Global Prefrontal and Fronto-Amygdala Dysconnectivity in Bipolar I Disorder with Psychosis History

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Background: Pathophysiological models of bipolar disorder postulate that mood dysregulation arises from fronto-limbic dysfunction, marked by reduced prefrontal cortex (PFC) inhibitory control. This might occur due to both disruptions within PFC networks and abnormal inhibition over subcortical structures involved in emotional processing. However, no study has examined global PFC dysconnectivity in bipolar disorder and tested whether regions with within-PFC dysconnectivity also exhibit fronto-limbic connectivity deficits. Furthermore, no study has investigated whether such connectivity disruptions differ for bipolar patients with psychosis history, who might exhibit a more severe clinical course.

Methods: We collected resting-state functional magnetic resonance imaging at 3 T in 68 remitted bipolar I patients (34 with psychosis history) and 51 demographically matched healthy participants. We employed a recently developed global brain connectivity method, restricted to PFC (rGBC). We also independently tested connectivity between anatomically defined amygdala and PFC.

Results: Bipolar patients exhibited reduced medial prefrontal cortex (mPFC) rGBC, increased amygdala–mPFC connectivity, and reduced connectivity between amygdala and dorsolateral PFC. All effects were driven by psychosis history. Moreover, the magnitude of observed effects was significantly associated with lifetime psychotic symptom severity.

Conclusions: This convergence between rGBC, seed-based amygdala findings, and symptom severity analyses highlights that mPFC, a core emotion regulation region, exhibits both within-PFC dysconnectivity and connectivity abnormalities with limbic structures in bipolar illness. Furthermore, lateral PFC dysconnectivity in patients with psychosis history converges with published work in schizophrenia, indicating possible shared risk factors. Observed dysconnectivity in remitted patients suggests a bipolar trait characteristic and might constitute a risk factor for phasic features of the disorder.

Key Words: Amygdala, bipolar disorder, connectivity, prefrontal cortex, psychosis, resting-state

Bipolar disorder is characterized by prominent mood dysregulation (1). Pathophysiological models of bipolar illness suggest this dysregulation might arise from both dysfunction in prefrontal cortical (PFC) networks linked to cognitive control of emotion and disruptions in prefrontal control over subcortical regions involved in affective processing like the amygdaloid complex (2). Functional magnetic resonance imaging (fMRI) findings support this model by demonstrating abnormalities across subcortical/limbic and cortical structures, notably the amygdala and medial prefrontal cortex (mPFC) (3). These regions show mood-state-dependent activity alterations in bipolar disorder and have been linked to emotion generation and appraisal (4–7). Moreover, individuals with bipolar disorder show aberrant prefrontal activation across cognitive challenges (6,8), suggesting possible disturbances in prefrontal function. However, PFC is large and heterogeneous with widespread connectivity, and it is unclear which specific prefrontal circuits might be compromised in this disorder. Although evidence supports that localized structure and function of mPFC is disrupted in bipolar disorder (8), there is relatively little information about the relationships between PFC regions in bipolar illness. Complex neuropsychiatric disease like bipolar disorder might result from disrupted neural computations across networks of regions (9). Indeed, severe mood disorders are associated with abnormal structural plasticity and cellular resilience (10–12), which might give rise to impairments in distributed neural networks (9). Therefore, it is critical to identify prefrontal circuitry exhibiting distributed PFC functional abnormalities, which might relate to deficits in both PFC function and control over limbic structures. Yet, prefrontal dysconnectivity has not been systematically investigated in this illness.

A growing body of evidence shows that distributed neural circuits exhibit spontaneous activity at rest (13). These slow-frequency fluctuations are temporally correlated within spatially distinct but functionally related networks (14), establishing an intrinsic functional network architecture (15) across primate species (16). These networks show high concordance with other measures

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of structural and functional connectivity in healthy populations (17) and provide an opportunity to characterize distributed circuit abnormalities in neuropsychiatric illnesses (18). Prior research with resting-state techniques demonstrates that individuals with bipolar disorder show reduced connectivity within the "default mode network" (19), the pregenual anterior cingulate, thalamus and amygdala (20), as well as in the ventral prefrontal-amygdala pathways (21). Although these findings constitute important advances in our understanding of bipolar disorder, no study to date has investigated global prefrontal dysconnectivity patterns (i.e., across all prefrontal gray matter voxels). Such a global, data-driven approach is vital, because it allows comprehensive examination of prefrontal connectivity abnormalities. This in turn offers the potential to identify specific prefrontal nodes compromised in bipolar illness, which might also relate to regulation of limbic circuits.

Although identifying global prefrontal network disruption in bipolar illness is critical, such findings do not imply fronto-limbic dysconnectivity. To establish fronto-limbic dysconnectivity, both prefrontal and limbic connectivity must be assessed in the same subjects. It is well-recognized that amygdala shares dense connectivity with PFC, most notably caudal orbitofrontal cortex, mPFC, and anterior cingulate gyrus (22–25)—all regions implicated in regulation of emotion (among other functions). The critical point of such analyses is to independently test whether the same (or similar) regions identified via global connectivity might also exhibit connectivity disturbances with the amygdala. That is, examining deficits in limbic connectivity with broad PFC circuits is key to fully characterize deficits in fronto-limbic dysregulation in bipolar disorder.

Although we discussed bipolar disorder as a diagnostic category, bipolar illness is highly heterogeneous in terms of onset, symptom severity, comorbidity, clinical course, and outcome. Such diversity implies that distinct yet partially overlapping neurobiological mechanisms might be involved in patients with differing clinical presentations. Capitalizing on a dimensional approach (26), we can identify subpopulations of patients with common symptoms or illness course who might exhibit shared neural dysfunction. One potential axis upon which to subdivide bipolar disorder is the presence or absence of psychotic symptoms. Psychotic symptoms are present in 50%–70% of individuals with bipolar disorder (27,28), and psychosis aggregates within families of bipolar patients (29). Lifetime history of psychosis might represent a more severe form of the illness associated with poorer prognosis ([30,31]; but see [32]), cognitive performance (33), brain structure (34), and function (35). Recent reports of global prefrontal dysconnectivity in schizophrenia (36) raises the intriguing hypothesis that history of psychosis in bipolar disorder might be associated with more severe patterns of prefrontal dysconnectivity. However, prefrontal dysconnectivity has yet to be examined in psychotic bipolar disorder.

Our goal was to investigate prefrontal-limbic dysconnectivity in bipolar disorder. We tested three hypotheses. First, we examined whether there are global PFC connectivity abnormalities in this illness by applying a recently developed global brain connectivity (GBC) method (37–39), which might particularly manifest in mPFC. Second, we compared patients with a history of psychosis versus patients without psychosis to determine whether psychotic patients exhibit more severe PFC dysconnectivity, similar to findings in schizophrenia (36). Third, we examined functional connectivity between the amygdala and PFC with independent anatomically delineated seeds. We specifically tested whether regions showing global prefrontal disturbances exhibit convergence with amygdala dysconnectivity.

Methods and Materials

Participants

Participants provided informed consent approved by the institutional review board at Hartford Hospital and Yale University. Sixty-eight remitted patients with bipolar I disorder and 51 demographically matched healthy individuals participated in the study (Table 1). Patients were identified through outpatient clinics and community mental health facilities in the Hartford area. Inclusion criteria for patients were: 1) bipolar I disorder diagnosis as determined by the Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (40), administered by experienced M.A.- or Ph.D.-level research clinicians; 2) no history of major medical or neurological conditions (e.g. epilepsy, migraine, head trauma with loss of consciousness); and 3) IQ >80 assessed by Wechsler Abbreviated Intelligence Scale (41). To increase ecological validity of the patient sample, comorbid Axis I anxiety disorders and/or history of substance abuse (fully remitted >6 months before the study) were allowed. Healthy participants were recruited through media advertisements and flyers posted in the Medical Center area. Inclusion criteria for healthy participants were: 1) no current or lifetime Axis I psychiatric disorder as assessed by SCID Non-Patient edition; 2) no history of medical or neurological conditions; and 3) no history of psychotic or mood disorders in first-degree relatives (reported by detailed family history). Although groups were matched for age, ethnicity, and sex, the education attainment of healthy participants was greater than that of patients with bipolar disorder ($p = .01$) (42). Education differences are impacted by the illness course (43) and thus were not included as a covariate; alcohol, drug use, anxiety, age, illness duration, gender, and medication type did not alter reported effects (Table 2).

Current Symptoms and Medication

Severity of current mood symptoms was determined with the 21-item Hamilton Depression scale (44), the Young Mania Rating Scale (45), and the expanded version of the Brief Psychiatric Rating Scale (BPRS) (46). Only remitted patients were included in the current experiment (>1 week), defined with standardized cutoffs on the Hamilton Depression scale (≤ 7) and Young Mania Rating Scale (≤ 7) (Table 1). Of bipolar patients, 53% were receiving mood stabilizers, 43% were taking antidepressants, 34% were taking atypical antipsychotics, 35% were taking anxiolytics, 16% were receiving lithium, and 16% were unmedicated at the time of assessment (note: some patients were taking multiple medications). As noted, reported effects were not altered when we covaried for medication. For details on psychosis history evaluation for bipolar patients with psychosis versus those without psychosis, see Supplement 1.

GBC Analysis

Complete fMRI acquisition and preprocessing details are presented in Supplement 1. The GBC approach (36,38) was applied with in-house MATLAB tools (MathWorks, Natick, Massachusetts). The GBC method estimates the connectivity between each individual voxel and every other voxel in the brain. In contrast, restricted GBC estimates connectivity at every voxel with every other voxel in a restricted space (referred to hereafter as "restricted global brain connectivity" [rGBC]). Here we conducted rGBC analysis restricted to voxels within subject-specific Freesurfer-based (47) prefrontal gray matter masks (see

Table 1. Demographic Data

	Bipolar I, Psychosis Hx Mean (SD)	Bipolar I, No Psychosis Hx Mean (SD)	Healthy Comparison Mean (SD)	Significance (HC, BPP, BPW)		Significance (BPW vs. BPP)	
				F/χ^2	*p*, 2-tail	t/χ^2	*p*, 2-tail
Sample Size	34	34	51				
Female, *n* (%)	21 (62%)	26 (76%)	30 (59%)	2.96	.23	1.31	.19
Age (mean ± SD)	34.0 (10.8)	29.85 (11.9)	31.14 (10.6)	1.24	.29	1.49	.14
Education	13.94 (1.6)	14.38 (2.0)	15.1 (2.1)	3.80	.025[a]	1.01	.32
Mother's Education	13.62 (2.9)	14.45 (2.3)	13.25 (2.7)	2.02	.14	1.30	.20
Father's Education	14.62 (3.4)	15.27 (3.8)	12.6 (4.0)	5.80	.004[a]	.74	.46
Mean Parental Education	14.12 (2.8)	14.86 (2.7)	12.94 (3.1)	4.65	.02[a]	1.11	.27
Clinical Course							
Age at Diagnosis	18.06 (6.0)	17.88 (6.2)	N/A	—	—	.12	.91
Duration of Illness	14.5 (10.1)	13.38 (10.9)	N/A	—	—	.40	.69
Current Symptomatology							
Depression (HAMD)	3.29 (3.2)	4 (4.1)	.27 (.7)	21.03	.0001[a]	.78	.43
Mania (YMRS)	2.44 (3.2)	2.85 (3.8)	.2 (.5)	12.8	.0001[a]	.48	.63
Psychosis (BPRS)	28.85 (4.4)	27.71 (3.7)	24.5 (.9)	22.9	.0001[a]	1.17	.25
Medications, *n* (%)							
Mood Stabilizer(s)	19 (56%)	17 (50%)	N/A	—	—	.23	.62
Antidepressant(s)	12 (35%)	17 (50%)	N/A	—	—	1.5	.22
Atypical Antipsychotic(s)	15 (44%)	8 (24%)	N/A	—	—	3.2	.07
Anxiolytic/Benzodiazepine(s)	12 (35%)	12 (35%)	N/A	—	—	0	1
Lithium	7 (21%)	4 (12%)	N/A	—	—	.98	.32
Unmedicated	6 (18%)	5 (15%)	N/A	—	—	.1	.74
Typical Antipsychotic(s)	0 (0%)	1 (3%)	N/A	—	—	1.01	.31
Comorbid Diagnoses, *n* (%)							
Anxiety	15 (44%)	16 (47%)	N/A	—	—	.06	.81
Alcohol	18 (53%)	21 (62%)	N/A	—	—	.54	.46
Drug Use History	15 (44%)	14 (41%)	N/A	—	—	.06	.81

Age, education levels, parental education, age at diagnosis, and duration of illness are expressed in years.
BPP, bipolar patients with psychosis history; BPW, bipolar patients without psychosis history; BPRS, Brief Psychiatric Rating Scale; HAMD, Hamilton Depression Rating Scale; HC, healthy comparison; Hx, history; N/A, not applicable; YMRS, Young Mania Rating Scale.
[a]Significant *F* statistic for the one-way between-group analysis of variance. Of note, no pair-wise BPP—BPW comparisons reached significance.

Supplement 1 for FreeSurfer segmentations that comprised the mask). To account for between-subject differences in anatomy, before the analysis, blood oxygen level–dependent signal within the subject-specific cortical mask was spatially smoothed with a 6-mm full-width-at-half-maximum Gaussian kernel and dilated by two voxels (6 mm). Following our prior work (36), the rGBC analysis involved—for each PFC voxel—computing a correlation with every other PFC voxel, transforming the correlations to Fisher z-values, and computing the mean. This yielded a map for each subject where each voxel value represents the mean connectivity of that voxel with the rest of PFC.

Amygdala Seed-Based Functional Connectivity Analysis

The seed-based amygdala functional connectivity magnetic resonance imaging (fcMRI) closely followed our prior work (48). We employed in-house Matlab tools (49,50), as with rGBC, to examine the relationship between amygdala and all PFC voxels. To this end, we computed a seed-based amygdala correlation map by extracting average time-series across all voxels in the bilateral amygdala of each subject (anatomically defined through Freesurfer-based segmentation) (47,51), which was then correlated with each PFC voxel. Next we computed, as with rGBC, a Fisher r-to-Z transform, which yielded a map for each subject where each PFC voxel value represents connectivity with the amygdala.

Second-Level Group Analysis

Before computing group-level statistics, individual amygdala fcMRI and rGBC correlation maps were converted to Fisher-Z maps. To examine hypothesized between-group differences, these maps were entered into one-way analyses of variance (ANOVAs) with three across-group levels (control subjects, bipolar patients with psychosis, bipolar patients without psychosis). Both analyses were

Table 2. Region Coordinates

	x	y	z	Hemisphere	Anatomical Landmark
PFC rGBC Group Differences	3	32	1	Midline	Medial PFC/anterior cingulate gyrus
PFC-Amygdala fcMRI Group Differences	1	41	− 3	Midline	Medial PFC/anterior cingulate gyrus
	34	43	30	Right	Middle frontal gyrus/dorsolateral PFC

fcMRI, functional connectivity magnetic resonance imaging; PFC, prefrontal cortex; rGBC, restricted global brain connectivity.

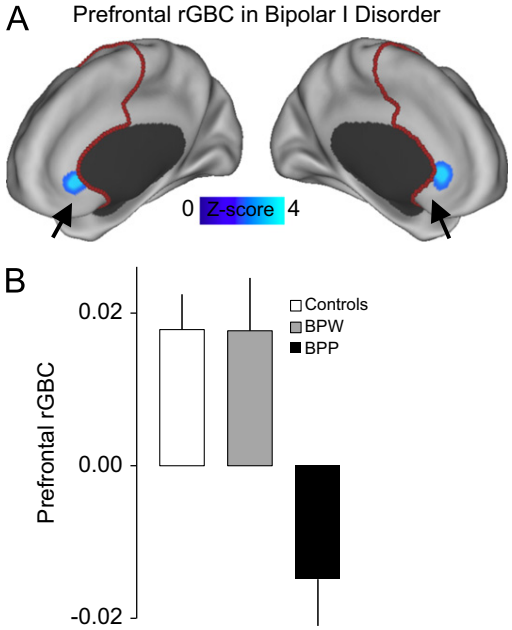

Figure 1. Global prefrontal dysconnectivity. **(A)** Significant between-group differences in prefrontal restricted global brain connectivity (rGBC) between bipolar patients and healthy participants revealed a medial prefrontal cortex region (mPFC) ($x = 3$, $y = 32$, $z = 1$). The red border approximately marks the restricted PFC analysis. **(B)** The rGBC values are shown for the mPFC region across the three groups; healthy participants (white), bipolar patients without psychosis history (BPW) (gray); bipolar patients with history of psychosis (BPP) (black). Error bars represent ± 1 SEM.

corrected within the anatomically defined PFC mask (95% overlap across all subjects). Type I error correction was based on peak voxel and cluster extent thresholds (52) ascertained via the AlphaSim of AFNI with exact smoothness estimates computed from the general linear model residuals ($p < .001$, $k = 14$ voxels for rGBC, and $k = 13$ for amygdala fcMRI). Results were visualized with Caret 5.5 software (http://brainvis.wustl.edu/wiki/index.php/Caret).

Results

Global Prefrontal Connectivity in Bipolar Disorder

To test hypothesized between-group difference in rGBC we computed a one-way ANOVA. Results revealed a significant Group effect centered on mPFC ($x = 3$, $y = 32$, $z = 1$) (Figure 1A). This effect was largely driven by reduced connectivity for bipolar patients with psychosis history. Notably, healthy participants did not exhibit any regions of reduced prefrontal connectivity relative to the bipolar group, despite virtually identical signal-to-noise ratio. To confirm that a history of psychosis is associated with more severe prefrontal dysconnectivity, we computed two follow-up independent-sample t tests. Patients with psychosis history showed lower mPFC rGBC compared with healthy control subjects [$t(83) = 4.31$, $p < .001$] and when compared with bipolar patients without psychosis history [$t(66) = 3.51$, $p < .001$] (Figure 1B). Pairwise comparisons were also significant when corrected within the PFC mask as a whole, illustrating the robustness of this effect. We also present a direct comparison of control subjects versus the entire sample of bipolar patients for qualitative inspection in Supplement 1 (Figure S1).

Amygdala–Prefrontal Connectivity in Bipolar Disorder

To circumvent region selection bias and to ensure complete independence from observed rGBC effects (see Supplement 1 for more detailed independence considerations), we computed a separate anatomically defined amygdala seed-based analysis with PFC and examined the main effect of Group in a one-way ANOVA. If we were to seed from the mPFC and indeed identify differences centered around the amygdala, one could raise the issue of circularity (because those functional voxels were defined with the present analysis) (53). Results revealed two foci showing significant between-group effects (Figure 2A, B): centered on mPFC ($x = 1$, $y = 41$, $z = -3$), and right dorsolateral prefrontal cortex (DLPFC) ($x = 34$, $y = 43$, $z = 30$). Again, amygdala-mPFC findings were predominantly driven by bipolar patients with psychosis history. However, in contrast to rGBC effects, patients with psychosis history showed focal increased connectivity between the amygdala and mPFC relative to healthy control subjects [$t(83) = 4.5$, $p < .001$] and relative to bipolar patients

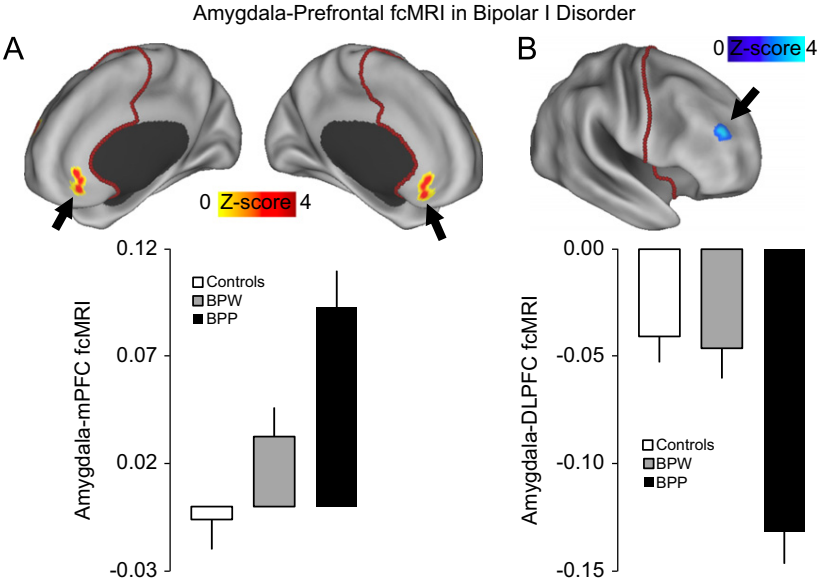

Figure 2. Amygdala prefrontal dysconnectivity. Significant group differences in amygdala-prefrontal functional connectivity magnetic resonance imaging (fcMRI) between bipolar disorder subgroups and healthy control subjects. **(A)** Yellow/red foci mark regions where bipolar patients with a history of psychosis showed increased amygdala connectivity relative to non-psychotic patients and healthy control subjects. This pattern was centered on the mPFC ($x = 1$, $y = 41$, $z = -3$). The red border approximately marks the restricted PFC analysis. **(B)** A right dorsolateral prefrontal cortex (DLPFC) region ($x = 34$, $y = 43$, $z = 30$) is shown in blue for which bipolar patients with a history of psychosis showed decreased amygdala connectivity relative to non-psychotic patients and healthy control subjects. The rGBC values are shown across both foci for control subjects (white), BPW (gray), and BPP (black). Error bars represent ± 1 SEM. Abbreviations as in Figure 1.

without psychosis [$t(66) = 2.76$, $p < .007$] (Figure 2A). Conversely, for the amygdala-DLPFC region, bipolar patients with psychosis history evidenced more negative connectivity relative to control subjects [$t(83) = 4.62$, $p < .001$] and patients without psychosis history [$t(66) = 4.11$, $p < .001$] (Figure 2B). To allow complete interpretation of amygdala findings, we present threshold-free patterns for control subjects and bipolar patients in Supplement 1; (Figure S2).

Testing for Convergence of rGBC and Amygdala Connectivity Effects

Given our questions with regard to both frontal and limbic dysconnectivity, we tested whether the voxels identified through a given analysis showed convergent effects with the other analysis. That is, given complete independence of identified regions, we tested rGBC effects in the mPFC voxels identified via amygdala connectivity and vice versa (i.e., amygdala connectivity effects in the mPFC voxels identified via rGBC). The purpose of the convergence analysis was to test whether identified voxels across the two approaches represent functionally distinct regions. Both effects converged: 1) the rGBC effect remained significant and consistent in the mPFC region identified via amygdala connectivity [$F(2,116) = 6.8$, $p < .002$]; and 2) the amygdala-mPFC effect remained significant and consistent in the mPFC region identified via rGBC analysis [$F(2,116) = 3$, $p = .05$]. Together, these findings further argue that functionally similar effects were present for both analyses across independently identified mPFC voxels.

Lifetime Psychotic Symptom Severity

To additionally examine the association between observed dysconnectivity and psychosis, we correlated measures of lifetime psychotic symptoms derived with the Lifetime Dimensions of Psychosis Scale (Supplement 1) with regions that revealed between-group effects. We computed a Spearman's correlation coefficient due to non-normally distributed symptom scores (i.e., some patients had no psychotic symptoms). We focused on positive symptoms, because few patients reported lifetime negative/disorganization symptoms. There was an inverse relationship between severity of lifetime positive symptoms and mPFC rGBC ($\rho = -.22$, $p = .07$, trend), indicating that patients with more severe lifetime positive psychotic symptoms (e.g., hallucinations and delusions) exhibit even lower mPFC rGBC (Figure 3A). In contrast, elevated amygdala–mPFC coupling was associated with increased lifetime psychotic symptom severity ($\rho = .31$, $p < .015$) (Figure 3B), whereas lower amygdala–DLPFC coupling was associated with more severe symptoms ($\rho = -.44$, $p < .0001$) (Figure 3C). We carried out further sub-group analysis with only those patients exhibiting psychotic symptoms ($n = 50$) (Supplement 1), which revealed a consistent but attenuated pattern.

Discussion

We investigated PFC connectivity in bipolar I disorder and found, consistent with predictions: 1) significant between-group differences in mPFC rGBC, particularly prominent for patients with psychosis history compared with those without and control subjects; 2) increased connectivity for amygdala–mPFC, and lower connectivity for amygdala–DLPFC networks in bipolar patients relative to control subjects that was exaggerated in patients with psychosis history; and 3) the magnitude of observed effects scaled with lifetime symptom severity. These findings provide evidence for distributed dysconnectivity between mPFC and other prefrontal regions and focal fronto-limbic dysconnectivity between mPFC and amygdala.

Global Prefrontal and Fronto-Limbic Connectivity

We hypothesized that bipolar patients would exhibit global prefrontal dysconnectivity in regions associated with affect regulation, such as mPFC, on the basis of prior work indicating their critical role in regulating emotion (24). We identified, consistent with predictions, a focal mPFC region for which patients showed reduced connectivity relative to healthy control subjects. These regional findings are highly consistent with both meta-analytic and seed-based neuroimaging studies reporting focal differences in bipolar disorder (6,54). However, this is the first investigation to directly document reduced functional integration between mPFC with the rest of PFC in bipolar disorder. Present findings illustrate that widespread prefrontal functional disruptions with mPFC might underlie risk for affect deregulation, which constitutes the

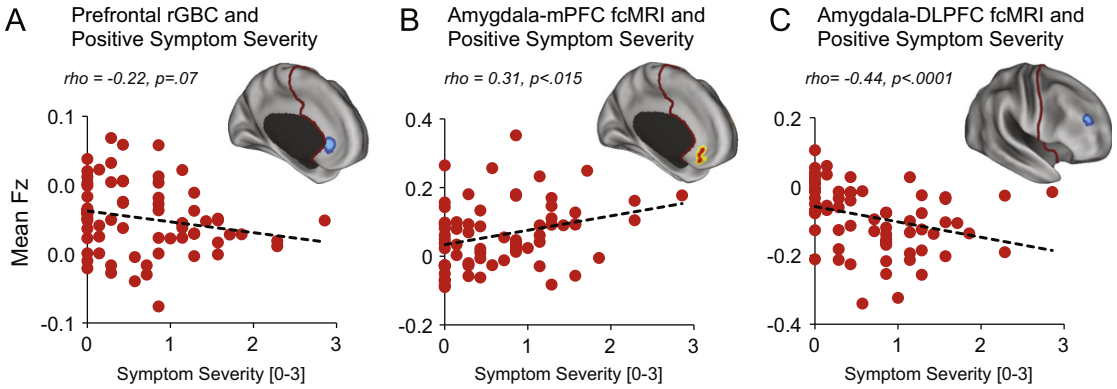

Figure 3. rGBC, amygdala-prefrontal dysconnectivity, and lifetime psychotic symptom severity. **(A)** Trend-level inverse relationship between mPFC rGBC and lifetime positive psychotic symptom severity across the entire sample of bipolar patients ($\rho = -.22$, $p = .07$). **(B)** Significant positive relationship between amygdala-mPFC fcMRI and lifetime positive psychotic symptom severity across the entire sample of bipolar patients ($\rho = .31$, $p < .015$). **(C)** Significant inverse relationship between amygdala-DLPFC fcMRI and lifetime positive psychotic symptom severity across the entire sample of bipolar patients ($\rho = -.44$, $p < .0001$). Direction of all reported individual difference effects show strong convergence with main effects. The scale on the x-axis captures a clinician-rated severity index that ranges from 0 (absent) to 4 (very severe; gross or nearly constant effect on function) (67). Abbreviations as in Figures 1 and 2.

hallmark symptom of this illness (because patients were euthymic at the time of the scan and therefore observed differences cannot be attributed to present affect regulation deficits). Interestingly, this region showed reduced global prefrontal connectivity in patients with psychosis history relative to other groups (discussed in the following text).

As noted, mPFC is involved in regulation of affect through dense and reciprocal connectivity with subcortical regions implicated in generation of affective states (e.g., amygdala) (22). Yet, the rGBC analysis does not guarantee that identified regions exhibit deficits in regulation of limbic circuits. That is, the rGBC analysis included PFC, not subcortical limbic regions, leaving open the possibility that the mPFC region identified as showing lower prefrontal connectivity might independently show reduced subcortical limbic connectivity. Thus, we examined potential convergence between rGBC and seed-based amygdala-PFC connectivity. Our independent amygdala analysis revealed a region in close proximity to the rGBC effect (although not precisely overlapping)—indicating that similar cortical territories that exhibit reduced PFC integration might also be involved in reduced limbic regulation in bipolar illness. Moreover, when we tested for convergence of effects across analysis (given their statistical independence), we found highly similar results across both identified regions. Present findings further solidify—through two independent but convergent approaches—that mPFC plays a critical role in the pathophysiology of bipolar illness.

Previous resting-state studies in humans and tracing studies in primates have shown that a portion of the mPFC exhibits positive connectivity with the amygdala (22,24,25,55–58), which we observed in our prior work (48) and here (threshold-free amygdala maps shown in Supplement 1). In Figure 2A the identified mPFC region exhibits low connectivity with amygdala in control subjects, which is increased in patients. Therefore, what does it mean if connectivity exists in a patient population that is "low" in healthy subjects? It has been well-established that functional connectivity is dynamic and state-dependent (59), whereby a low resting-state value might change and become more positive during times when emotional regulation is warranted. Thus, the observed increased values in bipolar illness might reflect a "state" that exists due to a heightened need for mood regulation (as proposed in the context of fear extinction [60]). There is also the possibility that the connection "weight" changes from frequent attempts to regulate mood. In other words, patients might be in a different state in day-to-day life frequently enough that resting amygdala-mPFC connectivity has altered (in a Hebbian sense) (59). We acknowledge that these hypotheses are speculative, yet they highlight scenarios where low coupling in the normative sample but an increase in the clinical sample might reflect a meaningful disturbance in amygdala-mPFC connectivity. Further work is needed to verify these possibilities. In addition, we opted for a PFC-wide amygdala seed-based analysis (as opposed to a restricted one) to verify whether amygdala seed-based results converge with those identified via rGBC (which might occur in places outside of functionally restricted patterns). Therefore, future studies should additionally constrain analyses to the mPFC showing significant connectivity with the amygdala in healthy subjects (to add further power).

Lastly, given present focal findings, one direction that might further elucidate the pathophysiology of bipolar illness is to relate observed dysconnectivity patterns that are predictive of symptoms with spatial patterns of gene expression known to affect cortical development (61). Recent advances in transcriptomics offer a quantitative approach toward characterizing the transcriptional landscape of PFC. Relating these spatial gene expression maps to fMRI offers ways to constrain our search for genes that exhibit expression in areas showing functional abnormalities with our neuroimaging markers. We acknowledge that bipolar illness is not exclusively genetic but rather that indexes of dysconnectivity derived with novel measures could be employed to track spatio-temporal expression of genes that confer risk for development of bipolar illness.

Prefrontal Dysconnectivity and Psychosis

We examined the association between psychotic symptoms and prefrontal dysconnectivity in three ways: 1) comparison of psychotic bipolar patients with control subjects; 2) comparison of patients with and without a history of psychosis; and 3) examination of lifetime history of psychosis severity and prefrontal dysconnectivity. All three comparisons indicated that psychotic bipolar patients exhibit a more severe pattern of mPFC rGBC and amygdala-mPFC/DLPFC coupling, further highlighted by individual-difference analyses. Interestingly, there was a mirror-like pattern between mPFC rGBC and amygdala-mPFC coupling, possibly reflecting reduced within-PFC integration but higher connectivity due to compensatory regulation over the amygdala (previously reported for mPFC-insula coupling [54]). Importantly, given that patients were asymptomatic at the time of assessment, our findings support the notion that observed dysconnectivity constitutes a trait-like feature and might be related to illness risk and relapse vulnerability rather than current psychotic symptom expression. Thus, mPFC dysconnectivity might be a marker for disease risk, a possibility worth examining in at-risk or prodromal populations.

These results also extend prior findings of reduced prefrontal connectivity in schizophrenia, which were centered on right DLPFC and left inferior frontal junction (36). Although present rGBC analysis in bipolar illness only identified mPFC dysconnectivity, we found reduced amygdala-DLPFC connectivity in bipolar disorder that was particularly associated with psychosis. In contrast, higher amygdala-mPFC connectivity was present even in patients without psychosis history. One possibility is that, although mPFC dysconnectivity might constitute a risk factor for bipolar disorder more generally, lateral prefrontal dysfunction might be particularly associated with risk for psychotic symptoms. Thus, present results suggest a two-part hypothesis, whereby different aspects of frontal dysconnectivity might be responsible for psychosis versus mood instability (62,63). One possibility is that psychosis and mood instability might arise due to separate processes that overlap in their anatomy and might be inherited together through distinct vulnerabilities combining via mechanisms such as assortative mating to yield psychotic bipolar illness. An alternative possibility is that these apparently separate clinical illnesses represent different phenomenological expressions of the same underlying problem at a neural circuit level, consistent with the proposal suggested by the Research Domain Criteria initiative (26).

Future studies should further delineate common and unique aspects of neuropathology underlying these comorbid but distinct symptom presentations. Current findings illustrate the need for a direct comparison of clinical groups presenting with psychotic symptoms but possibly uniquely different aspects of cortical neuropathology. A complicating factor between investigations is psychotic illness duration/severity and its effect on PFC circuits. It is possible that illness duration differentially impacts patterns of cortical connectivity. Similarly, acute psychotic states might be marked by a more distinct pattern of prefrontal

connectivity disruptions than those found in chronic patients (64). Thus, future work should quantify differences in prefrontal rGBC/fcMRI in psychotic illness that might relate to time, severity, and comorbidity. Such an approach, capitalizing on the data-driven advantages of GBC and ability to deal with individual differences in connectivity patterns (36), might provide a tool for linking patterns of prefrontal dysconnectivity with psychotic illness heterogeneity.

Study Limitations

Present findings should be interpreted within the confines of several limitations. First, we allowed for comorbid anxiety and history of drug/alcohol abuse/dependence to obtain a more ecologically valid sample (although effects remained unchanged when we covaried for these variables). Future studies should delineate to what extent present results replicate when examining subgroups with and without such comorbid diagnoses. Second, patients were remitted (2 weeks), and we examined findings as a function of psychotic history. An important future direction is to examine the extent to which these patterns hold as severity of psychosis increases during mood episodes and to fully rule out the possibility that differences in symptoms might reflect general psychopathology rather than psychosis history per se. Third, due to the correlational nature of the analyses, it is unclear whether changes in connectivity reflect the cause of the mood disturbance versus the consequence of the illness. Thus, it will be critical to examine whether connectivity patterns relate to illness duration, number of episodes, and/or frequency of cycling and manifest in at-risk populations. Fourth, despite convergence, the rGBC/seed-based findings are exploratory, given the voxel-wise search for prefrontal dysconnectivity, and should also be verified with an independent replication. Similarly, it will be important to verify amygdala findings with identified mPFC and DLPFC as seeds via an independent sample (to ensure region selection independence [53]). This also applies to the individual difference analyses, which are not completely orthogonal to the originally presented results (although they add convergent effects). Fifth, there is likely to be further functional specialization within the amygdala itself that we currently cannot capture in our study (65), which should be examined prospectively. Lastly, although when used as covariates medications did not alter the reported effects, reported patterns should be replicated in un-medicated samples (66).

Conclusions

Current findings substantially extend prior work in bipolar illness with a recently developed tool designed to detect global disruptions in prefrontal connectivity, applied to a well-powered sample with carefully matched across-group demographic data and signal-to-noise ratio. We found reduced mPFC connectivity with the rest of PFC in bipolar disorder—a pattern that was inversely correlated with psychosis history. Critically, an independent amygdala seed-based analysis revealed elevated connectivity with a highly proximal mPFC region. These convergent yet independent effects highlight that mPFC dysconnectivity might represent a potential trait characteristic or risk factor of the disorder. Furthermore, the observed pattern of prefrontal dysconnectivity varied as a function of psychosis history (similar to findings in schizophrenia) suggesting that disrupted PFC connectivity might be important for development of psychosis trans-diagnostically. Overall, our convergent findings highlight that disruption of prefrontal/limbic networks, particularly mPFC, might be a possible biomarker for bipolar disease risk.

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Supplementary material cited in this article is available online.

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