

Anomalous Prefrontal-Subcortical Activation in Familial Pediatric Bipolar Disorder

A Functional Magnetic Resonance Imaging Investigation

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Background: The neurobiological features of pediatric bipolar disorder (BD) are largely unknown. Children and adolescents with BD may be important to study with functional neuroimaging techniques because of their unique status of early-onset BD and high familial loading for the disorder. Neuroimaging studies of adults with BD have implicated the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) in the development of this disorder.

Objectives: To study children and adolescents with BD via functional magnetic resonance imaging using cognitive and affective tasks and to examine possible abnormalities in the DLPFC and ACC, as well as selected subcortical areas, in pediatric familial BD.

Design: We evaluated 12 male subjects aged 9 to 18 years with BD who had at least 1 parent with BD as well as 10 age- and IQ-matched healthy male controls. Stimulants were discontinued for at least 24 hours; other medications were continued. Subjects underwent functional magnetic resonance imaging at 3 T while performing a 2-back visuospatial working memory task and an affective task involving the visualization of positively, neutrally, or negatively valenced pictures.

Setting: An academic referral setting, drawing from the Bay Area of San Francisco, Calif.

Results: Compared with controls, for the visuospatial working memory task, subjects with BD had greater activation in several areas including the bilateral ACC, left putamen, left thalamus, left DLPFC, and right inferior frontal gyrus. Controls had greater activation in the cerebellar vermis. In viewing negatively valenced pictures, subjects with BD had greater activation in the bilateral DLPFC, inferior frontal gyrus, and right insula. Controls had greater activation in the right posterior cingulate gyrus. For positively valenced pictures, subjects with BD had greater activation in the bilateral caudate and thalamus, left middle/superior frontal gyrus, and left ACC, whereas controls had no areas of greater activation.

Conclusions: Children and adolescents with BD may have underlying abnormalities in the regulation of prefrontal-subcortical circuits. Further functional magnetic resonance imaging studies of attention and mood with greater sample sizes are needed.

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PEDIATRIC BIPOLAR DISORDER (BD) carries high morbidity and psychosocial dysfunction because of its chronic and frequently rapid-cycling symptoms, high comorbidity with disruptive behavioral disorders, and relative treatment resistance.^{1,2} However, little is known about the neuropathophysiologic features of pediatric BD. Neuroimaging studies of children and adolescents with BD may be of particular interest to pursue because these patients often have not had as many years of substance use or medication exposure, which may confound similar studies in adults.

Neuroimaging studies of adults with BD and a few in children with BD have supported the involvement of prefrontal brain

regions in this disorder. Positron emission tomographic studies have found that adults in manic states, compared with depressed states may have increased overall brain activity,³ particularly in the inferior frontal areas.⁴ Increased activity in the anterior cingulate cortex (ACC) has also been reported in bipolar manic states vs euthymic states.⁵ Compared with healthy controls, adults with BD reportedly have hypometabolism in the dorsolateral prefrontal cortex (DLPFC) according to fluorodeoxyglucose F 18–positron emission tomographic studies.⁶ A functional magnetic resonance imaging (fMRI) study also reported increased left amygdalar and decreased right DLPFC activation in adults with BD viewing fearful faces.⁷ Spectroscopic studies have reported decreased

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DLPFC *N*-acetylaspartate levels, a marker of neuronal density, in adults⁸ and children⁹ with BD. Additionally, children with BD during a manic episode were reported to have increased *myo*-inositol levels in the ACC.¹⁰ In light of these findings, it is likely that these prefrontal areas are involved in BD.

A hypothesis implicating dysfunction of the DLPFC and ACC in BD appears appropriate because both regions are involved in normal mood regulation, as supported by studies of healthy volunteers. Increased activity in the right ACC, bilateral frontal and prefrontal cortices,¹¹ and DLPFC¹² has been observed during transient induced sadness in healthy volunteers. Other investigators have found reductions in blood flow of the right dorsal and ventral prefrontal lobes and dorsal ACC during more sustained sadness inductions in healthy volunteers.¹³

The DLPFC and ACC also have crucial roles in attention processing, relevant when considering that 60% to 94% of children with BD have comorbid attention-deficit/hyperactivity disorder (ADHD).¹⁴ The DLPFC is activated during the implementation of control in cognition, necessary in color-naming Stroop tasks¹⁵ and spatial working memory.¹⁶ Abnormalities in the DLPFC, as reflected by decreased levels of *N*-acetylaspartate, have been found in adults with ADHD.¹⁷ The ACC has been similarly implicated in the control of attention,^{18,19} specifically in error recognition and overriding a prepotent response bias.²⁰ Thus, Stroop tasks have caused activation in the ACC in healthy subjects^{15,21} and lesser activation in subjects with ADHD.²²

Because of these findings, the prefrontal cortex, including the DLPFC and ACC, is postulated to contain cortical control areas that regulate both mood and attention. Accordingly, these areas are prime candidates for investigation in childhood BD. We tested the hypothesis that children with BD would show anomalous prefrontal activation compared with healthy controls by using fMRI experiments that tap brain function related to both attention and emotion. These experiments consisted of a cognitive task involving visuospatial working memory and an affective task involving the viewing of emotionally valenced pictures from the International Affective Picture System (IAPS).²³ Because of research suggesting sex differences in emotional reactivity in children²⁴ and because of the higher incidence of pediatric BD in boys,²⁵ we limited this initial study to males only. Furthermore, because we were interested in the involvement of prefrontal-subcortical circuits, we conducted whole-brain analyses of the fMRI data.

METHODS

SUBJECTS

Subject families were recruited from the Stanford Adult and Pediatric Bipolar Disorders Clinics (Stanford, Calif) and from the surrounding community. Written and oral informed consent were obtained from at least 1 parent, and assent was obtained from the subject after explaining possible adverse effects and alternatives to study participation. The study met all requirements of the institutional review board at Stanford University.

Inclusion criteria for bipolar subjects were age between 9 and 18 years, at least 1 biological parent with bipolar I or II

disorder, and diagnosis of bipolar I disorder. Exclusion criteria were the presence of a pervasive developmental disorder, a neurological condition (such as a seizure disorder), a substance use disorder, an IQ less than 80, or the presence of metallic implants or braces.

Parents were diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition (SCID-I/P).²⁶ Family history was obtained using the Family History—Research Diagnostic Criteria.²⁷ Children were assessed with the affective module of the Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia^{28,29} and the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version.³⁰ Subjects were evaluated either by a child psychiatrist (K.C.) or trained masters-level research assistants (K.D. or D.I.S.) who were aware of the parental diagnosis. Current and lifetime DSM-IV diagnoses were ultimately made by a board-certified child psychiatrist (K.C.) based on personal interview, discussion with the research assistant, and written notes of interview responses.

Healthy controls did not have a DSM-IV diagnosis, were not taking psychotropic medications, had both parents without any psychiatric diagnosis according to the SCID-I/P, and did not have a first- or second-degree relative with BD as determined using the Family History—Research Diagnostic Criteria.

Subjects were all outpatients at the time of scanning. Subjects with BD were administered the Young Mania Rating Scale^{31,32} and completed the Childhood Depression Inventory,³³ with the help of a parent if they were younger than 12 years, within 3 days of fMRI. Stimulants were discontinued for at least 24 hours prior to imaging; other medications were continued. The IQ was assessed with the Wechsler Abbreviated Scale of Intelligence.³⁴

The pool of subjects with BD was the same for both tasks. However, those who had movement greater than 3 mm (translation) or greater than 3° (rotation) during imaging were disqualified from further analysis owing to spatial data inaccuracy. Therefore, 11 subjects with BD were analyzed for the visuospatial working memory task (mean ± SD age, 15.3 ± 2.5 years; range, 9.7–18.6 years), and 11 were analyzed for the affective task (mean ± SD age, 14.5 ± 3.0 years; range, 9.2–18.6 years). Ten subjects were included in both groups. Ten healthy controls (mean ± SD age, 14.4 ± 3.2 years; range, 10.0–17.7 years) completed both the visuospatial working memory and affective tasks.

TASKS

Visuospatial Working Memory Task

The visuospatial working memory task consisted of 6 alternating experimental and control epochs (**Figure 1**). Each experimental and control epoch consisted of 16 stimuli presented for 500 milliseconds each, with a 1500-millisecond interstimulus interval. The stimulus was the letter *O* presented in 1 of 9 spatial locations in a 3 × 3 matrix. In the experimental epoch, subjects were instructed to press a button if the stimulus was in the same location as it was 2 trials previously. In the control epoch, subjects were instructed to respond if the stimulus was in the center position. Correct response rate, incorrect response rate, and reaction times were recorded. Further details of the task have been described elsewhere.^{35,36}

IAPS Task

The IAPS²³ is a stimulus set that has been used in other functional imaging studies of affective stimulation.^{37,38} Specific negative (eg, a mutilated dog) and positive (eg, a hot fudge sundae) picture stimuli were selected that were deemed acceptable to a pediatric population. Neutral (eg, a plate) pictures were selected for the control condition. Valence was determined using previously published ratings of the specific pictures.²³ The 4 types of

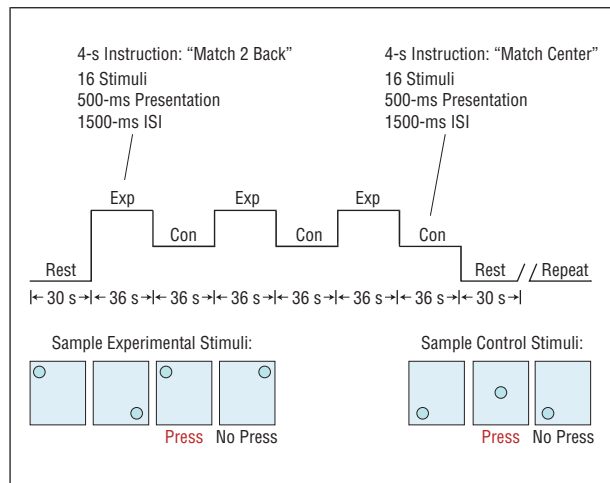


Figure 1. Visuospatial working memory task sequence consisting of 6 alternating experimental (exp) and control (con) epochs. Each epoch consisted of 16 stimuli presented for 500 milliseconds each, with a 1500-millisecond interstimulus interval (ISI). In the experimental epoch, subjects were instructed to press a button if the stimulus was in the same location as it was 2 trials previously. In the control epoch, subjects were instructed to respond if the stimulus was in the center position.

stimuli were organized into blocks, each with 6 stimuli, with each stimulus presented for 4500 milliseconds with a 500-millisecond interstimulus interval (**Figure 2**). Subjects were asked to indicate how each picture made them feel by pressing 1 of 3 buttons corresponding to negatively, neutrally, and positively.

STIMULUS PRESENTATION

The tasks were programmed using Psycscope software (<http://psycscope.psy.cmu.edu>) on an Apple G3 notebook computer (Cupertino, Calif). Stimuli were projected onto a screen using a custom-built magnet-compatible projection system (Sanyo, San Diego, Calif). A custom-built button box was used to measure behavioral responses.

fMRI DATA ACQUISITION

Images were acquired with a 3-T GE Signa scanner using a standard whole-head coil (General Electric, Milwaukee, Wis). The following spiral pulse sequence parameters were used: time to repeat, 2000 milliseconds; echo time, 30 milliseconds; flip angle, 80°; and 1 interleave. To reduce field inhomogeneities, an automated high-order shimming method based on spiral acquisitions was used before acquiring fMRI data.³⁹ To aid in localization of the functional data, we used high-resolution, T1-weighted, spoiled gradient-recalled acquisition in the steady state (GRASS) 3-dimensional magnetic resonance imaging sequences with the following parameters: time to repeat, 35 milliseconds; echo time, 6 milliseconds; flip angle, 45°; field of view, 24 cm; 124 slices in the coronal plane; and a 256 × 192 matrix.

IMAGE PREPROCESSING

Images were reconstructed for each time point using inverse Fourier transform. The fMRI data were preprocessed using SPM99 software (<http://www.fil.ion.ucl.ac.uk/spm>). Images were corrected for movement using least squares minimization without higher-order corrections for spin history and were normalized to Montreal Neurological Institute (Montreal, Quebec) coordinates.⁴⁰ Images were then resampled every 2 mm using sinc interpolation and smoothed with a 4-mm gaussian kernel to decrease spatial noise. The Montreal Neurological Institute co-

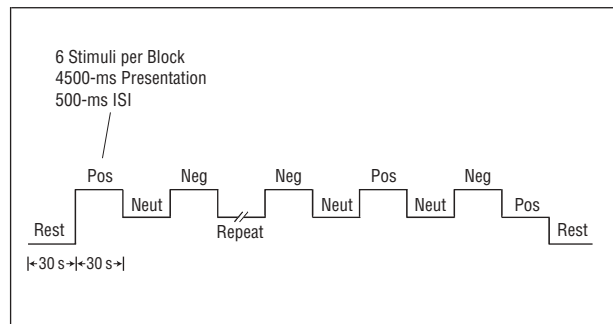


Figure 2. International Affective Picture System task sequence. Specific negative (neg) and positive (pos) picture stimuli were selected, and neutral (neut) pictures were selected for the control condition. Stimuli were organized into blocks of 6, with each stimulus presented for 4500 milliseconds with a 500-millisecond interstimulus interval (ISI).

ordinates were transformed into stereotactic Talairach coordinates⁴¹ using nonlinear transformation.⁴²

fMRI DATA ANALYSIS

Statistical analysis was performed for individual and group data using the general linear model and the theory of gaussian random fields as implemented in the SPM99 program.⁴⁰ Activation foci were superimposed on high-resolution T1-weighted images, and their locations were interpreted using the Talairach atlas⁴¹ and known neuroanatomical landmarks.⁴³

A within-subjects procedure was used to model all effects of interest for each subject. Individual subject models were identical across subjects (ie, a balanced design was used). Confounding effects of fluctuations in the global mean were removed using proportional scaling with the global mean at each time point. Low-frequency noise was removed with a high-pass filter (0.5 Hz) applied to the fMRI time series at each voxel. Group analysis was performed using a random-effects model that incorporated a 2-stage hierarchical procedure. This model estimates the error variance for each condition of interest across subjects rather than across images⁴⁴ and therefore provides a stronger generalization to the population studied. Individual contrast images were computed for experimental minus control conditions in the visuospatial working memory task and for negative minus neutral and positive minus neutral conditions in the affective task. These contrast images were analyzed using a general linear model to determine voxelwise *t* statistics. Appropriate *t* tests were then used to determine group activation and between-group differences for each contrast of interest. Finally, the *t* statistics were normalized to *z* scores, and significant clusters of activation were determined using the joint expected probability distribution of height and extent of *z* scores, with height ($z > 1.67$; $P < .05$) and extent thresholds ($P < .05$).⁴⁵

RESULTS

COHORT

Overall, the pool of subjects with BD (all males) had a mean ± SD age of 14.7 ± 3.0 years, whereas controls had a mean ± SD age of 14.4 ± 3.2 years (**Table 1**). The mean socioeconomic status, as determined with the Hollingshead 2-factor method,⁴⁶ was 3.9 for subjects with BD and 4.7 for controls. Subjects with BD did not significantly differ from controls in age, sex, IQ, handedness, or socioeconomic status (Table 1). Of the parents with BD,

Table 1. Demographics of Subjects

| | Bipolar Disorder (n = 12) | Controls (n = 10) |
|---|---------------------------|-------------------|
| Age, mean ± SD, y | 14.7 ± 3.0 | 14.4 ± 3.2 |
| Sex, % male | 100 | 100 |
| SES, mean ± SD | 3.9 ± 0.8 | 4.7 ± 0.7 |
| Race, No. (%) | | |
| African American | 1 (8) | 0 (0) |
| Hispanic | 1 (8) | 0 (0) |
| Asian | 0 (0) | 1 (10) |
| White | 10 (83) | 9 (90) |
| IQ, mean ± SD | 109 ± 8.6 | 118 ± 6.1 |
| Handedness, % right | 91 | 90 |
| Comorbid diagnoses, No. (%) | | |
| ADHD | 11 (92) | 0 (0) |
| Anxiety disorder | 4 (33) | 0 (0) |
| ODD | 7 (58) | 0 (0) |
| Current psychotropic medications, % | | |
| TCAs | 8 | 0 |
| SSRIs | 25 | 0 |
| Atypical ADs | 33 | 0 |
| Lithium | 42 | 0 |
| Valproate | 33 | 0 |
| Carbamazepine | 8 | 0 |
| Antipsychotics | 33 | 0 |
| Other anticonvulsants | 25 | 0 |
| Past psychotropic medication exposure, % | | |
| Stimulants | 75 | 0 |
| TCAs | 42 | 0 |
| SSRIs | 58 | 0 |
| Atypical ADs | 58 | 0 |
| Lithium | 42 | 0 |
| Valproate | 75 | 0 |
| Carbamazepine | 8 | 0 |
| Antipsychotics | 50 | 0 |
| Any mood stabilizer | 92 | 0 |
| First- or second-degree relatives with a mood disorder, % | 56 | 0 |

Abbreviations: AD, antidepressant; ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder; SES, socioeconomic status; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

58.3% had bipolar I disorder, 41.7% had bipolar II disorder, and 83% were women.

For the subjects with BD, mean duration of illness was 3.1 years. Of the patients, 92% had at least 1 comorbid psychiatric diagnosis; 92% had ADHD, 58% had oppositional defiant disorder, and 33% had an anxiety disorder. Two subjects (16.7%) had experienced psychotic symptoms in the past. One subject (8.3%) was not taking medication at the time of fMRI. The mean ± SD number of medications at the time of imaging was 4.6 ± 2.0 (Table 1). The mean ± SD Young Mania Rating Scale score was 11.8 ± 7.8, and the mean ± SD Childhood Depression Inventory score was 14.1 ± 8.2.

VISUOSPATIAL WORKING MEMORY TASK ANALYSIS

Behavioral

Subjects with BD were slightly less accurate on the visuospatial working memory task than controls, al-

though this difference did not reach statistical significance (86% vs 93% correct; $P = .08$). Reaction times were not significantly different between subjects with BD and controls (mean ± SD, 628 ± 138 milliseconds vs 534 ± 141 milliseconds, respectively; $P = .12$).

Brain Activation

For the 2-back task minus control condition contrast, within-group analyses showed that subjects with BD activated the bilateral DLPFC among other prefrontal areas as well as the left caudate, left inferior parietal lobule, right precuneus, and right thalamus (**Table 2**). Controls activated the right DLPFC and other prefrontal areas, the right precuneus, and the right superior parietal lobule. Subjects with BD had significantly greater ($P < .05$) activation than controls in the following regions: the bilateral anterior cingulate, left putamen, left thalamus, left DLPFC, left middle frontal gyrus, left superior frontal gyrus, left superior temporal gyrus, and right inferior frontal gyrus (**Figure 3**). Within the left superior temporal gyrus, greater left insular activation was also seen in subjects with BD (Table 2). Controls showed greater activation than subjects with BD in areas within the cerebellum, predominantly the vermis (Figure 3).

IAPS TASK ANALYSIS

Behavioral

Each individual's ratings were averaged across pictures of the same valence, as classified by the IAPS,²³ to give a subject's mean rating for each valence of the pictures. Across both groups, there was a significant effect (Hunyh-Feldt statistic; $P < .001$) of valence, indicating significant differences between subjects' ratings for differently valenced IAPS pictures. Follow-up paired *t* tests revealed that subjects with BD had significantly different ratings for positively and neutrally valenced pictures ($P = .001$) and for negatively and neutrally valenced pictures ($P = .003$). Within the control group, ratings for both positively vs neutrally valenced pictures and neutrally vs negatively valenced pictures were significantly different ($P < .001$). There was no interaction effect between subjects' ratings of valenced pictures and diagnosis (Hunyh-Feldt statistic; $P = .12$).

Brain Activation

Negative-Neutral Contrast. Subjects with BD who were exposed to negative visual stimuli activated the bilateral DLPFC, left inferior frontal gyrus, and inferior/middle temporal gyrus, among other areas (**Table 3**). Control group activation in response to negative stimuli included the bilateral DLPFC, left ACC, and inferior temporal gyrus. Compared with healthy controls, subjects with BD showed significantly greater activation in the bilateral DLPFC, left superior/middle temporal gyrus, left inferior frontal gyrus, and right insula (**Figure 4**). Controls showed greater activation than subjects with BD in response to negative stimuli in the right posterior cingulate gyrus (Figure 4).

Table 2. Brain Regional Activations in the Visuospatial Working Memory Task

| Activated Region | BA | No. of Voxels | Cluster P Value | z Score, Maximum Primary Peak | Primary Peak Location (x, y, z)* |
|--------------------------------|---------|---------------|-----------------|-------------------------------|----------------------------------|
| BD – controls | | | | | |
| Left putamen | | 8808 | <.001 | 4.65 | -28, -8, -6 |
| Left STG† | 22/21 | | | 4.15 | -50, 2, -4 |
| Left thalamus‡ | | | | 3.95 | -6, -8, 14 |
| Right IFG | 11 | 813 | <.001 | 3.58 | 24, 30, -4 |
| Right ACC† | 32/24 | | | 3.27 | 18, 40, 6 |
| Left DLPFC (MFG) | 9 | 752 | <.001 | 3.44 | -38, 16, 28 |
| Left precuneus | 30/31 | 572 | .002 | 3.32 | -12, -66, 26 |
| Left cingulate gyrus | 32 | 435 | .02 | 2.88 | -16, 38, 0 |
| Left SFG† | 10 | | | 2.70 | -16, 58, 20 |
| Left ACC | 32 | | | 2.67 | -6, 32, -2 |
| Controls – BD | | | | | |
| Right cerebellum] | | 364 | .05 | 3.51 | 6, -72, -26 |
| Left cerebellum‡ | | | | 3.23 | -2, -56, -26 |
| BD individual group | | | | | |
| Right precuneus | | 6101 | <.001 | 4.87 | 0, -56, 48 |
| Left inferior parietal lobule‡ | | | | 4.54 | -50, -40, 52 |
| Right MFG | 6/45 | 5919 | <.001 | 4.57 | 4, 16, 46 |
| Right DLPFC (IFG) | 9/45/46 | 881 | <.001 | 4.38 | 36, 20, -10 |
| Left IFG | 47 | 671 | <.001 | 4.16 | -36, 24, -4 |
| Left SFG | 10 | 3038 | <.001 | 3.91 | -30, 54, -2 |
| Left DLPFC (MFG) | 9 | | | 3.63 | -36, 30, 28 |
| Right thalamus | | 583 | <.001 | 3.87 | 12, -10, 2 |
| Left caudate body | | 388 | .008 | 3.59 | -12, 6, 12 |
| Control individual group | | | | | |
| Right SPL | 7 | 6004 | <.001 | 4.53 | 36, -70, 44 |
| Right precuneus† | 7 | | | 4.33 | 4, -64, 48 |
| Right MFG | 8 | 5285 | <.001 | 4.37 | 4, 24, 44 |
| Right DLPFC‡ (MFG) | 9/46 | | | 4.32 | 42, 30, 22 |
| Left IFG | 47 | 463 | .01 | 4.15 | -32, 30, -4 |
| Left MFG | 6/8 | 850 | <.001 | 3.68 | -24, 2, 52 |

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BD, bipolar disorder; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; SPL, superior parietal lobe; STG, superior temporal gyrus.

*x, y, z, indicate axis coordinates in Talairach spaces.

†Secondary peak.

‡Tertiary peak.

Positive-Neutral Contrast. In response to positive stimuli, subjects with BD activated the bilateral middle occipital gyrus, left medial frontal gyrus, left ACC, and right cerebellum (**Table 4**). Controls activated the right cuneus and middle occipital gyrus. Subjects with BD showed significantly more activation than controls in response to positive stimuli in the bilateral caudate and thalamus and left middle/superior frontal gyrus, ACC, precentral gyrus, paracentral lobule, and precuneus (**Figure 5**). Controls did not show greater activation than subjects with BD in any region when viewing positive stimuli.

COMMENT

Consistent with our hypothesis, children and adolescents with BD demonstrate significant differences in brain activation patterns in prefrontal areas compared with controls when performing both cognitive and affective tasks. The differences we detected were mostly increases in cerebral activation in subjects with BD, regardless of task. Brain areas differing in activation patterns included the DLPFC and ACC as well as other prefrontal areas and extended to the limbic structures (insula), striatum (cau-

date and putamen), and thalamus. These areas have all been implicated in the pathophysiologic mechanisms of BD.⁴⁷

There are several possible explanations for why we detected overall increased task-related brain activation in subjects with BD. First, pediatric BD may be associated with a hyperreactive brain state, particularly in response to affective stimulation or any performance demand, even during euthymic periods. Positron emission tomographic studies of patients with mania have shown increased cerebral blood flow at rest.⁴ Because our subjects were euthymic, overactivation observed in fMRI experiments may be a trait marker of this disorder. However, it is also possible that these findings reflect a developmental stage of BD so that activation patterns begin to decrease, even to lower than normal, after years of sustained illness. For example, it has been shown that the ACC is activated by transient induced sadness¹¹ but deactivated in response to more sustained sadness¹³ in healthy volunteers and patients with depression.⁴⁸ Therefore, with extended duration of an emotional state or illness, overall activation patterns may progress from overactivation to underactivation in BD. Our findings should be gauged with these possible developmental considerations in mind.

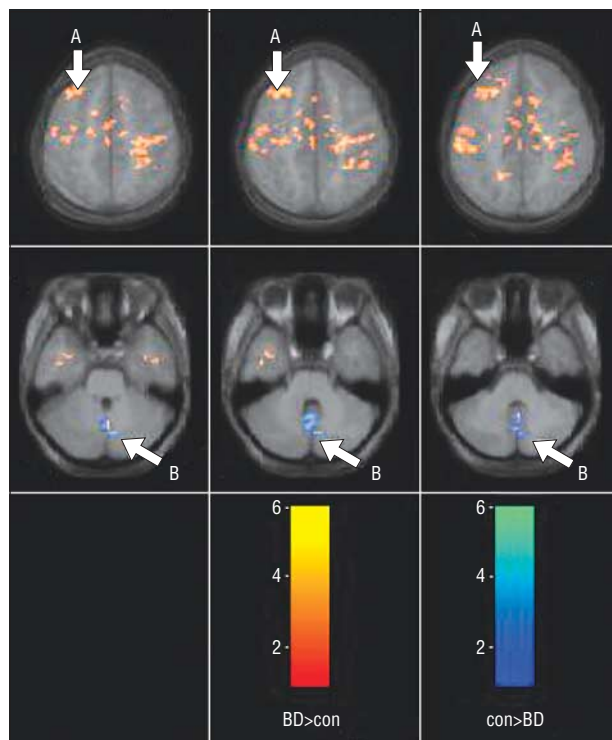


Figure 3. Activation in subjects with bipolar disorder (BD) compared with controls (con) for the visuospatial working memory task. A indicates increased activation in the left dorsolateral prefrontal cortex; B, decreased activation in the cerebellar vermis.

PREFRONTAL CORTEX

Visuospatial working memory tasks have been reported to activate the right DLPFC in healthy adults^{16,49-51} and children,^{16,52} and studies using the IAPS in healthy adults have also demonstrated DLPFC activation.³⁷ In our study, DLPFC activation was greater for subjects with BD than for controls, on the left (Brodmann area [BA] 9) in the visuospatial working memory task and bilaterally (BA 9 and BA 45) in the negative-stimuli condition of the IAPS task.

Previous studies in adults and children support the involvement of the DLPFC in the neuropathophysiologic underpinnings of BD. In an fMRI study, adults with BD watching fearful faces had less activation in the right DLPFC than healthy controls.⁷ Neuronal and glial DLPFC density may be reduced in adults with BD.^{8,53} We previously found decreased *N*-acetylaspartate levels, signifying decreased neuronal density, in the right DLPFC in pediatric familial BD,⁹ albeit to a lesser extent than was found in adults with BD.⁸ Therefore, the abnormalities in DLPFC activation reported in this article may be related to underlying DLPFC abnormalities in neuronal density or function.

As hypothesized, we also found differences in ACC activation between subjects with BD and controls. In our visuospatial working memory task, subjects with BD had greater activation in the right (BA 24 and BA 32) and left (BA 32) ACC than controls. In the positive-stimuli condition of the IAPS task, subjects with BD demonstrated increased activation in the left ACC (BA 24). Abnormalities in the ACC have previously been reported in children and adults with BD, including increased ACC blood

flow during rest⁵ and while performing a decision-making task⁵⁴ and increased ACC *myo*-inositol.¹⁰ Our findings further support the existence of abnormalities in ACC function in pediatric BD.

Researchers have suggested a functional division of the ACC, with caudal portions associated with cognitive functions and ventral portions responding to emotional stimuli.^{19,21,22,55} In our study, most of the ACC overactivation in subjects with BD was in the ventral portions, but we did not find differences in activation of the subgenual ACC (a portion of BA 24). Abnormalities of the subgenual cingulate have been reported in familial BD^{56,57} and in unipolar depression in adults⁴⁸ and children.⁵⁸ The IAPS task might have been expected to elicit functional differences in this area owing to its affective component; however, it is possible that the task was not sufficient to probe for subgenual ACC activation or that our subjects simply did not have functional abnormalities in this region.

Other prefrontal structures were activated to a greater extent in subjects with BD, most notably the orbitofrontal cortex (OFC). In the visuospatial working memory task, subjects with BD had greater activation in the right inferior OFC (BA 11). Subjects with BD also had greater activation in the left inferior OFC (BA 47) during the negative-stimuli condition of the IAPS task and greater activation in the left medial OFC (BA 10) during the positive-stimuli condition. The OFC has reciprocal connections with limbic structures, including the insula, amygdala, and subgenual cingulate, and OFC lesions may result in behavioral disinhibition and emotional lability.⁵⁹ In a positron emission tomographic study, decreased orbitofrontal blood flow was noted in adults with BD and mania compared with euthymia, both during rest and during a word generation task.⁶⁰ Our finding of increased orbitofrontal activity during the visuospatial working memory and IAPS tasks could represent compensatory overactivation to modulate overactive limbic areas in our subjects with BD.

ADDITIONAL STRUCTURES

In subjects with BD, we found increased left thalamic activation during the visuospatial working memory task and increased bilateral thalamic activation during the positive-stimuli condition of the IAPS task. The thalamus, which has multiple functions, also has significant connections to the prefrontal cortex and may be a crucial component of limbic circuits, including the DLPFC and OFC circuits. Thalamic abnormalities have been reported in BD, including increased^{61,62} and decreased⁶³ thalamic volume or density and increased thalamic *N*-acetylaspartate levels.⁶⁴

Subjects with BD also had greater activation of the bilateral caudate during the positive-stimuli condition of the IAPS task. Increased caudate volumes have been reported in men with BD⁶⁵ and in monozygotic twins discordant for BD.⁶⁶ In a positron emission tomographic study, adults with mania had increased blood flow in the left caudate while at rest.⁵ Our findings further support these previous suggestions of striatal abnormalities in BD.

Increased activation of the left insula (BA 21 and BA 22) during the visuospatial working memory task and the right insula (BA 21) during the negative-stimuli condition of the IAPS task were seen in subjects with BD.

Table 3. Brain Regional Activations for the IAPS Task: Negative Stimuli

| Activated Region | BA | No. of Voxels | Cluster P Value | z Score, Maximum Primary Peak | Primary Peak Location (x, y, z) |
|---------------------------------|------|---------------|-----------------|-------------------------------|---------------------------------|
| BD—controls | | | | | |
| Left STG | 38 | 489 | <.001 | 3.80 | -46, 6, -16 |
| Left IFG* | 47 | | | 3.33 | -32, 20, -12 |
| Right DLPFC (IFG) | 9 | 374 | .003 | 3.69 | 48, 16, 22 |
| Left DLPFC (IFG) | 9/45 | 333 | .008 | 3.27 | -48, 12, 28 |
| Right MTG | 21 | 476 | <.001 | 3.19 | 56, 4, -18 |
| Right insula* | | | | 2.92 | 40, -2, -6 |
| Controls—BD | | | | | |
| Right posterior cingulate gyrus | 31 | 281 | .03 | 3.07 | 16, -44, 28 |
| BD individual group | | | | | |
| Left fusiform | 37 | 938 | <.001 | 4.54 | -46, -60, -18 |
| Left ITG† | | | | 3.95 | -52, -70, 2 |
| Right IFG | 44 | 896 | <.001 | 4.22 | 56, 14, 18 |
| Right cerebellum | | 636 | <.001 | 3.78 | 40, -60, -18 |
| MFG | 8 | 977 | <.001 | 3.66 | 0, 38, 40 |
| Right DLPFC* (MFG) | 9 | | | 3.24 | 28, 36, 34 |
| Left MTG | | 739 | <.001 | 3.64 | -40, -2, -20 |
| Left IFG* | 47 | | | 3.30 | -32, 26, -4 |
| Left cuneus | 18 | 431 | .001 | 3.60 | -4, -88, 10 |
| Left SOG* | 19 | | | 3.26 | -28, -76, 30 |
| Left DLPFC (MFG) | 9 | 401 | .001 | 3.33 | -36, 18, 30 |
| Left precentral gyrus* | 6 | | | 3.18 | -46, 2, 34 |
| Left DLPFC (MFG) | 46/9 | 293 | .01 | 3.25 | -36, 38, 26 |
| Left SFG* | | | | 2.88 | -14, 30, 44 |
| Control individual group | | | | | |
| Left ITG | 37 | 1005 | <.001 | 3.66 | -54, -64, 0 |
| Left ACC | 32 | 1835 | <.001 | 3.57 | -12, 34, 24 |
| Left DLPFC (MFG) | 9 | | | 3.45 | -2, 50, 16 |
| Right fusiform gyrus | 37 | 985 | <.001 | 3.45 | 44, -60, -12 |
| Right DLPFC (IFG) | 45 | 286 | .02 | 3.16 | 42, 12, 20 |
| Right SFG | 9/8 | 306 | .01 | 3.13 | 6, 50, 32 |
| Left supramarginal gyrus | | 264 | .04 | 2.79 | -52, -48, 28 |

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BD, bipolar disorder; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; SFG, superior frontal gyrus; SOG, superior occipital gyrus; STG, superior temporal gyrus.

*Tertiary peak.

†Secondary peak.

Left insular activation has been noted in positron emission tomographic studies of transient induced sadness,¹² whereas left insular hypermetabolism in adults with BD may predict the response to carbamazepine.⁶⁷ The role of the insula in autonomic arousal suggests that future studies could indirectly assess insular overactivation via psychophysiological measures.

It is notable that we did not find differences in amygdalar activation in either between-groups or within-groups comparisons. Activation of this mesial temporal structure may occur by using strong emotional stimuli.^{38,68,69} Increased amygdalar activation has been reported in adults with BD performing affect-related tasks.⁷ However, it is unclear if children activate the amygdala to the same extent in these tasks. Also, amygdalar dysfunction could occur later in the course of BD, only after sustained disrupted prefrontal modulation of amygdalar input. Alternately, the IAPS task may not be as suited to elicit amygdalar activation as, for example, a task involving facial expressions of fear or disgust.⁷⁰ Finally, the amygdala may reportedly habituate after repeated affective stimuli.⁷¹

The only areas in which controls showed greater activation were the cerebellar vermis, in the visuospatial working memory task, and the posterior cingulate, when viewing negative IAPS pictures. The vermis is a neocerebellar structure that has multiple higher cognitive functions, including executive function and working memory.⁷² It was also found to be relatively atrophied in adults with familial BD⁷³ and to have decreased *N*-acetylaspartate levels in offspring of parents with BD.⁷⁴ Therefore, the cerebellar vermis may represent an area in which patients with BD do not (or are not able to) preferentially activate compared with healthy individuals when performing a visuospatial working memory task. Possible reasons for decreased posterior cingulate activation in subjects with BD are less clear. This region receives major input from the DLPFC and OFC and may promote the evaluative function of emotional memory. A relationship has also been found between the right retrosplenial cortex and unpleasant pictorial stimuli in healthy subjects,⁷⁵ so patients with pediatric BD may not have this association to the same degree.

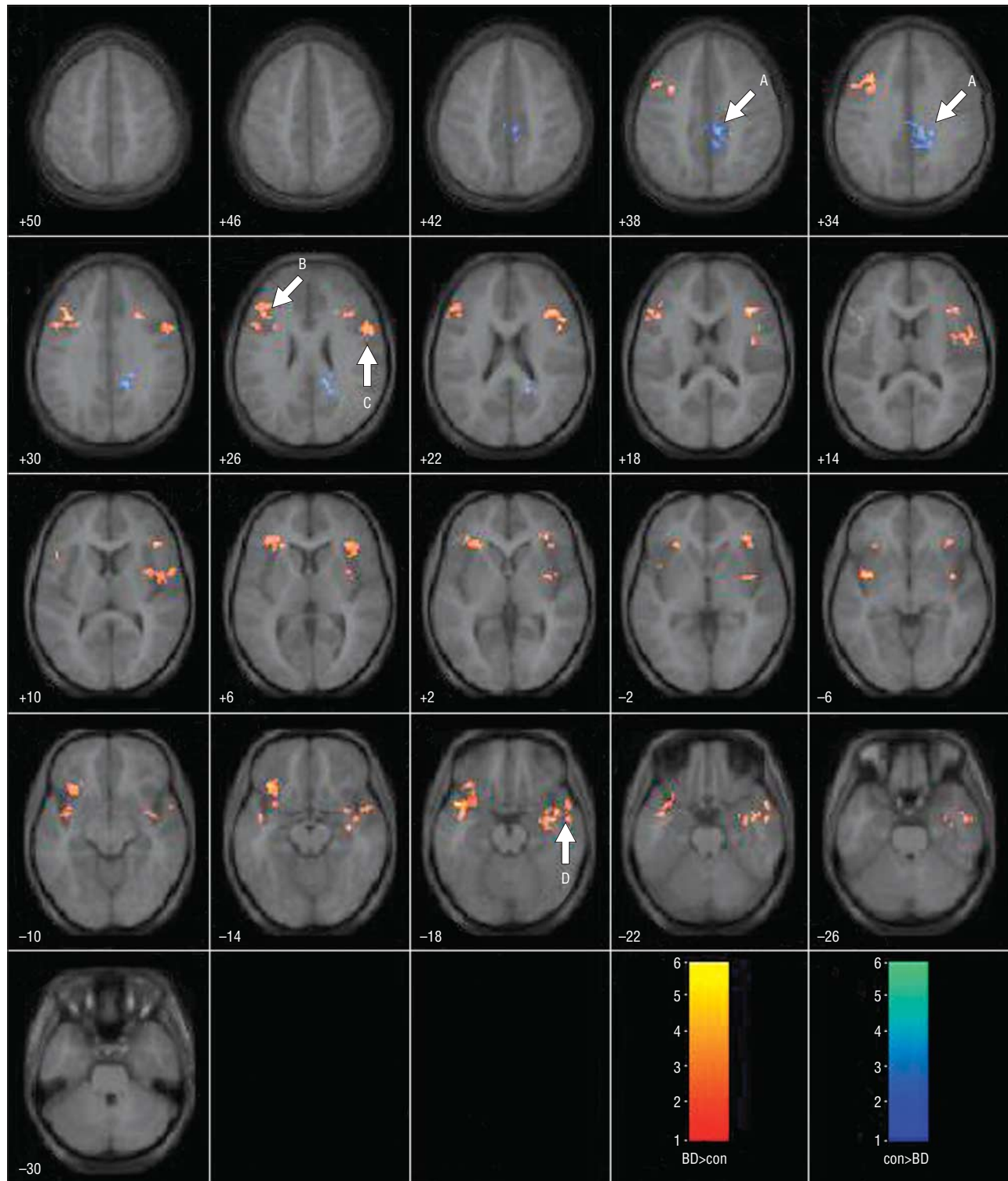


Figure 4. Activation differences between subjects with bipolar disorder (BD) and controls (con) for the negative condition of the International Affective Picture System²⁹ task. Red areas indicate increased activation and blue areas indicate decreased activation when compared with controls. Numbers in the lower left corners indicate z-axis coordinates in the Talairach space. A indicates right posterior cingulate; B, left dorsolateral prefrontal cortex (DLPFC); C, right DLPFC; and D, right insula.

COMORBID ADHD

Of our subjects with BD, 92% also met the criteria for ADHD. Owing to the additional role of many of the discussed brain structures in the regulation of attention, it could be argued that increased activation of these areas

reflects the underlying pathophysiologic mechanisms of ADHD rather than BD. It is difficult to separate the contributions of these 2 disorders to our findings. However, given the high comorbidity of ADHD in pediatric BD,¹⁴ it is likely that pediatric BD is a single underlying disorder that adversely affects both mood and attention

Table 4. Brain Regional Activations for the IAPS Task: Positive Stimuli*

| Activated Region | BA | No. of Voxels | Cluster P Value | z Score, Maximum Primary Peak | Primary Peak Location (x, y, z) |
|--------------------------|-----|---------------|-----------------|-------------------------------|---------------------------------|
| BD – controls | | | | | |
| Left MFG | 10 | 704 | <.001 | 3.81 | -6, 60, 2 |
| Left paracentral lobule | 5/4 | 590 | <.001 | 3.68 | -18, -38, 48 |
| Left caudate/thalamus | | 273 | .04 | 3.65 | -16, -28, 20 |
| Right caudate/thalamus | | 3292 | <.001 | 3.64 | 20, -32, 18 |
| Left caudate head | | 327 | .01 | 3.42 | -4, 14, 0 |
| Left MFG | | 571 | <.001 | 3.31 | -24, -10, 44 |
| Left ACC† | 24 | | | 2.96 | -14, -14, 34 |
| Left precuneus | 7 | 331 | .01 | 3.26 | 0, -46, 54 |
| Left SFG | | 392 | .003 | 2.95 | -20, 14, 42 |
| Left MFG† | 6 | | | 2.71 | -36, 6, 34 |
| BD individual group | | | | | |
| Right MOG | 37 | 735 | <.001 | 3.49 | 46, -70, 4 |
| Right cerebellum‡ | | | | 3.30 | 40, -62, -18 |
| Left MFG | 10 | 482 | <.001 | 3.49 | -8, 60, 4 |
| Left ACC‡ | 32 | | | 3.44 | -2, 46, -4 |
| Left MOG | 18 | 723 | <.001 | 3.47 | -28, -88, 4 |
| Control individual group | | | | | |
| Right cuneus | 18 | 830 | <.001 | 3.56 | 14, -98, 2 |
| Right MOG† | 19 | | | 3.25 | 48, -74, -4 |

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BD, bipolar disorder; MFG, middle frontal gyrus; MOG, middle occipital gyrus; SFG, superior frontal gyrus.

*For controls minus BD, no clusters reached significance at $P < .05$.

†Tertiary peak.

‡Secondary peak.

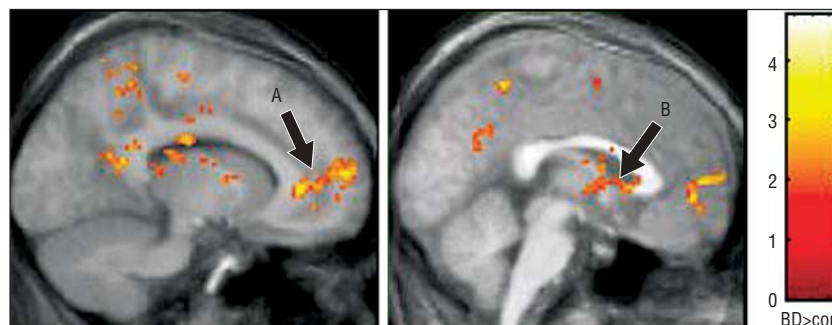


Figure 5. Areas of greater activation in subjects with bipolar disorder (BD) compared with controls (con) for the positive condition of the International Affective Picture System²³ task. A indicates left anterior cingulate; B, bilateral caudate and thalamus.

regulation and that our fMRI data reflect the underlying disorder of pediatric BD as a whole.

A PROPOSED INTERACTIVE MODEL

A model of brain circuitry dysfunction in BD consistent with our results centers around a prefrontal-subcortical theory of mood regulation.^{59,76,77} Subcortical structures such as the amygdala and hippocampus have long been thought to interact with cortical areas (eg, the cingulate, OFC, and insula) to create and process emotions.⁷⁸⁻⁸⁰ Whereas some subcortical structures bypass higher cortical input in circumstances requiring a quick reaction, they are also significantly interconnected with the prefrontal cortex, striatum, and thalamus.⁵⁹ Thus, prefrontal areas such as the DLPFC, ACC, and OFC have been postulated to reciprocally modulate limbic areas to exert cognitive control of affective responses.⁵⁹ Disruptions in the normal balance of activity in these 2 broad areas (ventral-limbic and dorsal-cortical) may lead to the

disruption of mood regulation. For example, adults with major depressive disorder may have increased ventral activity and decreased dorsal activity during depressed states,⁸¹ a finding that reverses during remission.^{48,81}

Although it is not possible to discern temporal sequences of activation within the tasks in our blocked design, increased prefrontal activation in our subjects with BD during both cognitive and affective tasks may be in response to increased activation in the ventral-limbic areas. Children with BD may require increased activation of prefrontal areas during euthymic periods to oppose or cortically control a hyperactive limbic system (**Figure 6**). Limbic areas may be overactivated by the emotional demands of a difficult task (visuospatial working memory task) or by direct affective stimuli (IAPS task). However, our subjects with BD did not display consistent limbic overactivity across both tasks, perhaps because of their euthymic state or the success of prefrontal structures in suppressing limbic hyperreactivity. Additionally, patients with BD may have relative deficiencies in more ef-

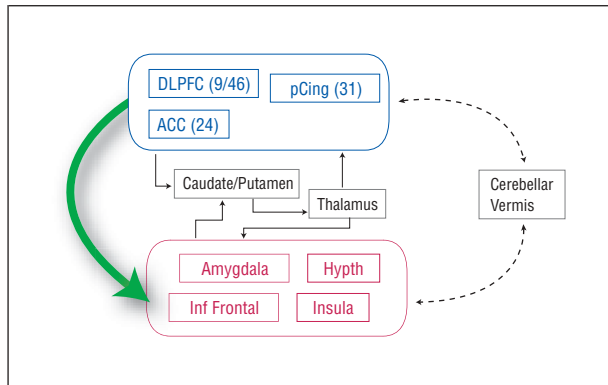


Figure 6. Cortical-limbic model of mood regulation showing relationships between the dorsolateral prefrontal cortex (DLPFC), posterior cingulate cortex (pCing), anterior cingulate cortex (ACC), amygdala, hypothalamus (hypth), inferior (inf) frontal area, and insula. Adapted from *Am J Psychiatry*, 156, 675-682, 1999.⁴⁸ Copyright 1999, the American Psychiatric Association; <http://ajp.psychiatryonline.org>. Reprinted by permission.

ficient prefrontal-limbic circuits, necessitating compensatory activation of other prefrontal areas.

According to this theory, patients with acute mania might demonstrate similar limbic overactivity but without sufficient prefrontal activity to remain euthymic. This manifestation would be consistent with findings of decreased prefrontal activity and neuronal and glial density in adults with BD; that is, with a longer duration of illness, prefrontal deficits may enlarge and eventually lead to reduced or less effective activation instead of overactivation in response to relevant tasks. A patient with BD in this latter state would theoretically be more vulnerable to stressors triggering mood episodes without sufficient prefrontal input to modulate increased subcortical activity, a theory in line with the kindling hypothesis of illness progression in BD.⁸² Further study of patients with BD across different mood and developmental states is needed to test these hypotheses.

LIMITATIONS AND STRENGTHS

All subjects with BD in our study were taking concomitant psychotropic medications, of which the effects on cerebral activation patterns are unknown. Stimulants, however, were withheld for 24 to 48 hours before fMRI to minimize their behavioral and cerebral effects. There have been reports of increased caudate activity⁸³ and decreased ACC activity⁸⁴ associated with antipsychotic medications as well as decreased ventral ACC activity associated with antidepressants.^{81,85} Although between-group caudate differences may have been related to this phenomenon, it is unlikely to explain the findings of increased ACC activity in subjects with BD. Unfortunately we were not able to divide the subjects into groups based on medication types that would be meaningful for statistical analyses owing to the wide variety of medications (Table 1).

Because there was a trend for subjects with BD having less accuracy in the 2-back task, it is possible that these subjects were using more effort to perform the task. Additional effort could result in patterns of increased activation. Although the sample size was small, the success-

ful completion of an fMRI study in 12 children with a serious neuropsychiatric disorder such as BD is an accomplishment given pragmatic issues such as subject compliance. All of our subjects were male, primarily white, so these findings may not be generalizable to girls or boys of other ethnicities who have BD. Finally, we did not formally assess pubertal status, which may have affected the analyses considering the substantial hormonal and potential neurobiological changes associated with puberty.

The strengths of the study included a relatively homogeneous subject group, with both subjects and parents diagnosed using semistructured interviews. Our controls were also screened with high scrutiny; other studies often have not considered extended family history. This is essential in studies of children because they retain the potential to develop affective disorders; historically the most common age at onset of BD has ranged from 15 to 19 years.⁸⁶ Furthermore, this study was performed using a high-field magnet (3 T), which provides a significantly higher signal-to-noise ratio compared with 1.5-T studies, increasing the specificity of the findings and decreasing type II error.

Finally, our study design is also unique because we used a dual approach of cognitive and affective tasks to probe the brain regions relevant to pediatric BD. Temporal analysis of results from future event-related tasks may help to prove or disprove theories of disrupted prefrontal-subcortical reciprocal modulation in BD, as suggested by our results. Longitudinal fMRI studies of the brain, with greater numbers of subjects and of patients with early forms of BD, would aid in discerning the role of these brain areas in the pathophysiologic mechanisms of BD and in bridging the gap between studies of children and studies of adults with this disorder.

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REFERENCES

- Geller B, Zimmerman B, Williams M, Bolhofner K, Craney JL, Delbello MP, Soutullo CA. Six-month stability and outcome of a prepubertal and early adolescent bipolar disorder phenotype. *J Child Adolesc Psychopharmacol*. 2000;10:165-173.
- Findling RL, Gracious BL, McNamara NK, Youngstrom EA, Demeter CA, Branicky LA, Calabrese JR. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. *Bipolar Disord*. 2001;3:202-210.

3. Baxter LR Jr, Phelps ME, Mazziotta JC, Schwartz JM, Gerner RH, Selin CE, Sumida RM. Cerebral metabolic rates for glucose in mood disorders: studies with positron emission tomography and fluorodeoxyglucose F 18. *Arch Gen Psychiatry*. 1985;42:441-447.
4. Silfverskiold P, Risberg J. Regional cerebral blood flow in depression and mania. *Arch Gen Psychiatry*. 1989;46:253-259.
5. Blumberg HP, Stern E, Martinez D, Ricketts S, de Asis J, White T, Epstein J, McBride PA, Eidelberg D, Kocsis JH, Silbersweig DA. Increased anterior cingulate and caudate activity in bipolar mania. *Biol Psychiatry*. 2000;48:1045-1052.
6. Ketter TA, George MS, Kimbrell TA, Benson BE, Post RM. Functional brain imaging, limbic function, and affective disorders. *Neuroscientist*. 1996;2:55-65.
7. Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD. fMRI during affect discrimination in bipolar affective disorder. *Bipolar Disord*. 2000;2(suppl 3, pt 2):237-248.
8. Winsberg ME, Sachs N, Tate DL, Adalsteinsson E, Spielman D, Ketter TA. Decreased dorsolateral prefrontal *N*-acetyl aspartate in bipolar disorder. *Biol Psychiatry*. 2000;47:475-481.
9. Chang K, Adelman N, Dienes K, Barnea-Goraly N, Reiss A, Ketter T. Decreased *N*-acetylaspartate in children with familial bipolar disorder. *Biol Psychiatry*. 2003;53:1059-1065.
10. Davanzo P, Thomas MA, Yue K, Oshiro T, Belin T, Strober M, McCracken J. Decreased anterior cingulate *myo*-inositol/creatine spectroscopy resonance with lithium treatment in children with bipolar disorder. *Neuropsychopharmacology*. 2001;24:359-369.
11. George MS, Ketter TA, Parekh PI, Horwitz B, Herscovitch P, Post RM. Brain activity during transient sadness and happiness in healthy women. *Am J Psychiatry*. 1995;152:341-351.
12. Pardo JV, Pardo PJ, Raichle ME. Neural correlates of self-induced dysphoria. *Am J Psychiatry*. 1993;150:713-719.
13. Mayberg HS. The functional neuroanatomy of mood: clues from imaging studies of depression and normal sadness. Paper presented at: Sixth Annual Conference of the Rotman Research Institute; 1996; Toronto, Ontario.
14. Faraone SV, Biederman J, Wozniak J, Mundy E, Mennin D, O'Donnell D. Is comorbidity with ADHD a marker for juvenile-onset mania? *J Am Acad Child Adolesc Psychiatry*. 1997;36:1046-1055.
15. MacDonald AW III, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*. 2000;288:1835-1838.
16. Thomas KM, King SW, Franzen PL, Welsh TF, Berkowitz AL, Noll DC, Birmaher V, Casey BJ. A developmental functional MRI study of spatial working memory. *Neuroimage*. 1999;10(suppl 3, pt 1):327-338.
17. Hesselinger B, Thiel T, Tebartz van Elst L, Hennig J, Ebert D. Attention-deficit disorder in adults with or without hyperactivity: where is the difference? a study in humans using short echo (1)H-magnetic resonance spectroscopy. *Neurosci Lett*. 2001;304:117-119.
18. Vogt BA, Finch DM, Olson CR. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb Cortex*. 1992;2:435-443.
19. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain*. 1995;118(pt 1):279-306.
20. Barch DM, Braver TS, Sabb FW, Noll DC. Anterior cingulate and the monitoring of response conflict: evidence from an fMRI study of overt verb generation. *J Cogn Neurosci*. 2000;12:298-309.
21. Peterson BS, Skudlarski P, Gatenby JC, Zhang H, Anderson AW, Gore JC. An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems. *Biol Psychiatry*. 1999;45:1237-1258.
22. Bush G, Frazier JA, Rauch SL, Seidman LJ, Whalen PJ, Jenike MA, Rosen BR, Biederman J. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. *Biol Psychiatry*. 1999;45:1542-1552.
23. Lang PJ, Bradley MM, Cuthbert BN. *International Affective Picture System (IAPS): Technical Manual and Affective Ratings*. Gainesville, Fla: National Institute of Mental Health Center for the Study of Emotion and Attention; 1997.
24. McManis MH, Bradley MM, Berg WK, Cuthbert BN, Lang PJ. Emotional reactions in children: verbal, physiological, and behavioral responses to affective pictures. *Psychophysiology*. 2001;38:222-231.
25. Faedda GL, Baldessarini RJ, Suppes T, Tondo L, Becker I, Lipschitz DS. Pediatric-onset bipolar disorder: a neglected clinical and public health problem. *Harv Rev Psychiatry*. 1995;3:171-195.
26. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition (SCID-I/P, version 2.0)*. New York, NY: Biometric Research, New York State Psychiatric Institute; 1995.
27. Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria: reliability and validity. *Arch Gen Psychiatry*. 1977;34:1229-1235.
28. Geller BG, Williams M, Zimerman B, Frazier J. *WASH-U-KSADS (Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia)*. St Louis, Mo: Washington University; 1996.
29. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, DelBello MP, Soutullo C. Reliability of the Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. *J Am Acad Child Adolesc Psychiatry*. 2001;40:450-455.
30. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36:980-988.
31. Fristad MA, Weller RA, Weller EB. The Mania Rating Scale (MRS): further reliability and validity studies with children. *Ann Clin Psychiatry*. 1995;7:127-132.
32. Young RC. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429-435.
33. Kovacs M. The Children's Depression, Inventory (CDI). *Psychopharmacol Bull*. 1985;21:995-998.
34. Corporation TP. *Wechsler Abbreviated Scale of Intelligence (WASI)*. San Antonio, Tex: Harcourt Brace & Co; 1999.
35. Kwon H, Reiss AL, Menon V. Neural basis of protracted developmental changes in visuo-spatial working memory. *Proc Natl Acad Sci U S A*. 2002;99:13336-13341.
36. Kwon H, Menon V, Eliez S, Warsofsky IS, White CD, Dyer-Friedman J, Taylor AK, Glover GH, Reiss AL. Functional neuroanatomy of visuospatial working memory in fragile X syndrome: relation to behavioral and molecular measures. *Am J Psychiatry*. 2001;158:1040-1051.
37. Northoff G, Richter A, Gessner M, Schlagenhaut F, Fell J, Baumgart F, Kaulisch T, Kotter R, Stephan KE, Leschinger A, Hagner T, Barger B, Witzel T, Hinrichs H, Bogerts B, Scheich H, Heinze HJ. Functional dissociation between medial and lateral prefrontal cortical spatiotemporal activation in negative and positive emotions: a combined fMRI/MEG study. *Cereb Cortex*. 2000;10:93-107.
38. Simpson JR, Ongur D, Akbudak E, Conturo TE, Ollinger JM, Snyder AZ, Gusnard DA, Raichle ME. The emotional modulation of cognitive processing: an fMRI study. *J Cogn Neurosci*. 2000;12(suppl 2):157-170.
39. Kim D, Adalsteinsson E, Glover G, Spielman S. *SVD Regularization Algorithm for Improved High-Order Shimming: Proceedings of the 8th Annual Meeting of the International Society for Magnetic Resonance in Medicine*. Denver, Colo: ISMRM; 2000.
40. Friston KJ, Holmes AP, Worsley J-P, Poline CD, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp*. 1995;2:189-210.
41. Talairach J, Tournoux P. *Co-Planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging*. New York, NY: Thieme Medical Publishers, Inc; 1988.
42. Brett M, Johnsrude IS, Owen AM. The problem of functional localization in the human brain. *Nat Rev Neurosci*. 2002;3:243-249.
43. Duvernoy HM. *The Human Brain: Surface, Three-Dimensional Sectional Anatomy With MRI, and Blood Supply*. New York, NY: Springer; 1999.
44. Holmes AP, Friston KJ. Generalisability, random effects and population inference. *Neuroimage*. 1998;7:S754.
45. Poline JB, Worsley KJ, Evans AC, Friston KJ. Combining spatial extent and peak intensity to test for activations in functional imaging. *Neuroimage*. 1997;5:83-96.
46. Hollingshead A. *Two Factor Index of Social Position*. New Haven, Conn: Yale University Department of Sociology; 1957.
47. Strakowski SM, DelBello MP, Adler C, Cecil DM, Sax KW. Neuroimaging in bipolar disorder. *Bipolar Disord*. 2000;2(suppl 3, pt 1):148-164.
48. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry*. 1999;156:675-682.
49. Carlson S, Martinkauppi S, Rama P, Salli E, Korvenoja A, Aronen HJ. Distribution of cortical activation during visuospatial n-back tasks as revealed by functional magnetic resonance imaging. *Cereb Cortex*. 1998;8:743-752.
50. Casey BJ, Cohen JD, O'Craven K, Davidson RJ, Irwin W, Nelson CA, Noll DC, Hu X, Lowe MJ, Rosen BR, Truwitt CL, Turski PA. Reproducibility of fMRI results across four institutions using a spatial working memory task. *Neuroimage*. 1998;8:249-261.
51. D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J. Functional MRI studies of spatial and nonspatial working memory. *Brain Res Cogn Brain Res*. 1998;7:1-13.
52. Nelson CA, Monk CS, Lin J, Carver LJ, Thomas KM, Truwitt CL. Functional neuroanatomy of spatial working memory in children. *Dev Psychol*. 2000;36:109-116.
53. Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biol Psychiatry*. 2001;49:741-752.

54. Rubinsztein JS, Fletcher PC, Rogers RD, Ho LW, Aigbirhio FI, Paykel ES, Robbins TW, Sahakian BJ. Decision-making in mania: a PET study. *Brain*. 2001; 124(pt 12):2550-2563.
55. Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, Rauch SL. The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol Psychiatry*. 1998; 44:1219-1228.
56. Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, Raichle ME. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 1997; 386:824-827.
57. Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci U S A*. 1998;95:13290-13295.
58. Botteron KN, Raichle ME, Drevets WC, Heath AC, Todd RD. Volumetric reduction in left subgenual prefrontal cortex in early onset depression. *Biol Psychiatry*. 2002;51:342-344.
59. Lichten DG, Cummings JL. Introduction and overview. In: Lichten DG, Cummings JL, eds. *Frontal-Subcortical Circuits in Psychiatric and Neurological Disorders*. New York, NY: Guilford Press; 2001:1-43.
60. Blumberg HP, Stern E, Ricketts S, Martinez D, de Asis J, White T, Epstein J, Isenberg N, McBride PA, Kemperman I, Emmerich S, Dhawan V, Eidelberg D, Kocsis JH, Silbersweig DA. Rostral and orbital prefrontal cortex dysfunction in the manic state of bipolar disorder. *Am J Psychiatry*. 1999;156:1986-1988.
61. Dupont RM, Jernigan TL, Heindel W, Butters N, Shafer K, Wilson T, Hesselink J, Gillin JC. Magnetic resonance imaging and mood disorders: localization of white matter and other subcortical abnormalities. *Arch Gen Psychiatry*. 1995;52:747-755.
62. Dewan MJ, Haldipur CV, Lane EE, Ispahani A, Boucher MF, Major LF. Affective disorder, I: comprehensive quantitative computed tomography. *Acta Psychiatr Scand*. 1988;77:670-676.
63. Dasari M, Friedman L, Jesberger J, Stuve TA, Findling RL, Swales TP, Schulz SC. A magnetic resonance imaging study of thalamic area in adolescent patients with either schizophrenia or bipolar disorder as compared to healthy controls. *Psychiatry Res*. 1999;91:155-162.
64. Deicken RF, Eliaz Y, Feiwell R, Schuff N. Increased thalamic N-acetylaspartate in male patients with familial bipolar I disorder. *Psychiatry Res*. 2001;106:35-45.
65. Aylward EH, Roberts-Twillie JV, Barta PE, Kumar AJ, Harris GJ, Geer M, Peyser CE, Pearlson GD. Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. *Am J Psychiatry*. 1994;151:687-693.
66. Noga JT, Vldar K, Torrey EF. A volumetric magnetic resonance imaging study of monozygotic twins discordant for bipolar disorder. *Psychiatry Res*. 2001;106: 25-34.
67. Ketter TA, Kimbrell TA, George MS, Willis MW, Benson BE, Danielson A, Frye MA, Herscovitch P, Post RM. Baseline cerebral hypermetabolism associated with carbamazepine response, and hypometabolism with nimodipine response in mood disorders. *Biol Psychiatry*. 1999;46:1364-1374.
68. Irwin W, Davidson RJ, Lowe MJ, Mock BJ, Sorenson JA, Turski PA. Human amygdala activation detected with echo-planar functional magnetic resonance imaging. *Neuroreport*. 1996;7:1765-1769.
69. Garavan H, Pendergrass JC, Ross TJ, Stein EA, Risinger RC. Amygdala response to both positively and negatively valenced stimuli. *Neuroreport*. 2001; 12:2779-2783.
70. Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR. The amygdala response to emotional stimuli: a comparison of faces and scenes. *Neuroimage*. 2002;17:317-323.
71. Breiter HC, Etkoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, Strauss MM, Hyman SE, Rosen BR. Response and habituation of the human amygdala during visual processing of facial expression. *Neuron*. 1996;17:875-887.
72. Desmond JE, Gabrieli JD, Wagner AD, Ginier BL, Glover GH. Lobular patterns of cerebellar activation in verbal working-memory and finger-tapping tasks as revealed by functional MRI. *J Neurosci*. 1997;17:9675-9685.
73. Brambilla P, Harenski K, Nicoletti M, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC. MRI study of posterior fossa structures and brain ventricles in bipolar patients. *J Psychiatr Res*. 2001;35:313-322.
74. Cecil KM, DelBello MP, Sellars MC, Strakowski SM. Proton magnetic resonance spectroscopy of the frontal lobe and cerebellar vermis in children with a mood disorder and a familial risk for bipolar disorders. *J Child Adolesc Psychopharmacol*. 2003;13:545-555.
75. Maddock RJ. The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. *Trends Neurosci*. 1999;22:310-316.
76. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiatry Clin Neurosci*. 1997;9:471-481.
77. Blumberg HP, Charney DS, Krystal JH. Frontotemporal neural systems in bipolar disorder. *Semin Clin Neuropsychiatry*. 2002;7:243-254.
78. Papez JW. A proposed mechanism of emotion. *Arch Neurol Psychiatry*. 1937; 38:725-733.
79. Yakovlev PI. Motility, behavior, and the brain. *J Nerv Ment Dis*. 1948;107:313-335.
80. MacLean PD. Psychosomatic disease and the "visceral brain": recent developments bearing on the Papez theory of emotion. *Psychosom Med*. 1949;11:338-353.
81. Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, Jerabek PA. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biol Psychiatry*. 2000;48:830-843.
82. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry*. 1992;149:999-1010.
83. Buchsbaum MS, Hazlett EA, Haznedar MM, Spiegel-Cohen J, Wei TC. Visualizing fronto-striatal circuitry and neuroleptic effects in schizophrenia. *Acta Psychiatr Scand Suppl*. 1999;395:129-137.
84. Holcomb HH, Cascella NG, Thaker GK, Medoff DR, Dannals RF, Tamminga CA. Functional sites of neuroleptic drug action in the human brain: PET/FDG studies with and without haloperidol. *Am J Psychiatry*. 1996;153:41-49.
85. Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, Silva JA, McGinnis S, Glass TG, Martin CC, Fox PT. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport*. 1997;8:1057-1061.
86. Goodwin FK, Jamison KR. *Manic-Depressive Illness*. New York, NY: Oxford University Press; 1990.