

## Original Investigation | META-ANALYSIS

# Meta-analysis of Functional Neuroimaging of Major Depressive Disorder in Youth

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**IMPORTANCE** Despite its high prevalence and morbidity, the underlying neural basis of major depressive disorder (MDD) in youth is not well understood.

**OBJECTIVES** To identify in youth diagnosed as having MDD the most reliable neural abnormalities reported in existing functional neuroimaging studies and characterize their relations with specific psychological dysfunctions.

**DATA SOURCES** Searches were conducted in PubMed and Web of Science to identify relevant studies published from November 2006 through February 2015. The current analysis took place from August 21, 2014, to March 28, 2015.

**STUDY SELECTION** We retained articles that conducted a comparison of youth aged 4 to 24 years diagnosed as having MDD and age-matched healthy controls using task-based functional magnetic resonance imaging and a voxelwise whole-brain approach.

**DATA EXTRACTION AND SYNTHESIS** We extracted coordinates of brain regions exhibiting differential activity in youth with MDD compared with healthy control participants. Multilevel kernel density analysis was used to examine voxelwise between-group differences throughout the whole brain. Correction for multiple comparisons was performed by computing null hypothesis distributions from 10 000 Monte Carlo simulations and calculating the cluster size necessary to obtain the familywise error rate control at  $P < .05$ .

**MAIN OUTCOMES AND MEASURES** Abnormal levels of activation in youth diagnosed as having MDD compared with control participants during a variety of affective processing and executive functioning tasks.

**RESULTS** Compared with age-matched healthy control participants ( $n = 274$ ), youth with MDD ( $n = 246$ ) showed reliable patterns of abnormal activation, including the following task-general and task-specific effects: hyperactivation in subgenual anterior cingulate cortex ( $P < .05$ ) and ventrolateral prefrontal cortex ( $P < .05$ ) and hypoactivation in caudate ( $P < .01$ ) across aggregated tasks; hyperactivation in thalamus ( $P < .03$ ) and parahippocampal gyrus ( $P < .003$ ) during affective processing tasks; hypoactivation in cuneus ( $P < .001$ ), dorsal cingulate cortex ( $P < .05$ ), and dorsal anterior insula ( $P < .05$ ) during executive functioning tasks; hypoactivity in posterior insula ( $P < .005$ ) during positive valence tasks; and hyperactivity in dorsolateral prefrontal cortex ( $P < .001$ ) and superior temporal cortex ( $P < .003$ ) during negative valence tasks.

**CONCLUSIONS AND RELEVANCE** Altered activations in several distributed brain networks may help explain the following seemingly disparate symptoms of MDD in youth: hypervigilance toward emotional stimuli from the overactivation of central hubs in the subgenual anterior cingulate cortex and thalamus that lead to a cascade of other symptoms; ineffective emotion regulation despite increased activation of the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex during affective processing, which may reverse across development or the clinical course; maladaptive rumination and poor executive control from difficulties shifting from default mode network activity to task-positive network activity during cognitively demanding tasks; and anhedonia from hypoactivation of the cuneus and posterior insula during reward processing.

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Major depressive disorder (MDD) is recognized as a psychiatric illness with a course that frequently begins early in development and is characterized by enormous social, academic, and economic costs.<sup>1,2</sup> Indeed, MDD is now the leading cause of morbidity and disability among adolescents,<sup>3</sup> with a point prevalence rate in this age group of approximately 14%.<sup>4</sup> Moreover, 30% to 65% of depressed adolescents fail to respond to treatment<sup>5</sup>; thus, it is critical we increase our understanding of the pathophysiology and etiology of MDD and translate these findings to more effective approaches to prevention and treatment.

Advances in neuroimaging techniques have led to a growing interest in investigating abnormalities in the brain structure and function in individuals diagnosed as having MDD.<sup>6</sup> These advances provide promising opportunities to advance our understanding of the underlying pathophysiological effects of MDD and generate novel treatment targets for emerging technologies<sup>7,8</sup> and more conventional pharmacotherapy and psychotherapy.

Although most studies using neuroimaging in MDD have focused on depressed adults, there is a growing body of research using functional magnetic resonance imaging (fMRI) to examine neural function in children and adolescents diagnosed as having MDD. Two qualitative reviews of this literature<sup>3,9</sup> have noted findings largely consistent with prevailing neural models of adult depression that implicate frontal regions (eg, the prefrontal cortex and orbitofrontal cortex), striatal areas (eg, the caudate and putamen), and limbic structures (eg, the cingulate cortex, amygdala, and hippocampus) as well as other areas located outside this circuitry, such as the insula, cuneus, superior parietal cortex, and middle temporal cortex.

To our knowledge, there is presently no quantitative integration of this work to address issues of reliability across studies and examine consistency in neural activations that have been reported in investigations of MDD in youth. Studies of neural function in youth with MDD have yielded contradictory findings and reported results that diverge from those documented in the adult depression literature. In addition, many studies of neural functioning in depressed youth have taken a region of interest approach, analyzing a specified group of brain regions (eg, the striatum) while ignoring other potentially important areas (eg, the cuneus); this strategy results in a targeted but biased search for neural abnormalities. Finally, although most studies in this area have included youth as old as 18 years, neuroscientists have argued that the developmental period used to study young participants should extend to individuals aged 24 years to capture important maturational changes in the prefrontal cortex.<sup>3,10</sup>

To address these issues, we conducted a meta-analysis of fMRI studies that used a voxelwise whole-brain approach (WBA) to identify brain regions characterized reliably by abnormal activation in depressed youth. This approach enabled us to combine results quantitatively from several studies to obtain greater statistical reliability and address conflicting findings in the literature. This approach also avoided a biased focus on brain regions that have received the greatest atten-

tion and helped to prioritize subsequent investigations of neural abnormalities in youth with MDD. It also allowed us both to identify abnormalities that were robust across a variety of experimental conditions and elucidate their relations with psychological dysfunction.

## Methods

### Overview

We applied the multilevel kernel density analysis<sup>11</sup> to published fMRI studies that compared neural activation in groups of youth diagnosed as having MDD with age-matched healthy control participants.

### Study Selection

We conducted an extensive literature search with the PubMed and Web of Science databases for fMRI studies of MDD in youth published from November 2006 through February 2015. All analyses in this study were completed from August 21, 2014, to March 28, 2015. We also examined the reference lists and study tables of relevant review articles to identify other primary studies to include that may have been missed in the original search. We then inspected each article generated by this search process and retained only articles that satisfied the following inclusion criteria: (1) used an fMRI voxelwise WBA of task-based activation data; (2) compared a group of participants aged 4 to 24 years (mean, 18.36 years) diagnosed as having MDD according to *DSM* criteria<sup>12</sup> at the time of the scan with age-matched healthy control participants; and (3) reported coordinates of brain regions with abnormal activations in standard space, using the Talairach atlas or Montreal Neurological Institute template. Other details regarding this study selection process are provided in the eAppendix in the [Supplement](#).

### Data Analysis

For each included study, we first extracted published whole-brain activation coordinates presented in Talairach or Montreal Neurological Institute space of regions showing significant between-group differences. We then constructed indicator maps for each individual study in Talairach space at 1-mm isotropic voxel resolution using these reported coordinates. Next, we merged them to create a meta-analytic statistical map composed of global activation values computed as the weighted proportion of primary studies reporting statistically significant activation differences between MDD and control groups for each voxel throughout the whole brain.

To determine significance at a voxelwise level, we conducted 10 000 Monte Carlo simulations to generate null hypothesis distributions and then computed the cluster size necessary to obtain familywise error rate control at  $P < .05$  for the comparison of multiple voxels across the whole brain. As an additional constraint, only clusters that were reported in at least 2 primary studies were retained to prevent a single study from generating a significant meta-analytic finding. Further details about this process are provided in the eAppendix in the [Supplement](#).

Table 1. Included Whole-Brain fMRI Studies of Youth With MDD

Study	Sample, No.		Youth With MDD		Neuroimaging Conditions	
	Youth With MDD	Healthy Control Participants	Age, Mean (SD), y	Female, %	Task	Contrasts
Chantiluke et al <sup>13a,b,c,d,e</sup>	20	21	16.20 (0.80)	50.00	Rewarded continuous performance task	(1) Correct rewarded - correct nonrewarded (2) Correct nonrewarded - correct nontarget
Colich et al <sup>14a,b,c,d,f,g</sup>	18	15	15.61 (1.51)	83.33	Go - no go task (+ emotional distractor)	(1) Happy/go task (2) Happy/no go task (3) Sad/go task (4) Sad/no go task
Davey et al <sup>10a,c,d,f</sup>	17	19	18.60 (2.20)	64.70	Positive social feedback task	Feedback - fixation
Diler et al <sup>15a,c,d,f,g</sup>	10	10	15.90 (1.10)	80.00	Emotional face processing task (+ sex labeling)	(1) Happy - fixation (2) Fearful - fixation
Diler et al <sup>16b,e</sup>	10	10	15.90 (1.10)	80.00	Go task - no go task	(1) Go - baseline (2) No go - baseline
Gaffrey et al <sup>17a,f</sup>	23	31	5.04 (0.76)	43.50	Emotional face processing task (+ simple button press)	All faces - baseline
Halari et al <sup>18b,f</sup>	21	21	16.20 (0.83)	52.40	Simon task (selective attention); switch task (attentional switching); stop task (response inhibition and error detection)	(1) Successful incongruent - successful congruent (2) Successful switch - successful repeat (3) Successful stop - unsuccessful stop
Hall et al <sup>19a,f</sup>	32	23	15.54 (1.82)	78.10	Emotional face processing task (+ passive viewing)	Fearful - happy
Roberson-Nay et al <sup>20a,f</sup>	10	34	13.80 (2.70)	70.00	Emotional face processing task (+ memory encoding)	Successful - unsuccessful encoding
Sharp et al <sup>21a,c,d,f</sup>	14	19	13.42 (1.78)	100.00	Card guessing task (reward anticipation and outcome)	Reward outcome - baseline
Tao et al <sup>22a,d,f,g</sup>	19	21	14.20 (1.90)	57.90	Emotional face processing task (+ sex labeling)	Fearful - neutral
Yang et al <sup>23b,f</sup>	13	13	16.00 (1.50)	53.80	Stop task	All stop - nonstop
Yang et al <sup>24a,e</sup>	12	12	15.90 (1.40)	41.70	Emotional face processing task (+ matching)	(Fearful + happy + angry) - shapes
Zhong et al <sup>25a,d,f,g</sup>	27	25	20.37 (1.86)	59.30	Emotional face processing task (+ form matching)	(Fearful + angry) - form matching

Abbreviations: fMRI, functional magnetic resonance imaging; MDD, major depressive disorder.

<sup>a</sup> Categorized as affective processing.

<sup>b</sup> Categorized as executive function.

<sup>c</sup> Categorized as positive valence.

<sup>d</sup> Categorized as valence specific.

<sup>e</sup> Excluded from 1 or more analyses owing to nonindependent samples. Some studies reported separate results for more than 1 type of task or contrast.

<sup>f</sup> Categorized as aggregate.

<sup>g</sup> Categorized as negative valence.

## Study Groupings

We applied the meta-analytic procedure described earlier to several groupings of reported contrasts from primary studies to elucidate the psychological functioning associated with observed MDD abnormalities in neural activation. At the broadest level, we combined reported findings from all included studies (aggregated,  $n = 14$ ), excluding those with overlapping samples ( $n = 3$ ) to maximize statistical power and identify abnormalities in neural activations that were robust across diverse experimental conditions. Next, we separately analyzed findings from studies that involved either emotional processing tasks (affective processing,  $n = 11$ ) or executive functioning tasks (executive function,  $n = 5$ ) to examine specific abnormalities in activation associated with these neurocognitive systems. We then further decomposed the emotional processing tasks and separately analyzed findings from positive vs neutral contrasts (positive valence,  $n = 5$ ) and negative vs neutral contrasts (negative valence,  $n = 5$ ). Finally, to examine whether observed

differences between positive vs negative contrasts were statistically significant, we directly contrasted activation maps from these 2 conditions with one another (valence specific,  $n = 7$ ). The primary studies that contributed to each of these 6 groupings along with a description of the experimental task and reported contrasts are presented in **Table 1** and further details regarding these groupings are provided in the eAppendix in the **Supplement**.

## Neurosynth Decoding

We used the Neurosynth (<http://www.neurosynth.org>) package (<https://github.com/neurosynth>; Python) to decode whole-brain maps from each of the 5 groupings of primary studies described earlier to provide a systematic quantitative basis for inferring psychological functioning from observed brain activity,<sup>26</sup> which helped guide the interpretation of findings while avoiding many of the hazards of reverse inference.<sup>27</sup> This decoding process compared whole-brain activation levels in submitted activation maps

with those obtained in the Neurosynth database, which currently contains 9721 whole-brain human fMRI studies and automatically computes Pearson correlation coefficients between submitted whole-brain maps and 3160 key terms (features) used in titles and abstracts of published articles in the database. Importantly, the decoding process uses activation levels obtained throughout the whole brain rather than individual regions of interest to enable more comprehensive naturalistic inferences regarding underlying mental states.<sup>26,27</sup>

## Results

### Study Characteristics

Our literature search yielded 14 primary studies that satisfied the inclusion criteria described earlier and were used in 1 or more analyses. These studies collectively examined in-episode MDD ( $n = 246$ ) and healthy control participants ( $n = 274$ ) across a broad range of task conditions and ages (mean, 14.94 years) and also included a diverse set of other characteristics of MDD, such as youth with first-episode MDD and medication-naïve youth. Table 1 and eTable 1 in the Supplement summarize the major characteristics of participants with MDD and neuroimaging tasks used in each primary study.

### Neuroimaging Results

Results of our meta-analysis revealed that youth diagnosed as having MDD showed reliably different activation levels in several brain regions compared with age-matched healthy control participants, including both task-general (ie, aggregated) and task-specific (ie, affective processing, executive function, positive valence, and negative valence) effects. The main findings from these analyses organized by experimental task are described as follows and are also summarized in Table 2 and depicted graphically in Figure 1.

#### Aggregated

Across all experimental conditions combined, youth with MDD exhibited hyperactivity compared with healthy control participants in neural clusters centered at the left dorsolateral prefrontal cortex (dlPFC;  $P < .03$ ), left subgenual anterior cingulate cortex (sgACC;  $P < .05$ ), right anterior insula ( $P < .005$ ), bilateral thalamus ( $P < .01$ ), left parahippocampal gyrus ( $P < .003$ ), and left superior temporal cortex (STC;  $P < .03$ ) as well as hypoactivity centered at the right caudate ( $P < .03$ ).

#### Affective Processing and Executive Function

When the analyses were limited to affective processing tasks, youth with MDD continued to exhibit hyperactivity in clusters centered at the left dlPFC ( $P < .03$ ), bilateral thalamus ( $P < .03$ ), and left parahippocampal gyrus ( $P < .003$ ). In contrast, during executive function tasks, youth with MDD showed hypoactivity centered at the right dorsal cingulate cortex ( $P < .05$ ), right dorsal anterior insula ( $P < .05$ ), and left cuneus ( $P < .003$ ).

#### Positive and Negative Valence

During positive vs neutral conditions, youth with MDD exhibited hypoactivity centered at the right posterior insula ( $P < .005$ ). In contrast, during negative vs neutral conditions, depressed youth showed hyperactivity in the left dorsolateral prefrontal cortex ( $P < .001$ ) and left STC ( $P < .003$ ). Moreover, when positive and negative valence activation maps were contrasted directly with one another, each region reached significance ( $P = .03$  to  $P = .001$ ), strongly suggesting these effects are specific to youth with MDD in particular valence conditions.

#### Neurosynth Analysis

The Neurosynth features related to psychological functioning that most strongly correlated with each of the 5 whole-brain maps (youth with MDD minus healthy control participants) are presented in the eFigure and eTable 2 in the Supplement. For the aggregated and affective processing maps, the most highly correlated terms were predominantly related to general affective processing (eg, *emotion* and *emotional*), negative valence emotions (eg, *unpleasant* and *fear*), or high arousal (eg, *arousal* and *threat*). For the positive valence map, the same terms described earlier were also highly correlated as well as others more directly related to MDD (eg, *depressed* and *sad*) and a novel term (*conflicting*) whereas for the negative valence map, similar terms were highly correlated in addition to a novel term (*avoidance*). For the executive function map, general terms related to cognitive processing (eg, *cognition*, *cognitive control*, and *memory*) as well as terms more directly related to attentional shifting (eg, *shifting* and *competition*), error monitoring (eg, *monitoring*), and response inhibition (eg, *inhibition* and *competition*) were strongly and inversely correlated.

## Discussion

In this meta-analysis, we identified several brain regions in which youth diagnosed as having MDD reliably exhibited abnormal levels of activation compared with age-matched healthy control participants during affective processing and executive functioning tasks. In formulating a theoretically informative and clinically useful model of MDD, it is important to consider both the independent functioning of each brain region and how regions may interact with each other as key components of 1 or more distributed networks while acknowledging that this process of reverse inference is necessarily speculative.<sup>28</sup>

#### Analysis of Individual Brain Regions

We found that several brain regions were reliably under- or overreactive to specific stimuli in youth diagnosed as having MDD. Importantly, each region identified in this meta-analysis received substantial attention in neuroimaging studies of both clinical and nonclinical samples using a variety of experimental tasks designed to probe different cognitive functions. Thus, there is a relatively rich literature concerning the possible dysfunctions that might be associated with each of these regions.

**Table 2. Brain Regions With Significant Differences in Activation Between Youth With MDD and Age-Matched Healthy Control Participants During Different Experimental Conditions**

Brain Structure <sup>a</sup>	Hemisphere	Direction of Effect	Experimental Condition <sup>b</sup>	Talairach Coordinates, x, y, z <sup>c</sup>	Cluster Size, mm <sup>3</sup>	Statistical Threshold P Value <sup>d</sup>
Subgenual anterior cingulate cortex <sup>e</sup>	Left	Youth with MDD > control participants	Aggregate	1, -32, 1	12 088	<.05
Ventrolateral prefrontal cortex, <sup>e</sup> anterior insula <sup>f</sup>	Right	Youth with MDD > control participants	Aggregate	-47, 3, 14	4044	<.05
Caudate, <sup>e</sup> posterior insula <sup>f</sup>	Right	Control participants > youth with MDD	Aggregate	-40, 27, -6	13 153	<.01
Superior temporal cortex, <sup>e</sup> parahippocampus, <sup>e</sup> posterior insula <sup>f</sup>	Right	Control participants > youth with MDD	Aggregate	-41, 24, -5	8089	<.03
Cuneus <sup>e</sup>	Left	Control participants > youth with MDD	Executive function	4, 71, 13	1136	<.001
Dorsal cingulate cortex <sup>e</sup>	Right	Control participants > youth with MDD	Executive function	-6, -35, 22	12 033	<.05
Dorsal anterior insula <sup>e</sup>	Right	Control participants > youth with MDD	Executive function	-33, -18, 0	8304	<.05
Thalamus, <sup>e</sup> caudate <sup>f</sup>	Bilateral	Youth with MDD > control participants	Affective	1, 3, 9	13 037	<.03
Parahippocampal gyrus, <sup>e</sup> hippocampus, <sup>e</sup> putamen, <sup>f</sup> orbitofrontal cortex, <sup>f</sup> amygdala, <sup>f</sup> nucleus accumbens <sup>f</sup>	Left	Youth with MDD > control participants	Affective	14, 7, -15	2580	<.003
Posterior insula, <sup>e</sup> putamen, <sup>f</sup> claustrum <sup>f</sup>	Right	Control participants > youth with MDD	Positive <sup>g</sup>	-39, -8, 20	1383	<.005
Dorsolateral prefrontal cortex <sup>e</sup>	Left	Youth with MDD > control participants	Negative <sup>g</sup>	46, -5, 37	980	<.001
Superior temporal cortex <sup>e</sup>	Left	Youth with MDD > control participants	Negative <sup>g</sup>	52, 5, 0	4169	<.003

Abbreviation: MDD, major depressive disorder.

<sup>a</sup> Brain regions organized by experimental conditions that reached significance at  $P = .05$  (familywise error rate corrected) for the contrast of youth with MDD minus healthy control participants. Brain regions include the peak center of each cluster as well as surrounding areas.

<sup>b</sup> Categorized according to the study groupings previously described. Where a particular region reached significance under multiple experimental conditions, only the most specific designation is indicated. Possibilities include aggregate (low specificity), affective vs executive function (medium specificity), and

positive vs negative valence (high specificity).

<sup>c</sup> Of the center of peak signal.

<sup>d</sup> Thresholds are voxelwise and familywise (false discovery rate corrected) and were inspected at regular intervals from  $P = .05$  to  $P = .001$ .

<sup>e</sup> Corresponds to the peak center of each cluster.

<sup>f</sup> Surrounds the peak center and is still contained in cluster.

<sup>g</sup> Valence-specific effect as determined by the direct contrast of positive vs negative valence maps.

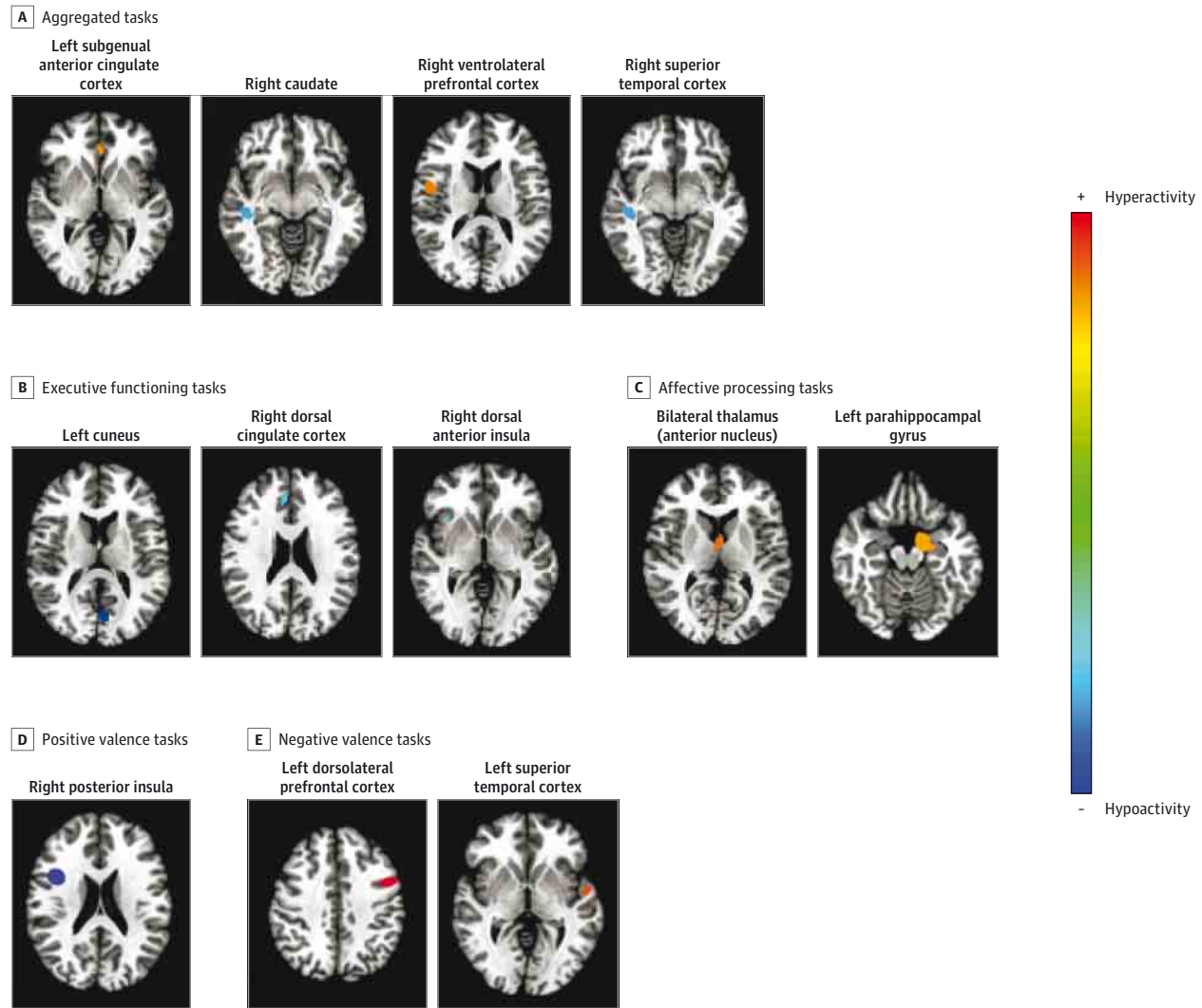
We observed reliable overactivation centered in the sgACC across experimental tasks and the thalamus during affective processing tasks in youth with MDD. These neural regions have been implicated in emotional attention and salience attribution and both have shown reliable overactivation at baseline or wakeful rest in meta-analyses of adult MDD.<sup>29,30</sup> In particular, the sgACC is a surgical target for deep-brain stimulation in treatment-refractory MDD<sup>8</sup> because of its extensive functional connectivity with other limbic regions that together form a medial prefrontal network.<sup>31</sup> Elevated activity in the sgACC and reduced functional connectivity between the sgACC and the cuneus and insula as well as elevated functional connectivity with the dlPFC have been associated with adolescent MDD<sup>32</sup>; importantly, these patterns correspond closely to our findings of hyperactivity in the sgACC and dlPFC and hypoactivity in the cuneus and insula. Similarly, the thalamus has

been postulated to potentiate activity in other distributed regions that together form a salience network for emotional processing.<sup>29</sup>

We found that the dlPFC was selectively overresponsive to negative stimuli and the ventrolateral prefrontal cortex was hyperactive across tasks in youth with MDD. These brain regions are among the most prominent components of fronto-limbic models of MDD and have been implicated consistently in neuroimaging studies of depressed adults as centers of cognitive control and emotional regulation.<sup>33,34</sup> However, studies of MDD in adults have typically found abnormally low levels of activation in these regions, a finding that was reversed in the present meta-analysis of youth with MDD. This age difference in activation suggests a possible biomarker or compensatory mechanism that changes during development and/or across the course of the disorder itself.



**Figure 1. Brain Regions With Significant Differences in Activation Between Youth With Major Depressive Disorder (MDD) and Age-Matched Healthy Control Participants During Different Experimental Conditions**



Brain regions reached significance at  $P = .05$  (familywise error rate corrected) for the contrast of youth with MDD minus healthy control participants. Each brain map displays regions of peak difference shown in Talairach standard space according to neurological format. Positive activation values (warm colors)

represent areas of hyperactivity (youth with MDD > healthy control participants) whereas negative activation values (cool colors) represent areas of hypoactivity (healthy control participants > youth with MDD).

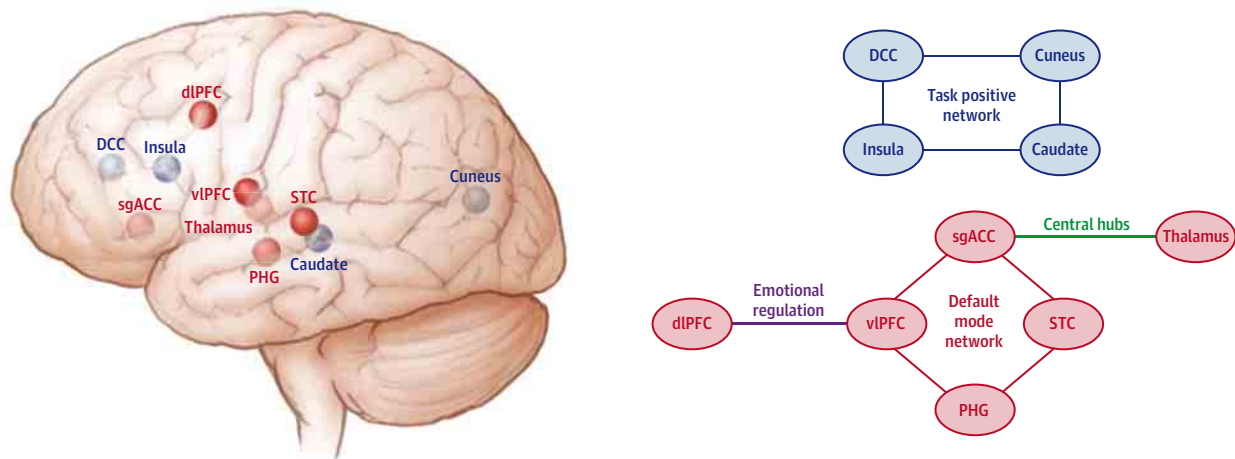
We also found reliable overactivity centered at the parahippocampal gyrus during affective processing tasks and in the STC during negative valence tasks in youth with MDD. These regions along with the sgACC and ventrolateral prefrontal cortex have been identified as components of the default mode network, a macroscale network that appears to subservise self-referential processing, particularly during wakeful rest. In the context of MDD, overactivation of these regions has been associated with maladaptive rumination and the inability to disengage in self-reflective thinking, particularly during affective processing and negatively valence conditions,<sup>29,34,35</sup> which is consistent with observed hyperactivation in these same conditions in the present meta-analysis.

In contrast, we found reliable underactivity centered on the dorsal cingulate cortex, dorsal anterior insula, and cu-

neus during executive functioning tasks, the posterior insula during positive valence tasks, and the caudate across all tasks combined in youth with MDD. These regions have been identified as major nodes of the task-positive network, another macroscale network typically anticorrelated with the default mode network. Activation of these regions appears to facilitate executive functioning and attentional shifting; in the context of MDD, underactivation in these regions is associated with difficulty transitioning from maladaptive rumination to adaptive processing.<sup>34,36-38</sup>

However, each task-positive network region has also been implicated in other types of cognitive processing related to deficits in MDD. In particular, the cuneus/precuneus has been linked to reward processing and underactivation in this region has been associated with anhedonia,<sup>39,40</sup> one of the car-

Figure 2. Neural Basis of Major Depressive Disorder (MDD) in Youth



Brain regions with significant ( $P < .05$ , familywise error rate corrected) activation differences between youth with MDD and healthy control participants. Red circles indicate hyperactivity (youth with MDD > healthy

control participants), and blue circles indicate hypoactivity (healthy control participants > youth with MDD).

dinal symptoms of MDD. In addition, dorsal cingulate cortex activation has been linked to the retrieval of autobiographical memories in healthy individuals<sup>41</sup> and negative memory bias in MDD<sup>42</sup>; activation of the caudate has been related to deficits in anticipated incentives and behavioral inhibition in adolescents with anxiety disorders.<sup>43</sup> Finally, activation of the insula has been associated with emotional salience and arousal as well as interoceptive awareness.<sup>29,44</sup> Examination of its functional subdivisions indicates the importance of the dorsal anterior region in executive control and the posterior region in the processing of painful or unpleasant stimuli,<sup>45</sup> findings that are congruent with the low arousal deficiencies in cognitive control and the persistence of negative affect in patients with MDD.

### Analysis of Whole-Brain Activation

Using the Neurosynth decoding framework, we found that youth with MDD compared with healthy control participants showed abnormal whole-brain activation patterns associated with altered cognitive processing. In particular, depressed youth showed brain activation patterns linked to increased engagement with negative emotions that persisted across conditions and during the presentation of positive stimuli. They also showed brain activation patterns associated with corresponding deficits in executive functioning, particularly in cognitive control, attentional shifting, and error monitoring. Importantly, these results are consistent with cognitive biases documented in depression<sup>46</sup> but were independently derived from quantitative analysis of whole-brain activation patterns.

### Neural Basis of MDD Symptoms in Youth

These findings show consistent anomalies in several distributed brain networks in youth diagnosed as having MDD (Figure 2) that might help explain the expression of specific

symptoms of depression in this population. First, the hypervigilance to emotional stimuli exhibited by youth with MDD may be owing to overactivity in the sgACC and thalamus, regions that serve as central hubs of emotional salience. Furthermore, the altered functional connectivity of the sgACC with other brain regions in depressed youth may result in the cascade of depressive symptoms described later. Second, the ineffective attempts at emotional regulation that have been documented in depressed youth may result from their elevated recruitment of the dlPFC and ventrolateral prefrontal cortex, which, nevertheless, ultimately fail to modulate responses in emotional circuitry. This pattern of activation may reverse with increasing age and/or the course of depression as functional connectivity with these regions is down-regulated, a possibility that should be examined in future longitudinal studies. Third, the rumination consistently associated with depression may be linked to maladaptive regulation of default-mode and task-positive network activity. In particular, excessive self-referential processing supported by the activation of default mode network structures, such as the parahippocampal gyrus and STC, appears to persist in depressed youth despite competing attentional demands that would normally disengage these regions and recruit task-positive network structures, such as the cuneus and caudate. Finally, the combination of diminished cuneus activation and posterior insula response to positive stimuli and the heightened activation in the dlPFC and STC during the processing of negative stimuli likely contributes to anhedonic symptoms and the maintenance of negative affect.

### Limitations

To our knowledge, this meta-analysis is the first to provide a quantitative synthesis of neuroimaging studies of MDD in youth and yielded several statistically robust and theoretically mean-

ingful neural abnormalities. Nevertheless, we should note 3 limitations of this study. First, the number of primary studies ( $n = 14$ ) included in this meta-analysis meant that we had relatively limited statistical power for detecting brain regions with abnormal activations. However, the total number of participants with MDD ( $n = 257$ ) and healthy control participants ( $n = 274$ ) was large and yielded several findings that satisfied highly stringent requirements for statistical significance ( $P < .001$ , familywise error rate corrected), demonstrating robust differences even with this relatively small number of primary studies. Second, the primary studies included in this meta-analysis did not use a standardized set of task conditions nor did they specifically examine the effects of participant characteristics, such as sex, pubertal status, or medication; they also included a relatively wide range of participant ages. While this increased the generalizability and clinical relevance of our results, it is possible that differences in these variables were related systematically to the observed effects in neural activity and we encourage investigators to examine these potentially important variables in future studies. Third, because we used the standard approach of other coordinate-based meta-analyses in which many of the primary studies did not report inferential statistics or cluster sizes for their obtained clusters, we could not compute effect sizes. We as-

signed a radius of 10 mm for each reported cluster in the initial indicator maps. This value has been used in other coordinate-based meta-analyses and is considered a suitable standard value for the desired sensitivity and spatial resolution of fMRI.<sup>29,47</sup>

## Conclusions

Although MDD is defined diagnostically as a clinical syndrome of co-occurring symptoms, clinical researchers are moving toward a biologically driven dimensional system based on neural models of psychological dysfunction<sup>48,49</sup> capable of linking together seemingly disparate symptoms to a coherent neural explanation. Accordingly, in this meta-analysis, we identified several brain regions in which youth with MDD reliably exhibited abnormal activations compared with age-matched healthy control participants during affective processing and executive functioning tasks. Based on these findings and the existing neuroscience literature, we propose that altered activation of several distributed brain networks described previously may help explain seemingly disparate symptoms in this population as well as develop targeted interventions for prevention and treatment.

### ARTICLE INFORMATION

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