	512	2.968

Abbreviations: FG, frontal gyrus; IFG, inferior frontal gyrus; L, left; NA, not applicable; R, right.

HC-adults in the bilateral IFG, putamen, and posterior visual perception regions (eTable 3 in the Supplement).

Developmental ALE analyses showed significantly greater convergence of hypoactivation in BD-youths than BD-adults in the right pgACC (Figure 2D). No areas showed significantly greater convergence of hypoactivation in BD-adults than in BD-youths, nor were there any significant between-group differences in the convergence of hyperactivation.

**Tertiary Analyses: All Paradigms**

Analyses from all task paradigms included 24 pediatric (241 coordinates) and 82 adult (575 coordinates) studies. Pairwise ALE analyses showed that BD-youths had significant convergence of hyperactivation vs HC-youths in regions that included the right amygdala, left PFC, and precuneus. The BD-youths had

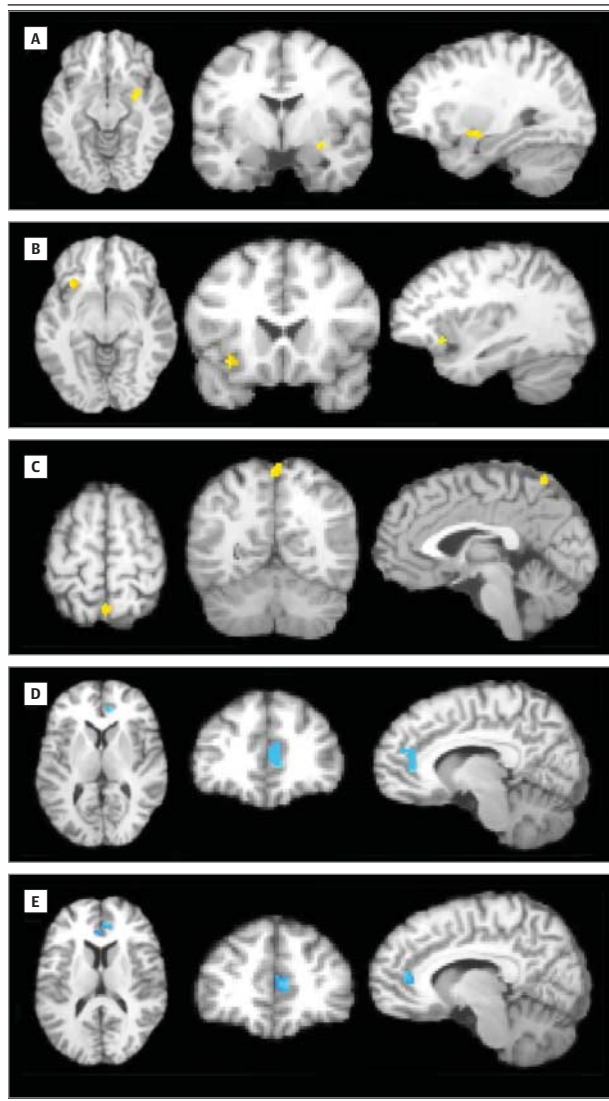
significant convergence of hypoactivation vs HC-youths in regions that included the right pgACC and caudate.

Pairwise ALE analyses showed that BD-adults had significant convergence of hyperactivation vs HC-adults in regions that included the left pgACC, left IFG, and right pallidus. The BD-adults had significant convergence of hypoactivation vs HC-adults in regions that included the bilateral putamen, bilateral IFG, and right lingual gyrus and inferior parietal lobe (eTable 4 in the Supplement).

Developmental ALE analyses showed significantly greater convergence of hypoactivation in BD-youths than BD-adults in the right pgACC (Figure 2E). No areas showed significantly greater convergence of hypoactivation in BD-adults than in BD-youths, nor were there any significant between-group differences in the convergence of hyperactivation.



Figure 2. Results From Developmental Contrasts of Pairwise Activation Likelihood Estimation Analyses



A, Greater convergence of hyperactivation in youths with bipolar disorder (BD-youths) than adults with bipolar disorder (BD-adults) in the emotional face perception tasks contrast ( $x = 28, y = -6, z = -10$ ; right amygdala cluster size,  $512 \text{ mm}^3$ ). B, Greater convergence of hyperactivation in BD-youths than BD-adults in the emotional tasks contrast ( $x = -34, y = 16, z = -8$ ; left inferior frontal gyrus cluster size,  $392 \text{ mm}^3$ ). C, Greater convergence of hyperactivation in BD-youths than BD-adults in the emotional tasks contrast ( $x = -31, y = 18, z = -9$ ; left precuneus cluster size,  $344 \text{ mm}^3$ ). D, Greater convergence of hypoactivation in BD-youths than BD-adults in the nonemotional tasks contrast ( $x = 9, y = 36, z = 7$ ; right pregenual anterior cingulate cortex cluster size,  $728 \text{ mm}^3$ ). E, Greater convergence of hypoactivation in BD-youths than BD-adults in the contrast that included data from all tasks ( $x = 8, y = 40, z = 12$ ; right pregenual anterior cingulate cortex cluster size,  $664 \text{ mm}^3$ ). The right side of all coronal and axial images corresponds to the right side of the brain. All images are thresholded at  $P < .05$ , whole-brain corrected.

## Discussion

Our study, the first developmental ALE meta-analysis to date to directly compare pediatric with adult BD fMRI studies, has several important findings. First, during emotional face per-

ception BD-youths showed greater convergence of right amygdala hyperactivation than BD-adults. Second, in response to emotional stimuli, BD-youths had greater convergence of hyperactivation in the left IFG and left precuneus than BD-adults. Third, during nonemotional tasks and across all paradigms, BD-youths had greater convergence of hypoactivation in the right pgACC than BD-adults. Our findings suggest potentially unique neurodevelopmental alterations associated with BD in youths vs adults that require further study to determine their longitudinal progress and if they may be used to improve diagnosis or treatment.

Greater convergence of amygdala hyperactivation in BD-youths than in BD-adults during emotional face perception aligns with several prior studies. Most important, we independently replicated the 2012 finding by Kim et al<sup>16</sup> of increased right amygdala activation to emotional faces among BD-youths vs both BD-adults and HC-youths, which was excluded from our present meta-analysis because their data were not reported in  $x, y, z$  coordinate space. Our result also aligns with a prior qualitative comparison of pediatric and adult BD fMRI studies that found more amygdala hyperactivation in BD-youths than in BD-adults during emotional face perception.<sup>42</sup> Although other mental illnesses (eg, depression, anxiety, and schizophrenia) also exhibit amygdala alterations,<sup>55-58</sup> we note that decreased amygdala size<sup>58-62</sup> and increased amygdala activation<sup>16,20,21,28</sup> in BD-youths are among the most replicated neuroimaging findings of any disorder or age group. In sum, these results suggest the need for greater study of amygdala hyperactivation in BD-youths in response to emotional faces, potentially as the target of biologically based treatments, including computer-assisted cognitive remediation.<sup>63,64</sup>

Across all emotional paradigms, BD-youths showed greater convergence of IFG and precuneus hyperactivation than BD-adults. Both the IFG and precuneus are involved in emotion-cognition interaction paradigms as shown in a recent ALE meta-analysis<sup>65</sup> among HCs. Moreover, the IFG facilitates inhibitory control of behavior, including emotional responding,<sup>66</sup> while the precuneus is involved in emotional processing via its roles in attention, autobiographical memory, and social processing.<sup>67</sup> The IFG exhibits prolonged neural pruning and myelination well into young adulthood<sup>68,69</sup> and a delayed maturational course in pediatric BD specifically.<sup>60,70,71</sup> BD-youths show greater precuneus gray matter volume than HC-youths, suggesting insufficient pruning and underdevelopment in pediatric BD.<sup>71</sup> Altogether, greater convergence of hyperactivation in the IFG and precuneus among BD-youths vs BD-adults during emotional tasks suggests that these regions have a more significant role in emotion-cognition interactions in BD-youths than in BD-adults. These findings warrant further study, potentially with ecologically valid psychosocial interaction tasks (eg, peer rejection<sup>72</sup>) to explore these alterations' developmental course in BD and their relationship to patients' real-world emotional impairment (eg, family functioning<sup>73</sup>).

During nonemotional tasks, BD-youths had greater convergence of hypoactivation in the right pgACC than BD-adults. A similar deficit was detected when all data were included, suggesting a common traitlike deficit present even

**Table 2. Activation Likelihood Estimation Meta-analyses Results for Emotional Task Paradigms Comparing Participants With Bipolar Disorder (BD) vs Healthy Control (HC) Participants**

Brain Side	Brain Region	Brodmann Area	Talairach Coordinate			Cluster Size, mm <sup>3</sup>	Extrema Value
			x	y	z		
<b>Pairwise Analyses</b>							
<b>BD-youths &gt; HC-youths</b>							
R	Amygdala	NA	24	-4	-10	1768	0.018
L	IFG	47	-30	18	-8	712	0.016
Midline	Precuneus	7	0	-62	58	448	0.013
R	pgACC	32	10	40	10	416	0.014
R	Medial FG	10	4	64	16	360	0.013
L	Putamen	NA	-28	-10	-8	272	0.011
R	Parahippocampal gyrus	35	20	-26	-14	248	0.012
R	Cingulate	24	12	12	30	224	0.011
<b>HC-youths &gt; BD-youths</b>							
L	pgACC	24	-4	28	10	536	0.011
L	Middle occipital gyrus	19	-40	-80	4	432	0.011
R	IFG	47	40	20	-4	344	0.008
<b>BD-adults &gt; HC-adults</b>							
R	Pallidus	NA	18	-8	-8	5256	0.028
L	Uncus	34	-22	2	-20	2896	0.016
L	Middle FG	47	-44	32	-2	2296	0.030
R	Dorsal anterior cingulate cortex	32	8	28	22	1072	0.013
R	Clastrum	NA	36	-18	8	432	0.017
R	Caudate	NA	8	8	-2	416	0.015
R	Insula	13	38	8	-6	408	0.017
L	IFG	46	-32	30	16	408	0.012
L	pgACC	32	-16	42	0	344	0.015
L	Caudate	NA	-16	16	18	272	0.013
<b>HC-adults &gt; BD-adults</b>							
R	Middle FG	9	50	12	30	1792	0.018
L	Amygdala	NA	-24	0	-22	1568	0.020
R	Amygdala	NA	22	-4	-12	1408	0.018
L	IFG	47	-46	32	-8	1064	0.023
R	Putamen	NA	24	6	0	984	0.017
R	Superior temporal gyrus	38	32	12	-22	928	0.021
L	pgACC	24	-2	36	0	912	0.015
R	Insula	13	32	24	10	792	0.021
R	Middle temporal gyrus	21	56	-10	-6	760	0.016
R	Lingual gyrus	18	18	-82	-6	592	0.017
R	Caudate	NA	8	8	-2	544	0.017
R	IFG	47	34	32	-4	456	0.014
L	Putamen	NA	-18	10	0	416	0.014
L	Middle FG	6	-30	0	44	288	0.013
R	Midcingulate	32	18	8	38	280	0.012
<b>Developmental Contrasts</b>							
<b>BD-youths &gt; HC-youths minus BD-adults &gt; HC-adults</b>							
L	IFG	47	-34	16	-8	392	3.011
L	Precuneus	7	-1	-59	59	344	3.011

Abbreviations: FG, frontal gyrus; IFG, inferior frontal gyrus; L, left; NA, not applicable; pgACC, pregenual anterior cingulate cortex; R, right.

during emotional tasks. The pgACC mediates activity between dorsal cognitive control prefrontal regions and ventral emotional regulatory regions,<sup>74</sup> so this deficit may reflect an

altered balance of cognitive and emotional activity in BD-youths. Bipolar disorder-youths show persistent cognitive difficulties even after several years of neural development and

mood symptom abatement,<sup>13</sup> so this pgACC activation deficit could underlie the cognitive control deficits that persist as BD-youths develop into adults. Further studies directly comparing youths and adults with BD on cognitively challenging and ecologically realistic paradigms (ie, similar to school or work) could reveal whether these alterations represent a persistent marker of cognitive dysfunction in BD.

As in a previous BD fMRI meta-analysis,<sup>32</sup> some regions (eg, the putamen) showed a convergence in both hyperactivations and hypoactivations vs HCs, particularly in BD-adults. While this may seem inconsistent, ALE evaluates the convergence of activations across studies, unlike individual fMRI studies whereby 2-group contrasts should produce either hyperactivation or hypoactivation in each brain region. Therefore, the convergence of both hyperactivation and hypoactivation in the same region may result from sufficient numbers of published studies supporting both positions. Despite differences in the direction of activation, these regions reliably differed from HCs, suggesting that they represent important targets for future longitudinal BD neuroimaging studies to examine their role in developmental change, illness progression, and treatment effects.

Our study has several limitations. These include (1) publication bias, (2) participant factors (eg, mood state, medication status, and psychiatric comorbidity), (3) a dichotomous categorization of pediatric vs adult studies, and (4) few pediatric BD studies evaluating language, memory, or social processing.

Addressing these limitations, first ALE relies on published data and is subject to publication bias. Although unable to include unpublished studies, we maximized our yield of published studies by using PsycINFO to confirm our PubMed search, yielding 102 additional studies not found by PubMed. None met our inclusion criteria, suggesting a thorough search. Also, because ALE is a coordinate-based meta-analysis, we had to exclude studies not reporting results in 3-dimensional coordinate space.

Second, several important factors, including mood state, medication status, and psychiatric comorbidity, are beyond the scope of our ALE meta-analysis because GingerALE does not allow covariates. To address this concern, pediatric and adult studies showed no significant differences in sample size, sex ratio, or mood state, although more adult than pediatric BD participants were taking medication. With respect to BD subtype, pediatric (15.6%) and adult (7.0%) studies did not significantly differ in their percentages of participants with bipolar II disorder ( $t_{8,4} = 1.47, P = .15$ ). Six participants with BD not otherwise specified were included in the context of 2 pediatric BD fMRI studies, both aggregated with a predominately bipolar I disorder sample. Several other important factors germane to BD were also beyond the scope of our analyses because few

fMRI studies report them or address retrospective recall bias inherent in their assessment (eg, BD onset or illness duration, severity or number of mood episodes, lifetime medication exposure, and substance use disorders).

Third, we used a dichotomous cutoff for pediatric vs adult studies, which is required for the subtraction contrasts used by any ALE meta-analyses examining developmental alterations associated with neuropsychiatric illness. This cutoff is commonly used in institutional review board regulation of research and bifurcates most published studies into pediatric vs adult regardless of technique (MRI, treatment, etc). Nevertheless, pioneering longitudinal MRI studies (eg, by Giedd et al<sup>68</sup> and by Gogtay et al<sup>69</sup>) have demonstrated that neural development continues throughout young adulthood.

One approach to address these 3 limitations would be to conduct a mega-analysis whereby original fMRI data are pooled and reanalyzed. Our present ALE results could guide a priori hypotheses about particular brain regions. Age could be evaluated as both a dichotomous and continuous factor. Individual participants' MRI data could be excluded to address participant or study factors (eg, the few participants with BD not otherwise specified, behavioral performance, or MRI scanner strength). However, a mega-analysis would still be subject to publication bias and issues of data sharing and quality control.<sup>29</sup> Longitudinal fMRI studies whereby BD participants are imaged annually from childhood through adulthood could also address these limitations but would require time because aging cannot be hastened.

Fourth, we note the relative dearth of BD-youth studies assessing language, memory, and social processing, which limited direct comparisons with BD-adults. This gap is fertile ground for future research.<sup>42</sup>

## Conclusions

Our results underscore important differences between pediatric and adult BD in amygdala, inferior PFC, and precuneus responses to emotional information and in pgACC responses to cognitive challenge. They also reveal numerous common regions exhibiting functional abnormalities in both age groups, including ventral PFC, amygdala, striatum, and posterior visual perception areas. Further cross-sectional fMRI studies involving groups of BD-youths and BD-adults compared with age-matched HCs, as well as longitudinal neuroimaging studies following up BD-youths as they become adults, are needed to provide more information about the developmental progression of neural alterations associated with BD, which may ultimately aid biologically based approaches to diagnosis and treatment for BD.

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