Fronto-Temporal Spontaneous Resting State Functional Connectivity in Pediatric Bipolar Disorder

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Background: The recent upsurge in interest about pediatric bipolar disorder (BD) has spurred the need for greater understanding of its neurobiology. Structural and functional magnetic resonance imaging studies have implicated fronto-temporal dysfunction in pediatric BD. However, recent data suggest that task-dependent neural changes account for a small fraction of the brain's energy consumption. We now report the first use of task-independent spontaneous resting state functional connectivity (RSFC) to study the neural underpinnings of pediatric BD.

Methods: We acquired task-independent RSFC blood oxygen level-dependent functional magnetic resonance imaging scans while participants were at rest and also a high-resolution anatomical image (both at three Tesla) in BD and control youths ($n = 15$ of each). We focused, on the basis of prior research, on the left dorsolateral prefrontal cortex (DLPFC), amygdala, and accumbens. Image processing and group-level analyses followed that of prior work.

Results: Our primary analysis showed that pediatric BD participants had significantly greater negative RSFC between the left DLPFC and the right superior temporal gyrus versus control subjects. Secondary analyses using partial correlation showed that BD and control youths had opposite phase relationships between spontaneous RSFC fluctuations in the left DLPFC and right superior temporal gyrus.

Conclusions: Our data indicate that pediatric BD is characterized by altered task-independent functional connectivity in a fronto-temporal circuit that is also implicated in working memory and learning. Further study is warranted to determine the effects of age, gender, development, and treatment on this circuit in pediatric BD.

Key Words: Adolescent, bipolar disorder, child, frontal lobe, magnetic resonance imaging, temporal lobe

Although it was once thought that mania could not occur in children, the past decade has witnessed an upsurge in research and clinical interest about pediatric bipolar disorder (BD). Recent data suggest that the incidence of pediatric BD has risen 40-fold in just 1 decade, with over 20% of all minors discharged from psychiatric hospitals now diagnosed with BD (1,2). Determining the validity of this dramatic increase is problematic because current psychiatric nosology is based entirely on clinical history that is considerably more difficult to elicit from children and adolescents than from adults. Thus, there is a pressing need for greater neurobiological understanding of pediatric BD.

Toward that end, structural magnetic resonance imaging (MRI) studies have implicated fronto-temporal alterations in pediatric BD. As summarized in a recent meta-analysis (3), the most consistent neuroanatomical finding in pediatric BD is decreased amygdala volume versus typically developing healthy control subjects (HC), now shown in seven of nine cross-sectional studies including our own (4–10) but not in two others (11,12). In Dickstein *et al.* 2005 (9), we used voxel-based morphometry (VBM) to compare gray matter volume in 20 age- and gender-matched pediatric BD versus HC participants. Our primary analyses showed that BD youths had decreased left dorsolateral prefrontal cortex (DLPFC) (Brodmann area [BA]9) volume and decreased left amygdala and left accumbens volume in secondary analyses using small volume correction within individual a priori regions of interest (ROIs). Other studies have shown decreased superior temporal gyrus (STG) and anterior cingulate cortex volume in pediatric BD (13,14).

Functional MRI (fMRI) studies have also demonstrated altered fronto-temporal neural activity in pediatric BD. Thus far, such studies have used a variety of cognitive tasks, including processing of emotionally valenced pictures and faces (10,15–17). However, such task-dependent changes in neural activation might represent a small fraction (perhaps $< 5\%$) of the brain's total activity (18,19).

To fully understand the neural pathophysiology of pediatric BD, it might be fruitful to examine how the brain allocates most of its resources (i.e., task-independent, spontaneous neural activity). This innovative approach evaluates spontaneous fluctuations in the blood-oxygen level dependent (BOLD) fMRI signal recorded without a specific task (i.e., while participants are at rest). The consistent observation of significant temporal correlations between spatially distinct loci has been termed "resting state functional connectivity" (RSFC) (18,19). The RSFC analyses have revealed abnormalities in the intrinsic connectivity networks in several psychiatric disorders but not in pediatric BD (20–22).

We report the first use of this novel approach to test the hypothesis that pediatric BD involves fronto-temporal alterations in spontaneous RSFC. We focused on the three a priori ROIs identified by our prior structural MRI study (left DLPFC, amygdala, and accumbens). We then conducted secondary analyses to elucidate the potential temporal relationships among our fronto-temporal ROIs.

Methods and Materials

Participants

Seven- to seventeen-year-old subjects were enrolled in an institutional review board-approved study at Bradley Hospital and

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Table 1. Participant Demographic Data in Pediatric BD Versus Typically Developing HC

Group	BD	HC	Statistics
Age	13.7 ± 3.3	14.0 ± 3.1	$p = .84, t = -.21$
Tanner Pubertal Stage			
Genitals	2.9 ± 1.6	3.5 + 1.7	$p = .3, t = -1.0$
Pubic hair	3.1 ± 1.6	3.7 + 1.7	$p = -.7, t = -1.1$
Verbal IQ	113.0 ± 10.0	118.6 ± 10.6	$p = .15, t = -1.49$
Performance IQ	104.1 ± 10.7	106.5 ± 11.9	$p = .57, t = -.58$
Full-Scale IQ	109.6 ± 9.0	114.0 ± 8.8	$p = .19, t = -1.35$
Gender			
Male	10	7	Pearson $\chi^2 = .56$ $p = .46$
Female	5	8	
Ethnicity	5	8	
Non-Hispanic/Latino	14 (93.3%)	14 (93.3%)	Pearson $\chi^2 = .00$ $p = 1.0$
Not reporting	1 (6.7%)	1 (6.7%)	
Race	5	8	
Black	2 (13.3%)	1 (6.7%)	Pearson $\chi^2 = 1.7$ $p = .64$
White	11 (77.3%)	12 (80%)	
>1 Race	2 (13.3%)	1 (6.7%)	
Young Mania Rating Scale Score	8.9 ± 5.0		
Children's Depression Rating Scale Score	33.4 ± 15.4		
Children's Global Assessment Scale Score	60.0 ± 20.1		
Current Comorbid KSADS Diagnoses			
Attention deficit/hyperactivity disorder	11 (73.3%)		
Oppositional defiant disorder	13 (86.7%)		
Obsessive-compulsive disorder	1 (6.7%)		
Generalized anxiety disorder	3 (20.0%)		
Specific phobia	3 (20.0%)		
Separation anxiety	2 (13.3%)		
Social phobia	2 (13.3%)		
Psychosis	1 (6.7%)		
Transient Tic disorder	1 (6.7%)		
Medications: Number and % of BD Participants			
Lithium	9 (60%)		
Atypical neuroleptics	13 (86.7%)		
Antidepressants	1 (6.7%)		
Stimulant medications[a]	6 (40%)		
Benzodiazepines	1 (6.7%)		

Bipolar disorder (BD) ($n = 15$) vs. typically developing healthy control subjects (HC) ($n = 15$).
KSADS, Child Schedule for Affective Disorders Present and Lifetime version.
[a] $n = 6/15$ BD participants were taking stimulant medications for attention-deficit/hyperactivity disorder ($n = 4$ taking methylphenidate, $n = 2$ taking dextroamphetamine). However, to minimize their impact on magnetic resonance imaging (MRI) data, all 6 held these medications for a minimum of 5 drug half-lives before their MRI scan in consultation with their treating physician.

Brown University. After study explanation, written informed consent/assent were obtained from parents/children. Recruitment included advertisements in physician offices, local newspapers, and support group websites.

The BD ($n = 15$) inclusion criteria were: 1) meeting DSM-IV-TR criteria for BD, including at least one episode meeting full DSM-IV-TR criteria for hypomania (≥ 4 days) or mania (≥ 7 days) (23); and 2) ongoing psychiatric treatment. Exclusion criteria were BD not otherwise specified, IQ ≤ 70, autistic or Asperger's disorder; medical illness that was unstable or could cause psychiatric symptoms; pregnancy; or substance abuse within ≤ 2 months of participation.

Healthy control ($n = 15$) inclusion criteria were a negative history of psychiatric illness in the control and in first-degree relatives. Exclusion criteria were IQ ≤ 70; ongoing medical or neurological illness; pregnancy; or past/present psychiatric or substance disorder.

All participants were evaluated by the same board-certified child/adolescent psychiatrist (DPD) with the Child Schedule for Affective Disorders Present and Lifetime version administered to parents and children separately (24). Comorbid diagnoses for BD youths were assessed by inquiring about symptoms during a time of relative euthymia to ensure that BD symptoms were not double-counted (Table 1).

All participants completed the Wechsler Abbreviated Scale of Intelligence as an overall measure of cognitive ability. The BD participants completed the Young Mania Rating Scale (YMRS) (25), Children's Depression Rating Scale (CDRS) (26), and Children's Global Assessment Scale (CGAS) (27).

MRI Data Acquisition

Scans were acquired on a Siemens Trio 3.0 Tesla scanner with a 12-channel head coil. The RSFC scan contained 256 continuous BOLD volumes ($TR_{epetition} = 2000$ msec, $TE_{cho} = 25$ msec, flip angle = 90°, slices = 35, field of view = 192 mm, voxels = 3 × 3 × 3 mm, duration = 8.36 min). During the scan, participants were instructed to rest with their eyes open while the word "relax" was back-projected via LCD projector. A high-resolution T1-weighted magnetization prepared rapid gradient echo anatomical image was also

acquired for normalization and localization ($TR_{epetition}$ = 2250 msec, TE_{cho} = 2.98 msec, T1 = 900 msec, flip angle = 9°, slices = 160, field of view = 256 mm, voxels = 1 × 1 × 1 mm, duration = 7.36 min).

Image Preprocessing and Nuisance Signal Regression

As described elsewhere (28), data were processed with both AFNI (Analysis of Functional NeuroImages, v. AFNI_2007_05_29_1644) and FSL (FMRIB Software Library, v. 4.1.2). The AFNI preprocessing included: 1) slice timing correction (for interleaved acquisitions), 2) motion correction (x, y, z, roll, pitch, yaw), and 3) despiking of extreme time series outliers and temporal band-pass filtering (.005–.1 Hz). The FSL preprocessing included: 1) mean-based intensity normalization (scaling) of all volumes by the same factor, 2) spatial smoothing with full-width half-maximum = 6 mm Gaussian kernel, 3) FSL's Linear Registration Tool (FLIRT) to register the anatomical scan to the Montreal Neurological Institute 152 template with (2 mm^3 resolution), and 4) FLIRT registration of each participant's RSFC time series to the same space as the anatomical scan.

To control the effects of physiological processes (e.g., cardiac/respiratory cycle fluctuations) and motion, we regressed the 4-dimensional (4D) volume of each participant on nine predictors to model nuisance signals from white matter, cerebrospinal fluid, global brain signal, and six motion parameters (28). Correction for time series autocorrelation (prewhitening) was performed. This nuisance signal regression produced a 4D residuals volume for each participant. The time series of each voxel was scaled by its SD to ensure that the resultant RSFC estimates represented partial correlations rather than regression parameter estimates. Finally, the 4D volume of each participant was spatially normalized by applying the previously computed transformation to Montreal Neurological Institute 152 template.

Seed Selection

We created spherical seeds (diameter = 6 mm) on the basis of our work showing decreased gray matter in the left DLPFC (x = −32, y = 42, z = 32), amygdala (x = −24, y = 5, z = −15), and accumbens (x = −6, y = 9, z = −7) (9). Talairach coordinates for these ROIs were transformed into Montreal Neurological Institute space with the icbm2tal conversion (29).

Participant-Level Analyses

For each participant and each seed, we performed a separate multiple regression analysis in which we regressed the participant's 4D residuals volume on the seed time series, with FSL's Expert Analysis Tool. These analyses produced individual participant-level maps of all voxels that were positively and negatively correlated with the seed time series.

Primary Group-Level Analyses

Group-level mixed-effects analysis was conducted with FSL's Local Analysis of Mixed-Effects. The model included mean positive and negative vectors for the BD and HC groups separately, BD > HC, HC > BD, plus de-meaned values for age, full-scale IQ, and gender as nuisance covariates. To correct for multiple comparisons, group-level statistical maps were first thresholded at $Z > 2.3$, and then Gaussian random field theory was used to determine the significance of clusters surviving this threshold, with $p < .05$ whole-brain corrected as the criteria for cluster-wise significance.

To further characterize the underlying neurocircuitry, we created 6-mm "iterative seeds" centered at the peak of any ROI exhibiting significant between-group differences (whole-brain corrected) in RSFC with our three primary ROIs. We repeated the aforementioned participant-level and primary group-level analyses for any iterative seeds and included them in all secondary analyses. Post hoc analyses were conducted with extracted RSFC data from our primary analyses to determine the potential impact of age, Tanner pubertal stage, medication, global signal correction (GSC), and ROI selection with Statistical Package for Social Sciences (v. 17).

Secondary Analyses: Modeling Temporal Relationships

To elucidate the relationships among our three primary seeds and any iterative seeds, we conducted secondary analyses employing two complementary methods: Partial Cross Correlation (PCC), and Multivariate Autoregressive Modeling (MAR).

The PCC is a model-free method for studying cross-relationships between neural activation occurring simultaneously across several ROIs. The PCC gives a measure of direct linear connectivity between each pair of ROIs to answer the question: "Are the spontaneous RSFC in two ROIs simultaneously related at the same time point *t*?" Thus, PCC is ideal for multiple ROIs that might be interdependent (i.e., PCC is "0" even for a pair of ROIs that are highly cross-correlated if the correlation is being driven by another ROI).

The PCC values were Fisher-z transformed to yield normalized variance-stabilized values via $Y_{ij}^{s} = .5 \log[(1 + X_{ij}^{s})/(1 - X_{ij}^{s})]$ where X_{ij}^{s} is the partial cross-correlation value for subject s, between ROIs i and j. For each of the six pairs of ROIs (HC minus BD), joint 95% confidence intervals (Bonferroni-corrected) were calculated. The *p* values from the two-independent sample *t* test were calculated (30). Diagnostic procedures (Q–Q plots for the normality assumption and a formal test for equality of variance) confirmed that the assumptions (normality and equal variances) required for computing confidence intervals and *t* tests were valid.

PCC examines simultaneous relationships, but PCC does not capture dynamic (time lagged) relationships among ROIs. Instead, MAR modeling is a potential means to address the question: "Is the BOLD signal in one ROI associated with the past BOLD signal in other regions?" (31). The MAR modeling has been used to identify Granger-causality relationships (i.e., RSFC BOLD signal in one ROI predicted that in another). The distinction between physiological causality and Granger-causality has always been important, with the Granger-causality being a mathematical model used to explore sequential relationship between BOLD signal peaks whose inference at the neuronal level remains unknown (32,33). In particular, researchers have begun to appreciate alternative conditions under which significant MAR-based relationships might arise (e.g., regional differences in hemodynamic lag, regional differences in rise to peak for the hemodynamic response) (32). Thus, to balance the need for completeness with the rapidly evolving debate about the interpretations of MAR modeling, we present the full methods, results, and discussion of our MAR analyses in Supplement 1.

Results

Participants

The groups did not differ significantly in age, gender, Tanner pubertal stage, or Full-Scale IQ. The BD sample consisted of 15 participants with type I BD; none had type II BD, although it was not excluded. As a group, our BD participants were euthymic by mood ratings (YMRS 8.9 ± 5.0, CDRS 33.4 ± 15.4), and they were mildly impaired (CGAS 60.0 ± 20.1; nonclinical > 70), although none were acutely symptomatic at the time of the scan. All BD participants were receiving psychopharmacological treatment, including antimanic medications such as lithium (n = 6 [40%]) or atypical neuroleptics (n = 13 [87%]). Five BD participants (33%) had at least one first-degree relative with BD.

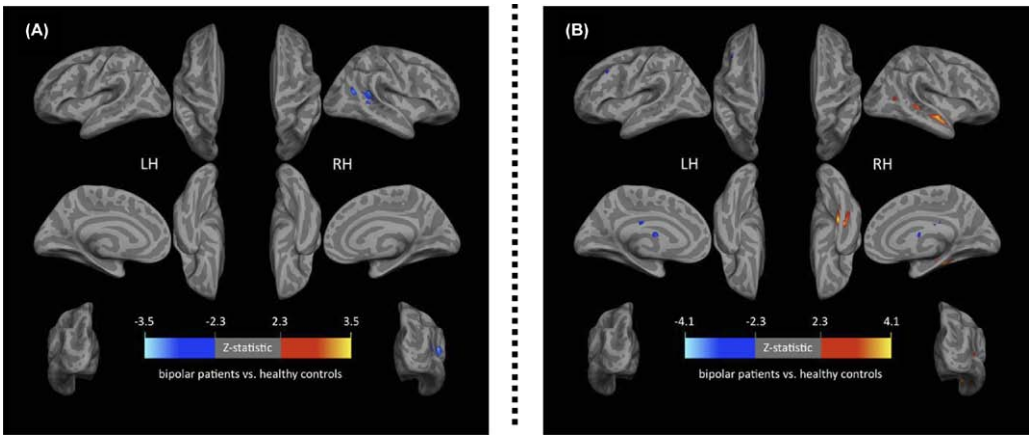

Figure 1. Whole-brain corrected significant between-group differences in resting state functional connectivity (RSFC) in pediatric bipolar disorder (BD) (n = 15) vs. Typically Developing healthy control subjects (HC) (n = 15). **(A)** Significantly decreased RSFC between left dorsolateral prefrontal cortex and right superior temporal gyrus (STG) in pediatric BD vs. control subjects (BA22, x = 54, y = −44, z = 8; voxels = 775, $p_{corrected}$ = .04). (**B**) Significantly altered RSFC between right STG and fronto-temporal regions in pediatric BD vs. control subjects. **(B)** Significantly decreased (blue) RSFC activity in BD vs. control youths between the right STG and: 1) left middle frontal gyrus (BA9, x = −48, y = 36, z = 28; Voxels = 953, $p_{corrected}$ = .009); 2) right superior frontal gyrus (BA9, x = 38, y = 58, z = 22; Voxels = 809, $p_{corrected}$ = .02), and 3) left thalamus/caudate body (x = −16, y = −12, z = 18; Voxels = 688, $p_{corrected}$ = .05). Significantly increased (orange) RSFC between STG and right parahippocampal gyrus (BA36, x = 38, y = −32, z = −20; Voxels = 1931, $p_{corrected}$ = .00007). Method: three Tesla Siemens Tim Trio BOLD scan ($TR_{epetition}$ = 2000 msec, TE_{cho} = 25 msec, flip angle = 90°, slices = 35, field of view = 192 mm, voxels = 3 × 3 × 3 mm, duration = 8.36 min) acquired while participant was at rest. To correct for multiple comparisons, group-level statistical maps were first thresholded at $Z > 2.3$, and then Gaussian random field theory was used to determine the significance of clusters surviving this threshold, with $p < .05$ whole-brain corrected as the criteria for cluster-wise significance. LH, left hemisphere; RH, right hemisphere.

Primary Analysis: Fronto-Temporal Functional Connectivity

With our primary left DLPFC seed, we found significantly decreased RSFC between BD and control youth in the right STG (BA22, x = 54, y = −44, z = 8; Voxels = 775, $p_{corrected}$ = .04). This was due to greater negative RSFC (anticorrelation) in the BD group than control subjects. For this same left DLPFC seed, we did not identify any regions where BD youth had greater RSFC than control subjects. We did not identify significant between-group RSFC differences with the left amygdala or left accumbens seeds (Figures 1 and 2, and Table 2).

Our iterative regression analysis used the right STG identified in our primary analysis as a seed. We found significantly decreased RSFC in BD versus control subjects in the left middle frontal gyrus (BA9, x = −48, y = 36, z = 28; Voxels = 953, $p_{corrected}$ = .009), right superior frontal gyrus (BA9, x = 38, y = 58, z = 22; Voxels = 809, $p_{corrected}$ = .02), and left thalamus/caudate body (x = −16, y =

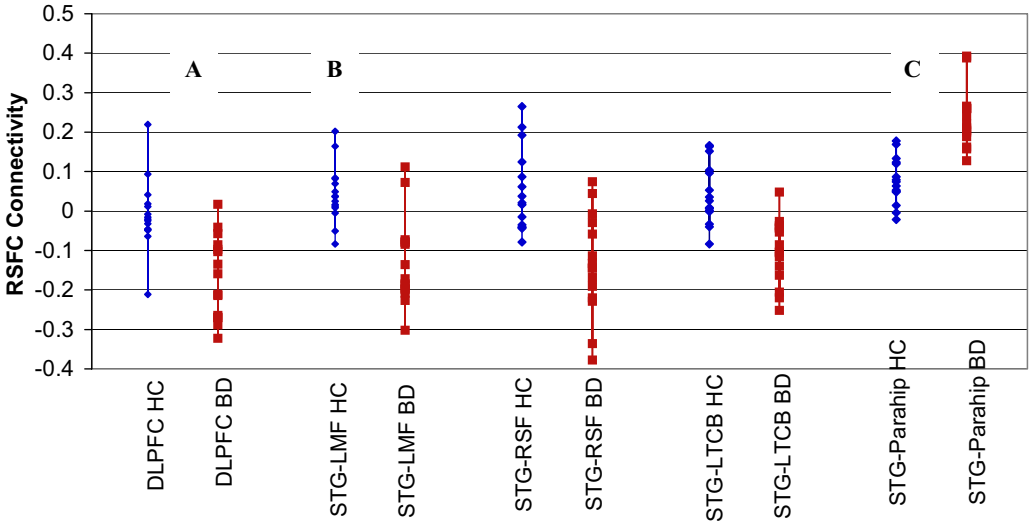

Figure 2. Significantly decreased fronto-temporal RSFC in pediatric BD (n = 15, red) vs. Typically Developing HC (n = 15, blue). (**A**) Primary analysis showed significantly decreased RSFC activity between the left dorsolateral prefrontal cortex and the right STG in BD vs. control youth (BA22, x = 54, y = −44, z = 8; Voxels = 775, $p_{corrected}$ = .04). (**B**) Then, with this iterative right STG seed, we found significantly decreased RSFC in BD vs. control youths in the left middle frontal gyrus (BA9, x= −48, y = 36, z = 28; Voxels = 953, $p_{corrected}$ = .009), right superior frontal gyrus (BA9, x = 38, y = 58, z = 22; Voxels = 809, $p_{corrected}$ = .02), and left thalamus/caudate body (x= −16, y = −12, z = 18; Voxels = 688, $p_{corrected}$ = .05) and (**C**) increased RSFC in BD vs. control youths between the iterative right STG seed and the parahippocampal gyrus (BA36, x = 38, y = −32, z = − 20; Voxels = 1931, $p_{corrected}$ = .0007). Method: three Tesla Siemens Tim Trio BOLD scan ($TR_{epetition}$ = 2000 msec, TE_{cho} = 25 msec, flip angle = 90°, slices = 35, field of view = 192 mm, voxels = 3 × 3 × 3 mm, duration = 8.36 min) acquired while participant was at rest. Abbreviations as in Figure 1.

Table 2. Significant Between-Group Differences in RSFC in Pediatric BD Versus Typically Developing HC

Seed	Between-Group Difference	Region	Cluster Size	x	y	z	$P_{corrected}$
Left DLPFC	HC > BD	Right STG (BA22)	775	54	−44	8	.04
Left amygdala	—						
Left accumbens area	—						
Iterative right STG seed from primary analysis	HC > BD	Left middle frontal gyrus (BA9)	953	−48	36	28	.009
	HC > BD	Right Superior frontal gyrus (BA9)	809	38	58	22	.02
	HC > BD	Left thalamus and caudate body	688	−16	−12	18	.05
	BD > HC	Right parahippocampal gyrus (BA36)	1931	38	−32	−20	.00007

Resting state functional connectivity (RSFC) in pediatric bipolar disorder participants (BD) ($n = 15$) vs. typically developing healthy control subjects (HC) ($n = 15$). To correct for multiple comparisons, group-level statistical maps were first thresholded at $Z > 2.3$, and then Gaussian random field theory was used to determine the significance of clusters surviving this threshold, with $p < .05$ whole-brain corrected as the criteria for cluster-wise significance.

DLPFC, dorsolateral prefrontal cortex; STG, superior temporal gyrus; BA, Brodmann Area.

−12, z = 18; Voxels = 688, $p_{corrected} = .05$). We also found significantly greater RSFC in BD versus control subjects between the right STG and the right parahippocampal gyrus (BA36, x = 38, y = −32, z = −20; Voxels = 1931, $p_{corrected} = .00007$).

Within the BD group, there were no significant correlations between RSFC in the right STG or the four regions identified by our iterative analysis and mood (YMRS, CDRS) or overall functioning (CGAS).

Secondary Analyses: Modeling Temporal Relationships

The PCC analyses tested the pair-wise relationship in RSFC, showing a significant between-group difference for the DLPFC-STG (Figure 3). Specifically, whereas the PCC was positive for control subjects (mean = .084 ± .151), the PCC was negative for BD youths (mean = −.148 ± .161; $p < .001$). In other words, among control subjects, increased spontaneous BOLD signal in the left DLPFC was associated with simultaneous increases in the right STG and vice versa (positive correlation), whereas the opposite was true for BD youths (i.e., increased spontaneous activity in the left DLPFC was associated with simultaneous decreases in the right STG [anticorrelation]). Among BD youths, there were no significant correlations between the DLPFC-STG PCC measures and measures of mood (YMRS, CDRS) or function (CGAS).

Significant group-differences were detected with MAR. See Supplement 1 for presentation of findings.

Post Hoc Analyses

Post hoc analyses examined the potential impact of development, medication, GSC, and ROI selection on the results of our primary analysis (Supplement 1). We did not find medication effects, but there was a suggestion of developmental differences in correlations between right STG–right parahippocampal RSFC and age that were in opposite directions in the BD versus HC groups (BD Pearson .51, $p = .05$, HC Pearson = −.58, $p = .02$). Re-analyzing our data without GSC incorporated as a nuisance variable showed that GSC successfully reduced intersubject variability without disproportionately affecting one group. Re-analyzing our data with anatomical ROIs from the Harvard-Oxford Brain Atlas confirmed that the failure of our primary analyses to find significant differences in the left amygdala or left accumbens was not due to our use of coordinate-based seeds.

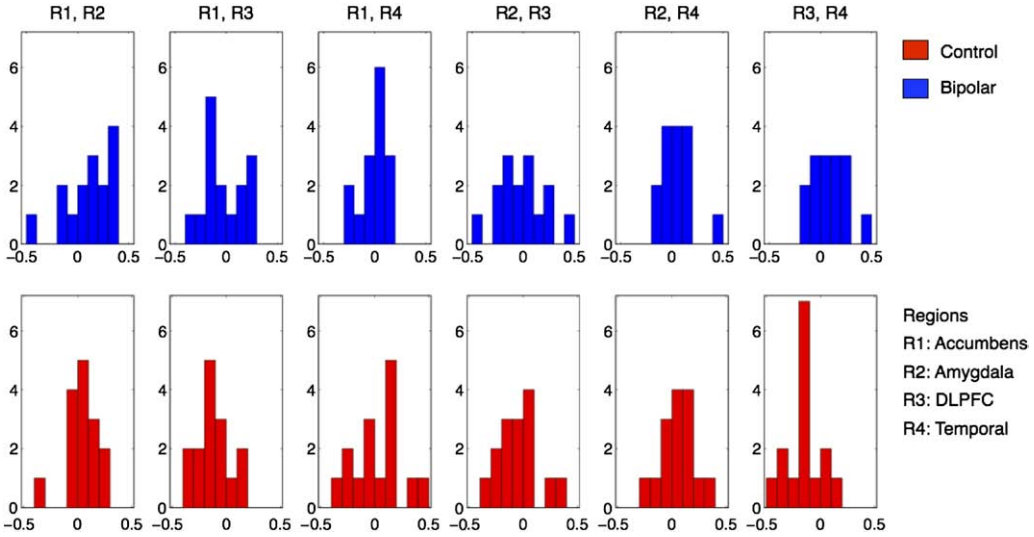

Figure 3. Partial Cross Correlation (PCC) analysis of RSFC in fronto-temporal regions of interest between pediatric BD (bottom, red) and Typically Developing HC (top, blue). Significant PCC between left dorsolateral prefrontal cortex (R3, DLPFC) and right superior temporal gyrus (R4, STG) indicating these regions are correlated in control subjects (blue, top) (i.e., increases in DLPFC lead to increases in STG), whereas they are anticorrelated in pediatric BD (red, bottom) (i.e., increases in DLPFC lead to decreases in STG) ($p < .001$). Other abbreviations as in Figure 1.

Discussion

Our examination of RSFC in youths with pediatric BD has three main findings. First, our primary analysis revealed a significant between-group difference in RSFC between the left DLPFC and right STG. In particular, pediatric BD participants had significantly greater negative RSFC between the left DLPFC and the right STG versus control subjects. Subsequent iterative analyses showed that pediatric BD participants had significantly decreased RSFC between the right STG and bilateral PFC (BA9), left thalamus/caudate, and increased RSFC between the right STG and the right parahippocampal gyrus. Second, PCC analysis showed that, when relationships with the other ROIs were taken into account, BD and control youths had opposite phase relationships between spontaneous BOLD fluctuations in the left DLPFC and right STG (i.e., whereas RSFC was in-phase for control subjects, it was 180 degrees out of phase [anticorrelated] for BD youths). Third, MAR analyses identified significantly different relationships among patterns of spontaneous fluctuation between BD and control youth in our circuits of interest, but caution is urged in interpreting these MAR analyses, given potential contributions of physiological variables—such as regional differences in the hemodynamic response—to the relationships observed (32).

The results from our primary analyses, showing that BD youths have altered RSFC between the DLPFC and STG, and iteratively between the STG and frontal, striatal, and parahippocampal areas, align with prior studies implicating working memory in BD (34,35). For example, BD youths have impaired working memory versus control subjects (36–38). Working memory deficits in BD youths have been associated with increased PFC and temporal fMRI activation (39). Similar fronto-temporal alterations have been shown in BD youths with emotionally valenced picture and face tasks (10,15–17).

Our results align with the small connectivity literature in BD. The only task-independent RSFC study in BD involved BD adults (n = 11), showing decreased RSFC between the pregenual anterior cingulate cortex and bilateral amygdala and thalamus (40). Task-dependent data from a face processing paradigm show that BD youths have decreased functional connectivity between the left amygdala and the right posterior cingulate/precuneus and fusiform/parahippocampal gyri (41). Therefore, our work is an important first step toward understanding how some of this fronto-temporal dysfunction might be intrinsic to pediatric BD rather than contingent upon a particular cognitive task or process.

Our data also suggest the importance of development in the pathophysiology of pediatric BD. Specifically, top-down control of cognitive processes, including declarative memory, requires interplay between the frontal cortex, especially DLPFC, and the striatum and temporal cortex (42–44). Longitudinal neuroimaging studies have shown that typical development involves the progressive maturation of phylogenetically older brain areas, like the temporal cortex and striatum, before newer ones, like the DLPFC (45). Some posit that typical adolescent characteristics, including identity formation and risk-taking, depend on the dynamic balance between the earlier maturing striatum and amygdala responsible for bottom-up reward processing and the later maturing PFC responsible for top-down cognitive control (46).

Three studies have robustly demonstrated developmental maturation effects on RSFC, showing that healthy adults have stronger, more focused within-network RSFC versus children or adolescents (47–49). Our data show that BD and control participants have the opposite correlation between age and RSFC between the right STG and parahippocampal gyrus. Given power issues, such post hoc comparisons should be interpreted with caution. Future longitudinal neuroimaging studies will be required to ascertain the developmental trajectories of spontaneous neural activity in pediatric BD, with sufficient power to address issues inherent in BD research, including potential neuromodulatory effects of medications and comorbidity.

Regarding the functional significance of negative (antiphase, anticorrelated) DLPFC/STG RSFC in BD participants and positive RSFC in control subjects, we note the continuing controversy in the RSFC literature surrounding negative connectivity (50,51). Authors agree that negative correlations can and do exist in the brain (51,52), but recent work has suggested that procedures, (e.g., GSC) might exaggerate them by shifting "zero" correlations into negative ones (53). However, reprocessing and reanalyzing our data without GSC confirmed that incorporating GSC reduced intersubject variability, thus enhancing our ability to detect between-group differences, rather than either altering negative correlations or disproportionately affecting one group versus another (see Supplement 1). This aligns with both mathematical and empiric investigations of the effect of GSC on RSFC, showing that GSC resulted in improved ability to detect system-specific correlations in RSFC and improved the correspondence between RSFC and anatomy (51,54). We conclude that our data indicate that pediatric BD involves a greater degree of segregation between the DLPFC and STG than was observed in control subjects.

Three issues related to our ROI approach bear further comment. First, both structural (55–57) and functional (58) ROIs have been used to guide RSFC analyses. In our current study, we chose to follow up on structural ROIs identified by our prior work, but functional ROIs would be equally important for future studies. Second, our failure to fully replicate our prior VBM results does not diminish the relevance of our ROIs, because they have been consistently implicated by other pediatric BD neuroimaging studies (17,59,60). Moreover, we note several important methodological differences between our original study and our current post hoc VBM analyses, including: 1) greater power to detect gray matter volume differences in our original study (20 vs. 15 participants/group); 2) lack of gender matching as in our original study; 3) different MRI manufacturers and field strengths (original = GE 1.5 Tesla vs. current = Siemens 3 Tesla); 4) different structural scan sequences [original = spoiled gradient recalled ($TR_{epetition}$ = 24 msec, TE_{cho} = 5.0 msec, slices = 124); current = magnetization prepared rapid gradient echo ($TR_{epetition}$ = 2250 msec, TE_{cho} = 2.98 msec, slices = 160)]; and 5) different statistical software (SPM vs. FSL). Third, although our post hoc analyses using an anatomic left amygdala ROI confirmed our lack of amygdala findings from our primary analysis, larger samples are necessary to evaluate RSFC alterations in other ROIs among BD youths.

Our study has several additional limitations, including psychotropic medications, comorbidity, and sample size. First, our post hoc analyses suggest that medications do not confound our current results. However, all BD participants were taking their usual psychotropic medications with the exception of psychostimulants, which were withheld for a minimum of 5 drug half-lives. The rationale was that psychostimulants are commonly held for drug holidays (e.g., school vacations) in clinical care, and they affect the BOLD signal (61,62), whereas it would be unethical to withhold antimanic, antidepressant, or antianxiety medications for research purposes alone; and brief discontinuations would be ineffective, given their longer half-lives. Recent BD research suggests that such medications might not influence BOLD signal in fMRI studies such as ours (63). Nevertheless, future work, perhaps with nonhuman primates,

is warranted to evaluate the effect of pharmacological treatment on fronto-temporal RSFC during development.

Second, our BD participants had rates of comorbid psychopathology corresponding to other pediatric and adult BD studies. Yet, future studies are needed to determine the specificity of these RSFC alterations, including comparisons with those with primary attention-deficit/hyperactivity disorder or anxiety (20). Third, although our BD and control samples are on par with the current literature in pediatric BD, we note the need for even larger studies with sufficient power to meaningfully explore the potential effects of age, gender, puberty, and treatment.

Conclusions

Our study is the first to evaluate spontaneous RSFC activity in pediatric BD. Our data indicate that pediatric BD is characterized by altered task-independent RSFC in fronto-temporal regions also implicated in working memory and learning. Further study is warranted to determine the effects of age, gender, development, and treatment on this circuit in pediatric BD.

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Supplementary material cited in this article is available online.

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