

Functional and Structural Connectivity Between the Perigenual Anterior Cingulate and Amygdala in Bipolar Disorder

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Objective: Abnormalities in the morphology and function of two gray matter structures central to emotional processing, the perigenual anterior cingulate cortex (pACC) and amygdala, have consistently been reported in bipolar disorder (BD). Evidence implicates abnormalities in their connectivity in BD. This study investigates the potential disruptions in pACC-amygdala functional connectivity and associated abnormalities in white matter that provides structural connections between the two brain regions in BD.

Methods: Thirty-three individuals with BD and 31 healthy comparison subjects (HC) participated in a scanning session during which functional magnetic resonance imaging (fMRI) during processing of face stimuli and diffusion tensor imaging (DTI) were performed. The strength of pACC-amygdala functional connections was compared between BD and HC groups, and associations between these functional connectivity measures from the fMRI scans and regional fractional anisotropy (FA) from the DTI scans were assessed.

Results: Functional connectivity was decreased between the pACC and amygdala in the BD group compared with HC group, during the processing of fearful and happy faces ($p < .005$). Moreover, a significant positive association between pACC-amygdala functional coupling and FA in ventrofrontal white matter, including the region of the uncinate fasciculus, was identified ($p < .005$).

Conclusion: This study provides evidence for abnormalities in pACC-amygdala functional connectivity during emotional processing in BD. The significant association between pACC-amygdala functional connectivity and the structural integrity of white matter that contains pACC-amygdala connections suggest that disruptions in white matter connectivity may contribute to disturbances in the coordinated responses of the pACC and amygdala during emotional processing in BD.

Key Words: Amygdala, anterior cingulate cortex, bipolar disorder, diffusion tensor imaging, fMRI, functional connectivity, magnetic resonance imaging

The perigenual anterior cingulate cortex (pACC) and the amygdala play key roles in the emotional processes disrupted in BD, thereby implicating them in the disorder. Convergent evidence suggests that the pACC shares extensive connections with the amygdala (1,2) and provides regulation of the amygdala response, essential to emotional processing (3). Morphometric magnetic resonance imaging (MRI) and conventional functional MRI (fMRI) analyses provide convergent evidence of morphological and functional abnormalities within the pACC and amygdala in BD (4–10). During emotional processing in persons with BD, dysregulated pACC responses are accompanied by excessive amygdala responses (4,5), suggesting a dis-

ruption in pACC-amygdala functional connections. However, conventional fMRI activation analyses do not assess the functional connections between brain structures. Herein we assessed the strength of the correlation in time between the blood oxygen level-dependent (BOLD) responses in the pACC and amygdala during the processing of emotional stimuli. This technique has been used previously as a measure of the strength of pACC-amygdala functional connectivity during emotional processing (11). We hypothesized that there would be reduced pACC-amygdala functional connectivity during emotional processing in BD.

Increasing evidence implicates abnormalities in the structural integrity of frontal white matter in BD. This includes recent evidence for susceptibility in individuals with BD to genetic variations with potential to influence adversely the development of white matter connectivity (12,13), as well as for decreases in the density of glia, including oligodendrocytes, and expression of oligodendrocyte- and myelination-related factors in postmortem studies of frontal cortex in BD (14–17). MRI studies provide further evidence for white matter abnormalities in BD, including abnormalities in the volume and structural integrity of frontal white matter (18–20).

Diffusion tensor imaging (DTI) presents the opportunity to measure the organization and coherence of white matter fibers (21). Fractional anisotropy (FA) is a DTI measure of white matter organization that provides an index of the coordinated directionality of fibers within a white matter region (22). In the study of neurologic disorders, functional connectivity and DTI methods have been combined to show abnormalities in both the functional connectivity and white matter connections between brain regions (23,24), suggesting that structural abnormalities might

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contribute to functional connectivity abnormalities in the disorders. A combination of functional and structural connectivity techniques was applied herein to test the second hypothesis of this study that there would be an association between the pACC-amygdala functional connections and the structural integrity of the pACC-amygdala white matter connections, including the uncinate fasciculus, which provides major white matter connections between these structures (25,26).

Methods and Materials

Subjects

The Structured Clinical Interview for DSM-IV Axis I Disorders Version 2.0 (27) confirmed the presence or absence of Axis I Disorders and mood state at scanning for the 33 BD and 31 healthy comparison (HC) participants. Symptoms were assessed using the Hamilton Depression Rating Scale (28) and Clinician-Administered Rating Scale for Mania (29). No subject had a history of neurologic illness, head trauma with loss of consciousness over 5 min, or major medical disorder with the exception of three female BD participants with treated hypothyroidism. The HC participants did not have a history of Axis I disorder themselves or a history of a mood, psychotic, anxiety, or substance-related disorder in their first-degree family members. Tables 1 and 2 provide sample details. After a complete description of the study, written informed consent was obtained from all participants in accordance with the human investigation committees of the Yale School of Medicine and the Department of Veterans Affairs.

MRI Data Acquisition

The fMRI and DTI data were acquired in the same scanning session for each subject with a 3-Tesla siemens Trio MR scanner (Siemens, Erlangen, Germany). The fMRI data were acquired with a single-shot echo planar imaging (EPI) sequence in alignment with the anterior commissure–posterior commissure plane

Table 1. Sample Demographics and Behavioral Measures

	HC	BD
Number (Male)	31 (14)	33 (10)
Age (Years, Mean \pm SD)	30.4 \pm 10.8	31.8 \pm 9.6
HAMD (Mean \pm SD) ^a	0.7 \pm 1.2	10.8 \pm 12.8
CARS-M (Mean \pm SD) ^a	0.2 \pm 0.5	4.9 \pm 6.2
Current Tobacco Use (Yes:No) ^a	2:29	11:22
Reaction Time (msecs, Mean \pm SD)		
Fear	848.7 \pm 170.8	862.6 \pm 161.4
Happy	819.4 \pm 144.5	864.9 \pm 150.9
Neutral	812.0 \pm 153.3	858.8 \pm 158.5
Response Accuracy (% Correct, Mean \pm SD)		
Fear	97.3 \pm 4.6	98.6 \pm 3.0
Happy	97.3 \pm 4.1	98.3 \pm 3.2
Neutral	97.0 \pm 4.9	98.1 \pm 3.4

HC, healthy control subjects; BD, bipolar disorder patients; SD, standard deviation; HAMD, Hamilton Depression Rating Scale; CARS-M, Clinician-Administered Rating Scale for Mania.

^aGroup comparisons revealed significant differences (all P s < .05), with increased HAMD, CARS-M, and tobacco usage in the participants with BD relative to the HCs. For all other factors listed in this table, group comparisons were not significant (all P s > .10). HAMD scores as mean \pm SD for the different mood states: depressed, 28.14 \pm 7.1; euthymic, 7.12 \pm 6.7; manic/mixed or hypomanic, 4.60 \pm 4.6; CARS-M scores as mean \pm SD for the different mood states: depressed, 5.00 \pm 3.3; euthymic, 3.38 \pm 3.4; manic/mixed or hypomanic, 7.10 \pm 10.1.

Table 2. Comparisons of Functional Connectivity and Diffusion Tensor Imaging Indexes in Participants with Bipolar Disorder

Characteristics of Participants with Bipolar Disorder	n (%)	p Values		
		Fear FC ^a	Happy FC ^a	Ventrofrontal FA ^a
Mood State				
Manic/mixed or hypomanic	10 (30%)			
Depressive	7 (21%)	.883	.820	.104
Euthymic	16 (48%)			
Rapid Cycling	19 (58%)	.166	.395	.999
History of Substance-related Disorders ^b	17 (51%)	.390	.440	.095
Medication				
Unmedicated	6 (18%)	.518	.244	.993
Lithium carbonate	9 (27%)	.406	.734	.073
Anticonvulsants	16 (48%)	.279	.513	.885
Atypical antipsychotics	14 (42%)	.956	.791	.679
Antidepressants	12 (36%)	.510	.416	.398
Benzodiazepines	7 (21%)	.112	.135	.166

^aGroup comparisons were conducted for perigenual anterior cingulate cortex-amygdala functional connectivity (FC) during fearful and happy face processing and for ventrofrontal fractional anisotropy (FA). Comparisons were conducted across the three mood states and for the presence/absence of rapid cycling, history of substance related disorders, medications overall and each medication class at the time of scanning.

^bThis included 13 (39%) with a history of alcohol abuse or dependence, 9 (27%) of whom also had a history of other substance abuse or dependence, and an additional 4 (12%) BD participants who had a history of other substance abuse or dependence.

with the following parameters repetition time [TR] = 2000 msec; echo time [TE] = 25 msec; matrix = 64 \times 64; field of view [FOV] = 240 mm \times 240 mm and 32 three-millimeter slices without gap. The DTI data were acquired in alignment with the fMRI data with diffusion sensitizing gradients applied along 32 noncollinear directions with b-value = 1000 secs/mm², together with an acquisition without diffusion weighting (b-value = 0; TR = 7400 msec; TE = 115 msec; matrix = 128 \times 128; FOV = 256 mm \times 256 mm and 40 three-millimeter slices without gap).

Emotional Face Paradigm

During the fMRI runs, an event-related emotional face task was completed by each participant. Participants viewed faces from the Ekman series depicting fearful, happy, or neutral expressions and were instructed to press a button to make a male-female determination, as described previously (30).

Functional Connectivity Processing

Statistical Parametric Mapping (SPM) software (<http://www.fil.ion.ucl.ac.uk/spm>) was used for BOLD fMRI preprocessing, as described previously (30). Briefly, images were realigned, spatially normalized to a standard EPI template from the Montreal Neurological Institute (MNI), and spatially smoothed.

The pACC seed region of interest (ROI) was defined with the Wake Forest University PickAtlas Tool (<http://www.fmri.wfubmc.edu/download.htm>) on the basis of its ACC region excluding the dorsal component (31). For each subject, a mean time series for the pACC seed ROI was calculated by averaging the time series for all voxels within the pACC ROI. Correlational analyses were then performed between the pACC time series and the time series for each brain voxel (32,33), resulting in a correlation map for each subject that contained the correlation coefficient for

each voxel with that of the pACC ROI. For further statistical analysis, the correlation coefficients were transformed to *Z* values using Fisher *r*-to-*z* transformation (34).

DTI Data Processing

Diffusion-weighted data were first interpolated to 1.5-mm isotropic voxels and then denoised by a three-dimensional isotropic Gaussian kernel with Sigma 2 mm full-width-at-half-maximum (FWHM) Gaussian kernel. After diagonalization of the DTI data, diffusion eigenvectors, and corresponding eigenvalues (λ_1 , λ_2 , λ_3) were acquired. FA was then calculated according to the methodology of Basser *et al.* (35):

$$FA = \frac{\sqrt{3[(\lambda_1 - \langle\lambda\rangle)^2 + (\lambda_2 - \langle\lambda\rangle)^2 + (\lambda_3 - \langle\lambda\rangle)^2]}}{\sqrt{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}},$$

$$\langle\lambda\rangle = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

Whole brain FA maps were normalized with SPM5 to the standard MNI space using a tissue probability map of white matter as a template. The FA maps were resampled to 2 mm \times 2 mm \times 2 mm during the normalization. Furthermore, each FA map was spatially smoothed by a 10-mm FWHM. FA values at each brain voxel were submitted to a linear-regression analysis in SPM (discussed subsequently) to determine the relationship between FA values throughout the brain and pACC-amygdala functional connectivity.

Statistical Analyses

To test the primary study hypothesis, group differences were analyzed using two-sample *t* tests in SPM with the functional connectivity correlation coefficients (*Z* scores) from the pACC to all brain voxels as the dependent variables for each face condition (fearful, happy, and neutral face expressions). Findings were considered significant for $p < .005$ (uncorrected) and for clusters $>640 \text{ mm}^3$ (10 voxels).

To test the second study hypothesis regarding the relationship between functional and structural pACC-amygdala connectivity, correlation coefficients (*Z* scores) for each face condition in which group differences in pACC-amygdala connectivity were detected were extracted from the amygdala (defined with the MarsBar toolbox; <http://marsbar.sourceforge.net>). Whole-brain linear regression analysis was performed in SPM to investigate the association between these pACC-amygdala correlation coefficients (exploratory variables) and FA values (dependent variables) at all brain voxels for all participants. Findings were considered significant for $p < .005$ (uncorrected) and for clusters $>640 \text{ mm}^3$ (80 voxels). Finally, group differences in FA values from the point of highest association between FA and pACC-amygdala functional connectivity correlation coefficients were analyzed using two-sample *t* tests.

Results

There were no significant group differences in mean reaction time or response accuracy to the different face types (Table 1). We observed decreased pACC-amygdala functional connectivity in the BD group, compared with the HC group ($p < .005$), during fearful (Figure 1A and 1C) and happy (Figure 1B and 1D) face processing. No significant group differences in functional connectivity were detected during neutral face processing. Whole-brain analyses revealed additional group differences in functional connectivity from the pACC to the ventral caudate and

nucleus accumbens during fearful and happy processing, as well as decreased connectivity from the pACC to the right inferior temporal gyrus during fearful processing. Each of the amygdala findings remained significant after Bonferroni correction to account for the three face conditions considered; however, the additional findings in the striatum and cortex did not survive this correction.

Within the entire sample, regression analyses revealed a significant positive association between the pACC-amygdala functional coupling during fearful and happy face processing and FA values in the region of the uncinate fasciculus and neighboring ventrofrontal white matter ($p < .005$; Figure 2). These findings remained significant when Bonferroni correction was applied to account for analyses performed in the two emotional face conditions. Significant positive associations between pACC-amygdala functional connectivity and FA were also detected in other distributed white matter regions including regions of fronto-thalamo-striatal projections, as well as fronto-temporal projections to posterior association cortex. The association between pACC-amygdala functional coupling and FA in the uncinate fasciculus region found in the entire sample was also present within the BD group alone (Fear: $r = .308$, $p = .041$; Happy: $r = .3$, $p = .045$), as well as the HC group alone (Fear: $r = .401$, $p = .013$; Happy: $r = .371$, $p = .02$). FA values were significantly decreased ($p = .04$) in the BD group (mean \pm SD = $.28 \pm .08$), relative to the HC group (mean \pm SD = $.32 \pm .06$), in the region where the functional-structural connectivity associations were detected ($x = -18 \text{ mm}$, $y = 18 \text{ mm}$, $z = -10 \text{ mm}$; sphere of radius = 2 mm).

Post hoc exploratory analyses performed in patients did not reveal any significant effects of mood state, rapid cycling, history of substance-related disorders, or medication status on pACC-amygdala functional connectivity or ventrofrontal FA (Table 2).

Discussion

We detected disturbances in pACC-amygdala functional connectivity during the processing of faces depicting positive and negative emotions in BD. Moreover, we found an association between pACC-amygdala functional connectivity measurements and the structural integrity of ventrofrontal white matter, including the uncinate fasciculus where FA was also significantly decreased in the BD group. Taken together, these data provide some of the first evidence that abnormalities in the structural integrity of white matter may contribute to disruptions in the coordinated response of the pACC and amygdala to emotional stimuli in BD.

The pACC and amygdala are critical components of emotional processing circuitry and share extensive interconnections (1,2). Evidence has suggested that the pACC activates local inhibitory circuits in the amygdala, thereby regulating amygdala response (36,37). The decrease in pACC-amygdala functional connectivity in BD could reflect a reduction in the pACC's inhibitory control over the amygdala. Disrupted structural integrity of white matter bundles that contain pACC-amygdala connections, as reported herein, might contribute to pACC-amygdala functional connectivity deficits. PACC structural abnormalities (6,7) have also been reported in BD and may contribute to the circuitry dysfunction. Finally, abnormalities in a third structure with connectivity to both pACC and amygdala might play a role in the reduced functional connectivity between the regions. Therefore, further study of gray-white matter relationships and their associations to pACC-amygdala functional connectivity disruptions, and expo-

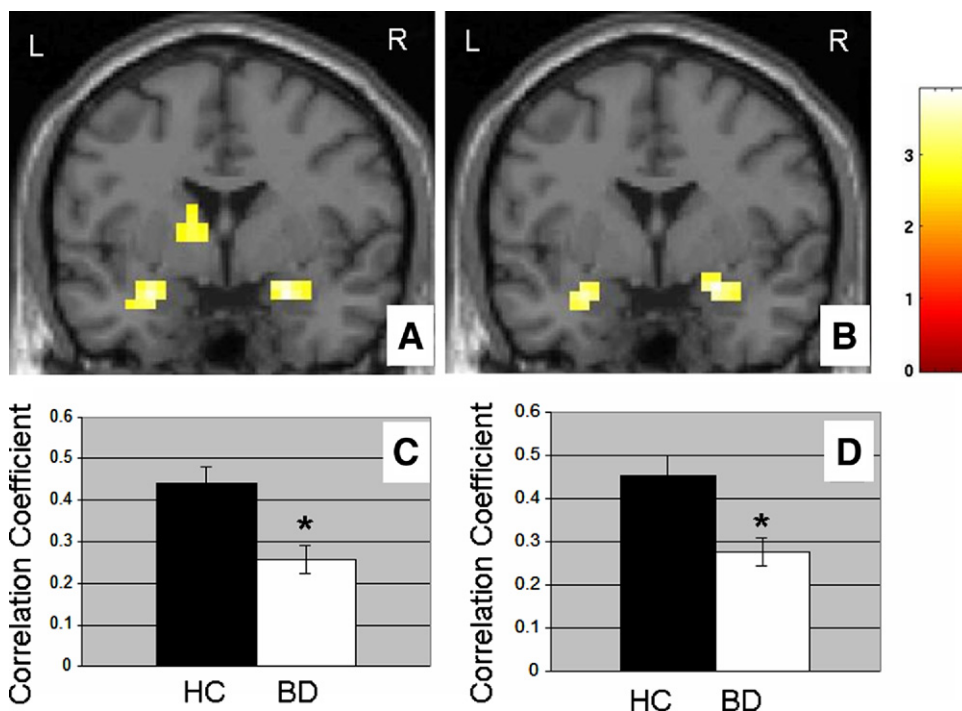


Figure 1. The coronal images (Montreal Neurological Institute [MNI] coordinates $y = 0$ mm) display the amygdala and ventral striatal regions where functional coupling to the perigenual anterior cingulate cortex (pACC) is decreased in the 33 participants with bipolar disorder (BD), compared with the 31 healthy comparison (HC) participants during (A) fearful face processing (MNI coordinates for the maximal point of difference in the amygdala: $x = -28$ mm, $y = 0$ mm, $z = -20$ mm, 22 voxels, $T = 3.63$, $p < .001$ uncorrected; $x = 24$ mm, $y = -4$ mm, $z = -20$ mm, 39 voxels, $T = 3.9$, $p < .001$ uncorrected) and (B) happy face processing (MNI coordinates for the maximal point of difference in the amygdala: $x = -28$ mm, $y = 0$ mm, $z = -20$ mm, 13 voxels, $T = 3.17$, $p = .001$ uncorrected; $x = 24$ mm, $y = 0$ mm, $z = -16$ mm, 28 voxels, $T = 3.46$, $p < .001$ uncorrected). The color bar represents the range of T values. The findings are displayed on a T1 image. L, left brain; R, right brain. The graph shows the mean correlation coefficients from the pACC to the amygdala and standard errors for the BD group ($n = 33$) and the HC ($n = 31$) group during (C) fearful face processing and (D) happy face processing. *denotes significant decreases.

ration of abnormalities in other regions with connectivity to pACC and amygdala, are required to advance understanding of the interconnections between the pACC and amygdala. Of note, results from conventional functional activation analyses show pACC activation decreases in the BD group compared with the

HC group, during fearful and happy face processing (Supplement 1). No group differences were observed in amygdala activation. The absence of group differences in amygdala activation, despite the significant decreases in pACC-amygdala connectivity, is unclear. A possible explanation is that our imaging

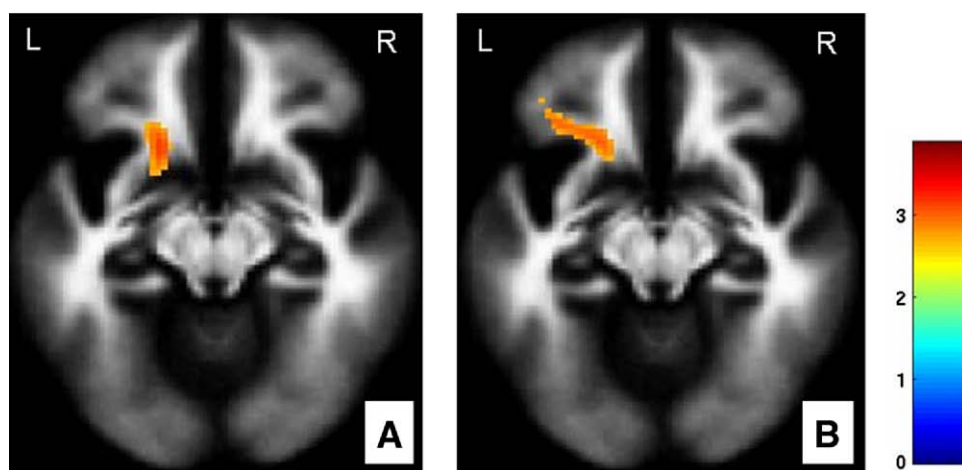


Figure 2. The axial-oblique images (Montreal Neurological Institute [MNI] coordinates $z = -12$ mm) display the regions in ventrofrontal white matter in which fractional anisotropy showed a positive association with functional coupling from perigenual anterior cingulate cortex to amygdala during (A) fearful processing (MNI coordinates for the point of maximal association: $x = -18$ mm, $y = 18$ mm, $z = -10$ mm, 107 voxels, $T = 3.32$, $p = .001$ uncorrected) and (B) happy processing (MNI coordinates for the point of maximal association: $x = -18$ mm, $y = 20$ mm, $z = -10$ mm, 157 voxels, $T = 2.88$, $p = .002$ uncorrected) in the entire cohort. The color bar represents the range of T values. The findings are displayed on a tissue probability map of white matter. L, left brain; R, right brain.

methods were more sensitive to detecting connectivity abnormalities than within-region amygdala abnormalities. Alternatively, connectivity abnormalities may have been especially prominent in this sample, or factors such as medication might have blunted amygdala differences (4). Other research groups that used similar functional connectivity methods to study disorders in which frontotemporal connectivity disturbances are implicated, such as schizophrenia, have similarly detected connectivity differences in the absence of activation differences within the connected brain regions (38).

White matter fibers that course through the ventral prefrontal cortex, including the uncinate fasciculus, are thought to provide the structural framework for the functional connections between the pACC and amygdala (25,26). We performed structural and functional connectivity measures in the same subjects, during the same scanning session, permitting examination of their relationship. Significant positive associations were identified between FA values in the region of the uncinate fasciculus and the correlation coefficients for functional coupling between the pACC and amygdala, suggesting that abnormalities in ventrofrontal white matter may contribute to disruptions in pACC-amygdala functional connectivity in BD. A recent DTI tractography study reported an increase in the number of fibers connecting the subgenual cingulate and amygdalohippocampal complex in BD (39), providing a view of white matter abnormalities in BD complementary to that described herein. However, this study did not detect FA reductions in these fibers. Potential explanations for the divergent results between the two studies may include variances in the specific fibers studied due to the different imaging processing and analysis methodologies and differences in sample characteristics. Future work using complementary DTI imaging methods in a single study, as well as collaborative studies across imaging centers using comparable methods, could help resolve discrepant results.

The functional connectivity analyses revealed significant decreases in pACC-amygdala functional coupling in BD during the processing of fearful and happy faces, but not during processing of emotionally neutral faces. This is consistent with previous functional neuroimaging studies that have shown engagement of this circuitry in response to both fearful and happy faces (40–42) and the efficacy of emotionally valenced faces as stimuli to study pACC-amygdala interactions in functional connectivity analyses (11). Moreover, it supports the utility of this approach to probe abnormalities in pACC-amygdala functional connectivity in disorders of affective regulation.

Reduced functional coupling from pACC was also detected in the ventral caudate and nucleus accumbens, although these findings did not survive more stringent corrections for multiple comparisons. The ventral caudate and nucleus accumbens are interconnected with pACC and amygdala (25,43) and are implicated in BD because of their role in motivated behaviors that are dysregulated in the disorder and findings of alterations in their shape, volume, and activation in BD (44–46). In addition to ventrofrontal areas, regions in which the structural integrity of white matter were associated with pACC-amygdala coupling included fronto-thalamo-striatal projections and projections to posterior sensory regions that provide connections within a more widely distributed neural system. This suggests that disruptions in pACC-amygdala connectivity may be associated with abnormalities in the development of a more widely distributed neural system subserving emotional regulation (47).

Participants with BD were in different mood states and had variable histories of rapid-cycling, comorbidity, and medication

and substance exposure. Although we did not detect significant main effects of these factors on pACC-amygdala functional connectivity or ventrofrontal FA, our ability to detect effects of these factors was potentially limited by inadequate power. We also performed our analyses with current tobacco use as a covariate, yielding equivalent results. Additional studies reporting reduced functional connectivity in manic participants (48), as well as across acute mood states and euthymia (49), suggest that functional connectivity disturbance may be a trait abnormality in BD. Most of our BD participants reported symptom onset in adolescence/early adulthood. Interestingly, ACC receives a progressive and dramatic growth of fibers originating from the amygdala during adolescence/early adulthood (50), a period coinciding with this peak in the onset of BD, suggesting that further study in the development of the ACC-amygdala connectivity in adolescence/early adulthood in BD may help to elucidate a neurodevelopmental mechanism contributing to the disorder.

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Supplementary material cited in this article is available online.

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