

Altered affective, executive and sensorimotor resting state networks in patients with pediatric mania

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Background: The aim of the present study was to map the pathophysiology of resting state functional connectivity accompanying structural and functional abnormalities in children with bipolar disorder. **Methods:** Children with bipolar disorder and demographically matched healthy controls underwent resting-state functional magnetic resonance imaging. A model-free independent component analysis was performed to identify intrinsically interconnected networks. **Results:** We included 34 children with bipolar disorder and 40 controls in our analysis. Three distinct resting state networks corresponding to affective, executive and sensorimotor functions emerged as being significantly different between the pediatric bipolar disorder (PBD) and control groups. All 3 networks showed hyperconnectivity in the PBD relative to the control group. Specifically, the connectivity of the dorsal anterior cingulate cortex (ACC) differentiated the PBD from the control group in both the affective and the executive networks. Exploratory analysis suggests that greater connectivity of the right amygdala within the affective network is associated with better executive function in children with bipolar disorder, but not in controls. **Limitations:** Unique clinical characteristics of the study sample allowed us to evaluate the pathophysiology of resting state connectivity at an early state of PBD, which led to the lack of generalizability in terms of comorbid disorders existing in a typical PBD population. **Conclusion:** Abnormally engaged resting state affective, executive and sensorimotor networks observed in children with bipolar disorder may reflect a biological context in which abnormal task-based brain activity can occur. Dual engagement of the dorsal ACC in affective and executive networks supports the neuroanatomical interface of these networks, and the amygdala's engagement in moderating executive function illustrates the intricate interplay of these neural operations at rest.

Introduction

Pediatric bipolar disorder (PBD) is a cyclical illness with episodes of mania and depression complicated by neurocognitive dysfunction.¹⁻³ Mania is characterized by symptoms such as grandiosity, decreased need for sleep, flight of ideas, distractibility, increased goal-directed activity and excessive risk-taking.⁴ Low-frequency (0.01–0.1 Hz) blood oxygen level-dependent (BOLD) signals at rest have been hypothesized to reveal the brain's intrinsic neural activity that could be abnormal during an episode of mania. Synchronized brain circuitries at rest have been consistently identified;^{5,6} they reflect underlying monosynaptically or polysynaptically interconnected anatomic regions^{7,8} and may be influenced by hist-

ory of coactivation during active behaviour.⁹ Given the structural abnormalities and the task-invoked functional activation abnormalities observed in children with bipolar disorder, it is plausible that the topography of the resting state networks (RSNs) may also be abnormal in these children. While the association between resting state activation and task-based functional activation is uncertain, elucidating the integrity of RSNs in children with bipolar disorder may shed light on functional abnormalities and lead to better understanding of intervention targets in pediatric mania.

Abnormal structural findings in children with bipolar disorder include decreased volume in the anterior cingulate cortex (ACC),¹⁰ dorsolateral prefrontal cortex (DLPFC) and amygdala,¹¹ and increased volume in the basal ganglia.¹²

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Altered white matter integrity with lower fractional anisotropy has also been reported in the limbic system, anterior and posterior corona radiata and the corpus callosum.^{13–17} Previous task-based functional magnetic resonance imaging (fMRI) studies probing the affective frontolimbic operations have reported abnormally decreased^{18–20} or increased^{21,22} activity in the ventrolateral prefrontal cortex (VLPFC) as well as increased activity in the amygdala^{19,21} and pregenual ACC¹⁹ in children with bipolar disorder. Also, fMRI studies probing motor response inhibition suggested VLPFC–DLPFC–striatal abnormalities in these children.²³ Previous literature on resting state connectivity has reported decreased connectivity between the PFC and the amygdala^{20,21} in adults with bipolar disorder and an anticorrelation between the DLPFC and the temporal cortex in children with bipolar disorder relative to healthy controls²⁴ using a seed-based correlation approach. The seed-based approach analyzes the association between the seed region and other voxels in the brain, producing a seed region dominant network that fundamentally tests an a priori RSN. Conversely, as a data-driven approach, independent component analysis (ICA)^{25,26} detects RSNs at individual and group levels^{5,27–29} without explicit pre-conceptualized models. Given the diverse structural and brain functional abnormalities observed in children with bipolar disorder, there are no definitive RSNs that are implicated in PBD. Thus we chose the ICA approach as its model-free flexibility allows us to simultaneously and comprehensively map multiple altered RSNs that could be implicated in pediatric mania.

Methods

Design

This is a cross-sectional study comparing patients with pediatric mania and healthy controls. The study was approved by the University of Illinois at Chicago's Institutional Review Board, and informed consent was obtained from at least 1 parent, while assent was obtained from all participants.

Sample

We recruited patients from our outpatient pediatric mood disorder clinic as well as the research screening clinic located in a large metropolitan area. Our goal was to recruit pediatric patients at the inception of the first manic episode to evaluate the early disease state not yet confounded by heavy use of psychotropic medications and other comorbid conditions. Inclusion criteria for patients were a *DSM-IV* diagnosis of bipolar disorder type I with manic episode⁴ and age 10–18 years. Exclusion criteria for all patients were pervasive developmental disorder, serious psychiatric disorders except for attention-deficit/hyperactivity disorder (ADHD), any neurologic disorder or history of head injury, any history of nonfebrile seizures and current or past substance abuse/dependence or use of illicit drugs or alcohol in the 3 months preceding the study. Inclusion criteria for healthy controls were no current or lifetime criteria for any *DSM-IV* diagnoses, medication-free status and no history of psychiatric illness in their first-degree relatives.

Assessment and clinical measures

Each child and a parent were interviewed using the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS),² supplemented by the episode characterization of mania from the KSADS Present and Lifetime version.³³ Diagnostic interviews were completed by doctoral-level clinicians along with research assistants with established inter-rater reliability (Cohen κ between 0.96 and 0.98). The clinical measures of symptom state in manic or mixed episodes included the clinician-rated Young Mania Rating Scale (YMRS)³² and the Child Depression Rating Scale–Revised (CDRS-R).³¹ We used the Behaviour Rating Inventory of Executive Function (BRIEF),³⁰ a parent-reported measure, to evaluate the baseline executive function in all participants. The BRIEF is composed of 86 items and yields an overall measure of executive functions as well as scores on 3 factors: metacognition, emotional regulation and behavioural regulation.

Image acquisition

We collected imaging data using a 3.0 T GE Signa HDx scanner (General Electric Health Care). Participants' heads were positioned comfortably within an 8-channel head coil, and head motion was minimized with firm cushions. We instructed participants to fixate on a central crosshair and to stay awake during image acquisition. Resting state functional images were acquired for 6 minutes and 40 seconds with a gradient-echo echo-planar imaging (EPI) sequence sensitive to BOLD contrast effects. We acquired 200 contiguous EPI resting state volumes, and the parameters for functional imaging were repetition time 2 seconds, echo time 30 ms, flip angle 90°, field of view 24 × 24 cm², acquisition matrix 64 × 64, 5 mm slice thickness with no gap, 30 slices. We also acquired anatomic images with 3-dimensional spoiled gradient recalled pulse sequence (1.5 mm thick contiguous slices) for coregistration with the functional data. Resting state data were obtained after a series of structural and task-based functional scans.

Image analysis

The resting state functional images were preprocessed in SPM8 (Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk/spm) for slice timing correction, motion correction, image normalization and 8 mm Gaussian imaging smoothing. We used Artifact Detection Tools (ART, www.nitrc.org/projects/artifact_detect) software for automatic detection of the global mean and motion outliers in the functional data (z-threshold 6, movement threshold 2 mm). We subsequently used a band-pass temporal filter with cutoff frequencies of 0.01–0.10 Hz on the normalized functional images to extract the low-frequency resting-state BOLD signal.³⁴ The band-pass filtered functional data from all participants were temporally concatenated to form a 4-dimensional data set that we then decomposed into group-level independent components (ICs) using probabilistic ICA, as implemented in MELODIC (Multivariate Exploratory

Linear Decomposition into Independent Components),²³ part of the FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl). We used the MELODIC automated dimensionality estimate to determine the model order of the ICA. Independent component analysis is capable of separating independent spatio-temporal components from resting state fMRI data, including identifying low-frequency RSNs and isolating physiologic, motion or scanner artifacts. Each component includes brain structures that share the same temporal pattern of signal (e.g., neuronal firing). The dual regression approach was subsequently used to back-reconstruct individual-specific connectivity maps associated with each group-level component.³² Group ICA combined with dual regression has been shown to be an effective and reliable approach to exploratory analyses of resting state fMRI data.²⁹ For each IC, we compared individual connectivity maps for voxel-wise differences between the PBD and control groups. We performed permutation testing (randomize, FSL)³¹ with a component-specific mask and 5000 permutations to correct for multiple comparisons at a threshold of $p < 0.05$, corrected. The component-specific mask was generated by thresholding the group-level IC probability map at a threshold of $p > 0.5$, which includes all the voxels that have 0.5 or more probability of belonging to the IC map.

Post hoc analyses

To explore the clinical relevance of the first network (i.e., component 1), which included affect regulation regions, such as the amygdala, we correlated clinical measures with the resting state connectivity at brain regions that showed significant group difference (PBD v. control). The regions where the PBD group showed greater connectivity than the control group included the left and right ACC, right amygdala, right insula and right orbitofrontal cortex (OFC). Region of interest masks for these brain regions were created as the conjunction of anatomic masks (from Harvard-Oxford cortical and subcortical structural atlases) and regions of significant group difference (thresholded at $p < 0.05$, corrected). The resting state connectivity at each region of interest (ROI) was averaged and correlated with clinical measures for the PBD and control groups.

Results

Sample

The total sample consisted of 83 participants. After excluding participants owing to motion artifacts (PBD: $n = 7$; control:

Table 1: Demographic variables and clinical characteristics of children with bipolar disorder and healthy controls

Characteristic	Group; mean (SD)*		Statistical test	<i>p</i> value
	Pediatric bipolar disorder, <i>n</i> = 34	Healthy controls, <i>n</i> = 40		
Age, yr†	13.9 (2.3)	14.9 (2.7)	$F_{1,72} = 2.71$	0.10
Estimated IQ‡	104.1 (9.6)	108.5 (11.2)	$F_{1,72} = 3.22$	0.08
YMRS score	22.8 (7.6)	2.4 (3.3)	$F_{1,72} = 237.30$	< 0.001
CDRS-R score	43.4 (9.9)	21.6 (5.0)	$F_{1,72} = 149.84$	< 0.001
BRIEF overall score§	166.1 (60.8)	80.3 (17.4)	$F_{1,58} = 55.30$	< 0.001
Metacognition/executive domain	94.4 (39.4)	47.2 (11.3)	$F_{1,58} = 39.71$	< 0.001
Emotional regulation	43.1 (18.8)	21.9 (5.9)	$F_{1,58} = 34.65$	< 0.001
Behavioural regulation	28.6 (7.7)	11.1 (2.35)	$F_{1,58} = 140.94$	< 0.001
Sex, no. (%)			$\chi^2_1 = 0.18$	0.67
Male	17 (50.0)	18 (45.0)		
Female	17 (50.0)	22 (55.0)		
Handedness, no. (%)			$\chi^2_1 = 0.94$	0.33
Left	2 (5.9)	5 (12.5)		
Right	32 (94.1)	35 (87.5)		
Race composition, no. (%)			$\chi^2_4 = 2.29$	0.68
White	17 (50.0)	18 (45.0)		
Black	10 (29.4)	11 (27.5)		
Hispanic	4 (11.8)	6 (15.0)		
Asian	2 (5.9)	5 (12.5)		
Other	1 (2.9)	0		
Comorbidity, no. (%)				
None	22 (64.7)	0		
ADHD	5 (14.7)	0		
ODD	4 (11.8)	0		
Other	3 (8.8)	0		

ADHD = attention-deficit/hyperactivity disorder; BRIEF = Behaviour Rating Inventory of Executive Function;³⁰ CDRS-R = Child Depression Rating Scale-Revised;³¹ ODD = oppositional defiant disorder; SD = standard deviation; YMRS = Young Mania Rating Scale.³²

*Unless otherwise indicated.

†Age range 10–18 years.

‡Estimate IQ range 85–134.

§Thirty of 40 in the control group and 30 of 34 in the pediatric bipolar disorder group had parent-reported BRIEF scores.

$n = 2$), 34 patients and 40 controls were included in the analysis. Participants in this final sample ranged in age from 10 to 18 (PBD mean 13.9, standard deviation [SD] 2.3; control mean 14.9, SD 2.7) years. Exactly half of the children with bipolar disorder and 45% of controls were boys. Both groups were within the average range of intelligence (PBD mean IQ 104.1, SD 9.6; control mean IQ 108.5, SD 11.2). Both groups were composed of primarily right-handed people (PBD 94.1%; control 87.5%). The patients and controls were matched on multiple demographic variables, including age, sex, IQ and race. Detailed demographic information and corresponding group statistics are provided in Table 1.

Compared with controls, children with bipolar disorder had significantly higher YMRS ($p < 0.001$), CDRS-R ($p < 0.001$) and BRIEF scores (indicating poorer executive functioning; $p < 0.001$). Within the PBD sample, 58.8% of the patients were classified as having manic episodes and 41.2% as having mixed episodes. During the structured interview, 7 of 34 children with bipolar disorder reported a history of depressive episodes. Eight of 34 patients received minimal doses of medication around the emergence of the disorder. Detailed clinical characteristics and group statistics are included in Table 1.

Primary analyses

Using the multivariate data-driven ICA algorithm, 21 independ-

ent components were automatically extracted, which comprehensively estimated independent signal sources within the data set. Visual examination of all extracted components revealed RSNs that have been consistently identified and documented in pediatric³⁵ and adult^{5,6} populations. In group comparisons using 2 sample t tests ($p < 0.05$, corrected), 3 components showed significant differences between the PBD and control groups, as shown in Figures 1, 2 and 3. These 3 components are described in more detail in the sections that follow.

Component 1 (Fig. 1)

One component consisted of the amygdala, OFC, ACC, insula, caudate and putamen. Activation of these structures correlated with each other during the resting state. The PBD group showed greater connectivity than the control group in many areas within this spatial component, including the bilateral ACC, right amygdala, right insula and right OFC.

Component 2 (Fig. 2)

A second component with synchronized resting state activity consisted of the DLPFC, VLPFC, ACC, basal ganglia, insula, thalamus and inferior parietal cortex. Within this network, the PBD group showed greater connectivity than the control group in the bilateral dorsal ACC only. Interestingly, this dorsal ACC region was also engaged in component 1 (Fig. 1).

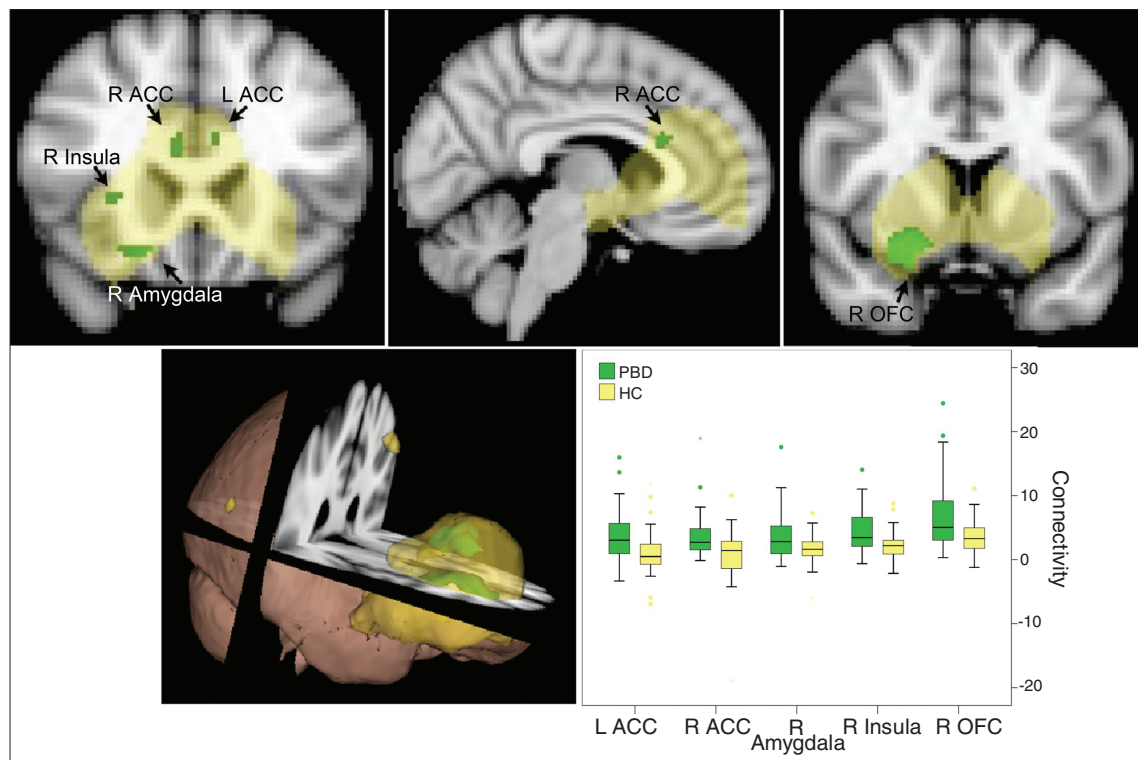


Fig. 1: Resting state affective network in the pediatric bipolar disorder (PBD) versus healthy control (HC) groups ($p < 0.05$, corrected). The yellow region is the identified resting state affective network commonly engaged in the PBD and control groups. The green regions indicate greater connectivity in children with bipolar disorder than controls within this network. ACC = anterior cingulate cortex; L = left; OFC = orbitofrontal cortex; R = right.

Component 3 (Fig. 3)

A third resting state component included the bilateral pre- and postcentral gyri as well as the supplementary motor area. The PBD group showed greater connectivity than the control group in widespread regions throughout this network.

Post hoc analyses

For the PBD group, the post hoc analyses revealed a significant negative correlation between the connectivity values of the right amygdala ROI and the total BRIEF index ($r = -0.439$, $p = 0.017$, uncorrected; Fig. 4). Further exploration of amygdala connectivity with BRIEF subindex scores in the PBD group revealed negative correlations with metacognition ($r = -0.448$, $p = 0.015$, uncorrected), emotional regulation ($r = -0.389$, $p = 0.037$, uncorrected) and behavioural regulation ($r = -0.433$, $p = 0.017$, uncorrected). The negative correlation between amygdala connectivity and BRIEF scores re-

mained significant, except for the emotional regulation index, when an outlier (± 2 SDs) was removed. Furthermore, we found no significant correlation with total YMRS or CDRS-R scores. We explored the correlation of amygdala connectivity with the “elevated mood” item (i.e., the hallmark symptom of a manic episode) on the YMRS, and we found a negative correlation ($r = -0.348$, $p = 0.044$, uncorrected). In the control group, there was no significant correlation between amygdala connectivity and BRIEF or CDRS-R scores. The correlation between amygdala connectivity and YMRS scores for the control group was not analyzed, as there was not enough spread in YMRS scores.

Discussion

Three resting state components differentiated patients with manic or mixed episodes from controls. The topography of the first component — amygdala, OFC, ACC, insula and

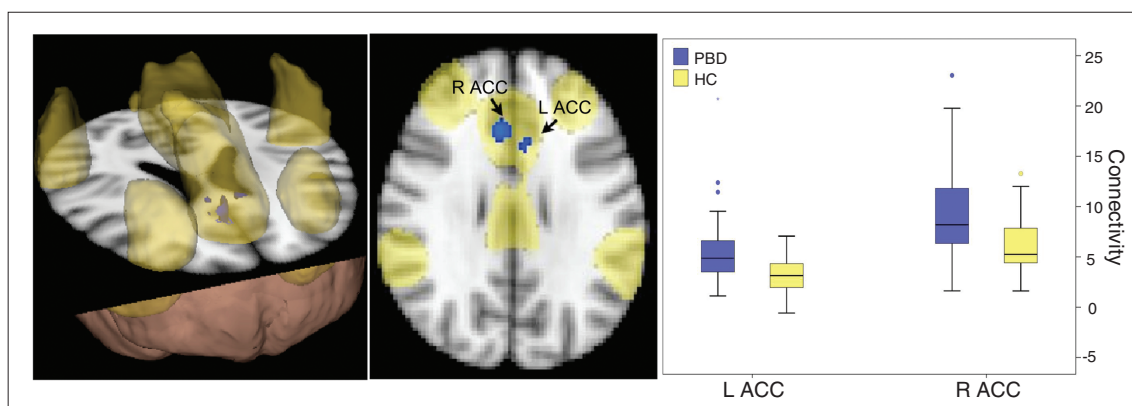


Fig. 2: Resting state executive network in the pediatric bipolar disorder (PBD) versus the healthy control (HC) groups ($p < 0.05$, corrected). The yellow region is the identified resting state cognitive network commonly engaged in the PBD and control groups. The blue regions indicate greater connectivity in children with bipolar disorder than controls. ACC = anterior cingulate cortex; L = left; R = right.

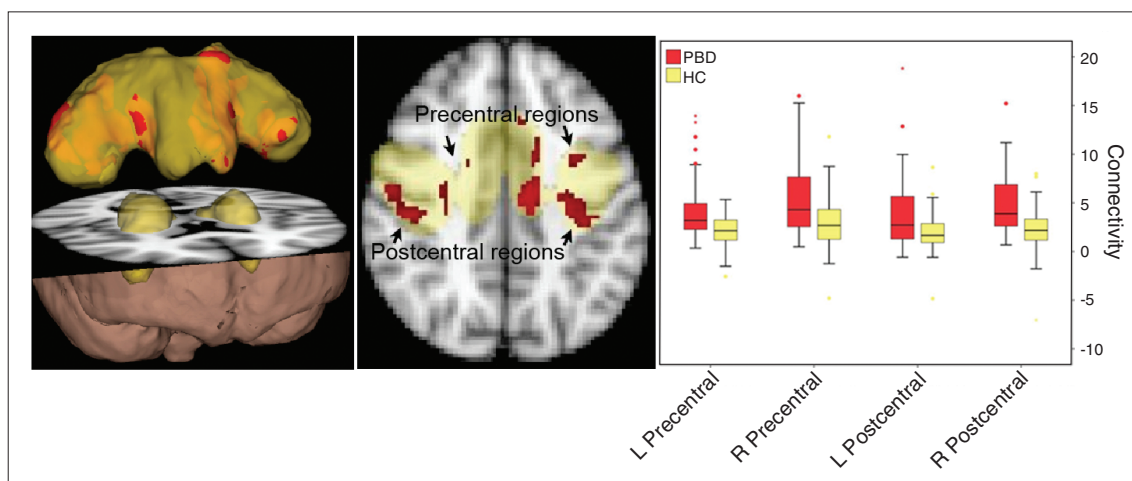


Fig. 3: Resting state sensorimotor network in the pediatric bipolar disorder (PBD) versus the healthy control (HC) groups ($p < 0.05$, corrected). The yellow region is the identified resting state sensory motor network commonly engaged in the PBD and control groups. Red regions indicate greater connectivity in children with bipolar disorder than controls. L = left; R = right.

striatum — included structures known to be involved in affect regulation. We label this as the affective network hereafter. The second resting state component included prefrontal regions, such as the DLPFC and VLPFC, and we label this as the executive network hereafter. The third component consists of sensorimotor cortices and the supplementary motor area; it is labelled as the resting state sensorimotor network hereafter.

Component 1: resting state affective network

The topography of this network includes the amygdala, OFC, ACC, insula and striatum. A similar RSN has been shown in adults with depression to be hyperconnected.³⁶ These brain regions are consistently engaged when probing emotional systems in children with bipolar disorder during conventional fMRI activity studies. For example, compared with controls, children with bipolar disorder showed increased activation in the amygdala across a range of paradigms, including processing faces with negative and positive emotional valence,¹⁹ incidental processing of emotional faces while estimating the age of the faces³⁷ or emotional words during a colour matching task³⁸ and evaluating the level of hostility in emotionally neutral faces.²¹ Diffusion tensor tractography studies have also found white matter tracts that connect the amygdala, OFC, ACC, insula and striatum.^{39–42} The present findings of abnormal hyperconnectivity in children with

bipolar disorder converge with these tractography, fMRI and depression resting state findings to support the hypothesis that there is a network involving the amygdala that is interconnected to subservise affective functioning. Our results indicate that the OFC, ACC, insula and striatum are part of this network. Interestingly, primarily the right side of this network appears to be hyperconnected in children with bipolar disorder relative to controls.

To capture the clinical applicability of the hyperconnectivity findings in children with bipolar disorder, we examined the association between the hyperconnectivity of the amygdala and daily-life functioning during the past month, reflected in the BRIEF score. A lower BRIEF value represents better executive functioning; therefore, our finding of negative correlation between right amygdala connectivity and the total BRIEF score indicates that those with stronger connectivity between the amygdala and the rest of this affective network have better overall function in daily life. Those with good metacognitive and behaviour regulation skills showed stronger resting state connectivity between the amygdala and the resting state of the identified affective network. That the hyperconnectivity in the affective network is related to metacognitive skills reflects the complex interplay between affective and cognitive processes. We also found a negative correlation of right amygdala connectivity with degree of “elevated mood” (hallmark symptom of mania on the YMRS), so stronger connectivity of the amygdala is associated with

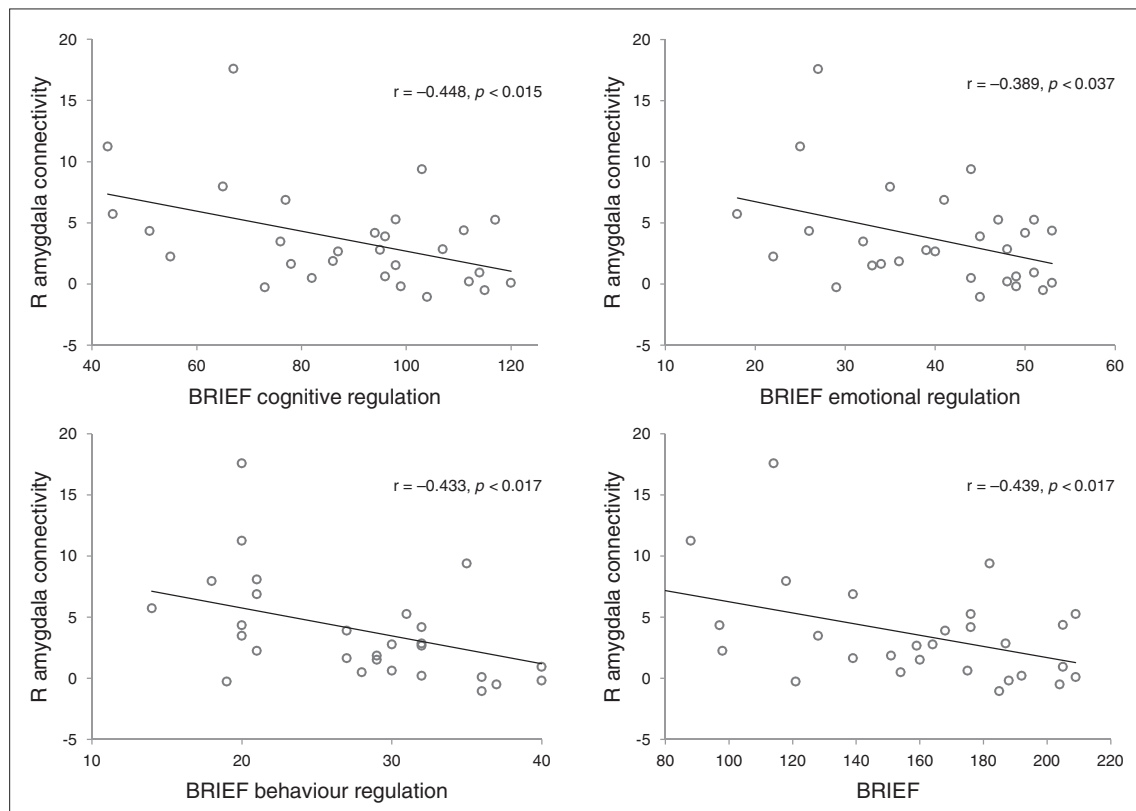


Fig. 4: The association between hyperconnectivity in the right amygdala in the resting state affective network and Behaviour Rating Inventory of Executive Function (BRIEF)³⁰ indices. R = right.

more stable mood status in children with bipolar disorder. These results are consistent with our recent task-based fMRI treatment study, which revealed significant correlation between increased amygdala connectivity during an event-related emotional task and clinical improvement on the YMRS.⁴³ The causal nature of these associations is not known. One possibility is that hyperconnected amygdala with the rest of the affective network within the PBD group reflects a stronger communication route, allowing other regions within the network (e.g., the OFC) to exert influence over amygdala activation, thereby permitting “better” cortical control over emotional response. Alternatively, amygdala hyperconnectivity may have developed as a compensatory mechanism indicating the effort required for some children with bipolar disorder to modulate their emotions. The former possibility suggests that better executive control is a consequence of existing amygdala hyperconnectivity, whereas the latter suggests that amygdala hyperconnectivity is a result of effortful control over functioning. A third possibility is that these correlations are mediated by a yet unknown third factor, and direct relationships between amygdala hyperconnectivity and executive functioning do not exist. The present correlational results are not able to address which of these dynamics is more probable.

Component 2: resting state executive network

The topography of this network included the DLPFC, VLPFC, ACC, basal ganglia, thalamus, insula and inferior parietal lobule. The lateral prefrontal regions are known to subservise executive functions, such as working memory.⁴⁴ For example, these regions are reliably activated on fMRI studies involving the Stroop⁴⁵ or Wisconsin Card Sorting Test.^{46,47} It is also known that prefrontal regions are connected with subcortical regions, such as the basal ganglia and thalamus, via cortico–striato–thalamo–cortical circuits in animals⁴⁸ and in humans,^{39,40} as observed in diffusion tensor tractography studies. Our resting state component shares the same topography with these prior findings, suggesting that these regions have synchronized firing patterns even at rest. Thus these structures may compose an RSN that subserves some executive functions when demanded by the external environment. Our PBD group showed hyperconnectivity in the ACC, part of this resting state executive network. That is, within this network of interconnected structures, only connectivity of the ACC region is stronger in the PBD than the control group. This hyperconnectivity may play a role in some executive function abnormalities that have been observed in patients with bipolar disorder.^{49,50}

It is noteworthy that the ACC is part of both the executive and affective networks during rest. This highlights that an anatomic structure may engage in multiple functions via intrinsic connections with distinct brain networks. The ACC’s involvement in both executive and affective networks may reflect its dual role in both executive functions and affective regulation. This is consistent with the idea that the ACC is a region of interface between affective and executive systems,^{51,52} potentially providing a mechanism for motivational

drives to influence decision-making and vice versa, and for executive evaluation of consequences to regulate limbic response. The PBD group showed hyperconnectivity of the ACC in both executive and affective networks. The functional significance of this hyperconnectivity is not known. One speculation is that the ACC may be part of a neural pathway through which affective dysregulation in children with bipolar disorder is accompanied by poor academic performance. Future studies are needed to focus on the role of ACC connectivity in an affective–cognitive task interface.

Component 3: resting state sensorimotor network

The topography of this network includes prominent involvement of bilateral primary motor and somatosensory cortices along with the bilateral basal ganglia and thalamus. The PBD group showed stronger connectivity than the control group in the cortical regions of this network, but not in the subcortical regions. The increased connectivity in the sensorimotor RSN may arise from the prominent motoric symptoms of increased agitation, restlessness and excessive motor activity during episodes of mania. Neurocognitive and functional imaging studies thus far have focused on deficits in response inhibition as a core component of mood dysregulation in children with bipolar disorder.^{23,53–55} Although motor inhibition is mainly operated by cognitive circuitry, the sensorimotor RSN may be involved. Volumetric structural analyses conducted in the same sample showed that patients with PBD had significantly increased grey matter within the sensorimotor network relative to controls.⁵⁶ These converging findings warrant future task-based studies conducted in parallel with resting state connectivity studies to clarify how connectivity within this network may influence sensitivity to perturbations in the sensorimotor region.

Limitations

One limitation of this study is the lack of generalizability in terms of the high degree of coexisting illnesses and the impact of pharmacotherapy that is often encountered in a PBD population. Patients in this study were recruited during their first episodes of mania. The advantage was that we were able to examine the RSNs during the early part of the disease process, at the cost of generalizability owing to lack of normally presenting comorbid disorders and heavy exposure to multiple medications. In addition, the association between clinical measures and resting state connectivity in the post hoc analyses did not survive multiple comparisons. Therefore, the interpretation of these results is exploratory. Another limitation is the inability to examine “effective” connectivity in our analyses. That is, the ICA approach (along with other methods of correlational analyses, such as seed-based analyses) is limited in its ability to test the directionality of influence, such as top–down (PFC modulating the amygdala) and bottom–up (amygdala modulating the PFC) pathway models.⁵⁷ Nevertheless, this study represents a step forward in elucidating the associations between brain regions in the resting state in children with bipolar disorder relative to

controls using a whole brain approach to allow an extensive characterization of overall network functions.

Conclusion

Compared with controls, children with bipolar disorder showed hyperconnectivity in affective, executive control and sensorimotor networks. In addition, hyperconnectivity of the right amygdala within the affective network in children with bipolar disorder was associated with higher clinical function in affective, cognitive and behavioural domains. Dual engagement of the dorsal ACC in affective and cognitive networks and the amygdala's engagement in moderating executive function may play a key role in the interplay between the affective and cognitive neural operations in the resting state.

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References

- Birmaher B, Axelson D, Goldstein B, et al. Psychiatric disorders in preschool offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring Study (BIOS). *Am J Psychiatry* 2010;167:321-30.
- Geller B, Warner K, Williams M, et al. Prepubertal and young adolescent bipolarity versus ADHD: assessment and validity using the WASH-U-KSADS, CBCL and TRF. *J Affect Disord* 1998;51:93-100.
- Pavuluri MN, West A, Hill SK, et al. Neurocognitive function in pediatric bipolar disorder: 3-year follow-up shows cognitive development lagging behind healthy youths. *J Am Acad Child Adolesc Psychiatry* 2009;48:299-307.
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington: The Association; 1994.
- Damoiseaux JS, Rombouts SA, Barkhof F, et al. Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A* 2006;103:13848-53.
- Chen S, Ross TJ, Zhan W, et al. Group independent component analysis reveals consistent resting-state networks across multiple sessions. *Brain Res* 2008;1239:141-51.
- Greicius MD, Supekar K, Menon V, et al. Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb Cortex* 2009;19:72-8.
- Damoiseaux JS, Greicius MD. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Struct Funct* 2009;213:525-33.
- Deco G, Corbetta M. The dynamical balance of the brain at rest. *Neuroscientist* 2011;17:107-23.
- Chiu S, Widjaja F, Bates ME, et al. Anterior cingulate volume in pediatric bipolar disorder and autism. *J Affect Disord* 2008;105:93-9.
- Dickstein DP, Milham MP, Nugent AC, et al. Frontotemporal alterations in pediatric bipolar disorder: results of a voxel-based morphometry study. *Arch Gen Psychiatry* 2005;62:734-41.
- Wilke M, Kowatch RA, DelBello MP, et al. Voxel-based morphometry in adolescents with bipolar disorder: first results. *Psychiatry Res* 2004;131:57-69.
- Kafantaris V, Kingsley P, Ardekani B, et al. Lower orbital frontal white matter integrity in adolescents with bipolar I disorder. *J Am Acad Child Adolesc Psychiatry* 2009;48:79-86.
- Adler CM, Adams J, DelBello MP, et al. Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. *Am J Psychiatry* 2006;163:322-4.
- Pavuluri MN, Yang S, Kaminen K, et al. Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2009;65:586-93.
- Frazier JA, Breeze JL, Papadimitriou G, et al. White matter abnormalities in children with and at risk for bipolar disorder. *Bipolar Disord* 2007;9:799-809.
- Barnea-Goraly N, Chang KD, Karchemskiy A, et al. Limbic and corpus callosum aberrations in adolescents with bipolar disorder: a tract-based spatial statistics analysis. *Biol Psychiatry* 2009;66:238-44.
- Passarotti AM, Sweeney JA, Pavuluri MN. Neural correlates of incidental and directed facial emotion processing in adolescents and adults. *Soc Cogn Affect Neurosci* 2009;4:387-98.
- Pavuluri MN, O'Connor MM, Harral E, et al. Affective neural circuitry during facial emotion processing in pediatric bipolar disorder. *Biol Psychiatry* 2007;62:158-67.
- Pavuluri MN, O'Connor MM, Harral EM, et al. An fMRI study of the interface between affective and cognitive neural circuitry in pediatric bipolar disorder. *Psychiatry Res* 2008;162:244-55.
- Rich BA, Vinton DT, Roberson-Nay R, et al. Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. *Proc Natl Acad Sci U S A* 2006;103:8900-5.
- Pavuluri MN, Passarotti AM, Harral EM, et al. Enhanced prefrontal function with pharmacotherapy on a response inhibition task in adolescent bipolar disorder. *J Clin Psychiatry* 2010;71:1526-34.
- Passarotti AM, Sweeney JA, Pavuluri MN. Neural correlates of response inhibition in pediatric bipolar disorder and attention deficit hyperactivity disorder. *Psychiatry Res* 2010;181:36-43.
- Dickstein DP, Gorrostieta C, Ombao H, et al. Fronto-temporal spontaneous resting state functional connectivity in pediatric bipolar disorder. *Biol Psychiatry* 2010;68:839-46.
- Beckmann CF, Smith SM. Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Trans Med Imaging* 2004;23:137-52.
- Beckmann CF, DeLuca M, Devlin JT, et al. Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc Lond B Biol Sci* 2005;360:1001-13.
- Greicius MD, Srivastava G, Reiss AL, et al. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A* 2004;101:4637-42.
- Shehzad Z, Kelly AM, Reiss PT, et al. The resting brain: unconstrained yet reliable. *Cereb Cortex* 2009;19:2209-29.
- Zuo XN, Kelly C, Adelstein JS, et al. Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach. *Neuroimage* 2010;49:2163-77.
- Gioia GA, Isquith PK, Retzlaff PD, et al. Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function (BRIEF) in a clinical sample. *Child Neuropsychol* 2002;8:249-57.

31. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp* 2002; 15:1-25.
32. Beckmann CF, Mackay C, Filippini N, et al. Group comparison of resting-state fMRI data using multi-subject ICA and dual regression [poster]. In: Pietrini P, Bookheimer S, Clark VP, editors. *15th Annual Meeting of the Organization for Human Brain Mapping*; 2009 June 18–23; San Francisco (CA). *NeuroImage* 2009;47(Suppl 1):S148.
33. Kaufman J, Birmaher B, Brent DA, et al. K-SADS-PL. *J Am Acad Child Adolesc Psychiatry* 2000;39:1208.
34. Lowe MJ, Mock BJ, Sorenson JA. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage* 1998;7:119-32.
35. Thomason ME, Dennis EL, Joshi AA, et al. Resting-state fMRI can reliably map neural networks in children. *Neuroimage* 2011;55:165-75.
36. Sheline YI, Price JL, Yan Z, et al. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci U S A* 2010;107:11020-5.
37. Pavuluri MN, Passarotti AM, Harral EM, et al. An fMRI study of the neural correlates of incidental versus directed emotion processing in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2009;48:308-19.
38. Pavuluri MN, O'Connor MM, Harral EM, et al. An fMRI study of the interface between affective and cognitive neural circuitry in pediatric bipolar disorder. *Psychiatry Res* 2008;162:244-55.
39. Lehericy S, Ducros M, Van de Moortele PF, et al. Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. *Ann Neurol* 2004;55:522-9.
40. Leh SE, Ptito A, Chakravarty MM, et al. Fronto-striatal connections in the human brain: a probabilistic diffusion tractography study. *Neurosci Lett* 2007;419:113-8.
41. Craig MC, Catani M, Deeley Q, et al. Altered connections on the road to psychopathy. *Mol Psychiatry* 2009;14:946-53.
42. Wakana S, Jiang H, Nagae-Poetscher LM, et al. Fiber tract-based atlas of human white matter anatomy. *Radiology* 2004;230:77-87.
43. Wegbreit E, Ellis JA, Nandam A, et al. Amygdala functional connectivity predicts pharmacotherapy outcome in pediatric bipolar. *Brain Connect* 2011;1:411-22.
44. Elliott R. Executive functions and their disorders. *Br Med Bull* 2003; 65:49-59.
45. Leung HC, Skudlarski P, Gatenby JC, et al. An event-related functional MRI study of the Stroop color word interference task. *Cereb Cortex* 2000;10:552-60.
46. Lie CH, Specht K, Marshall JC, et al. Using fMRI to decompose the neural processes underlying the Wisconsin Card Sorting Test. *Neuroimage* 2006;30:1038-49.
47. Monchi O, Petrides M, Petre V, et al. Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *J Neurosci* 2001;21:7733-41.
48. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986;9:357-81.
49. Pizzagalli DA, Goetz E, Ostacher M, et al. Euthymic patients with bipolar disorder show decreased reward learning in a probabilistic reward task. *Biol Psychiatry* 2008;64:162-8.
50. Adler CM, Holland SK, Schmithorst V, et al. Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. *Bipolar Disord* 2004;6:540-9.
51. Sheline YI, Price JL, Yan ZZ, et al. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci U S A* 2010;107:11020-5.
52. Pavuluri MN, Passarotti AM, Parnes SA, et al. A pharmacological functional magnetic resonance imaging study probing the interface of cognitive and emotional brain systems in pediatric bipolar disorder. *J Child Adolesc Psychopharmacol* 2010;20:395-406.
53. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord* 2009;113:1-20.
54. Mur M, Portella MJ, Martinez-Aran A, et al. Persistent neuropsychological deficit in euthymic bipolar patients: executive function as a core deficit. *J Clin Psychiatry* 2007;68:1078-86.
55. Leibenluft E, Rich BA, Vinton DT, et al. Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. *Am J Psychiatry* 2007;164:52-60.
56. Rich BA, Vinton D, Grillon C, et al. An investigation of prepulse inhibition in pediatric bipolar disorder. *Bipolar Disord* 2005;7:198-203.
57. Almeida JR, Versace A, Mechelli A, et al. Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. *Biol Psychiatry* 2009;66:451-9.

Correction

Reduced neural activity of the prefrontal cognitive control circuitry during response inhibition to negative words in people with schizophrenia

There was an error in the emotional go/no-go task description in the methods section of the above paper by Vercammen and colleagues (*J Psychiatry Neurosci* 2012;37(6):379-88). The original text, "Each trial consisted of a fixation cross for 300 ms, a word stimulus presented in the centre of the screen for 300 ms and a 900 ms response interval" should read "Each trial consisted of a fixation cross for 600 ms, a word stimulus presented in the centre of the screen for 600 ms and an 1800 ms response interval."

We apologize for this error.