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

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Introduction

Pediatric bipolar disorder (PBD) is a cyclical illness with episodes of mania and depression complicated by neurocognitive dysfunction. Mania is characterized by symptoms such as grandiosity, decreased need for sleep, flight of ideas, distractibility, increased goal-directed activity and excessive risk-taking. 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; they reflect underlying monosynaptically or polysynaptically interconnected anatomic regions and may be influenced by history of coactivation during active behaviour. 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), dorsolateral prefrontal cortex (DLPFC) and amygdala, and increased volume in the basal ganglia.
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. Previous task-based functional magnetic resonance imaging (fMRI) studies probing the affective frontolimbic operations have reported abnormally decreased or increased activity in the ventrolateral prefrontal cortex (VLPFC) as well as increased activity in the amygdala and pregenual ACC in children with bipolar disorder. Also, fMRI studies probing motor response inhibition suggested VLPFC–DLPFC–striatal abnormalities in these children. Previous literature on resting state connectivity has reported decreased connectivity between the PFC and the amygdala in adults with bipolar disorder and an anticorrelation between the DLPFC and the temporal cortex in children with bipolar disorder relative to healthy controls 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) detects RSNs at individual and group levels 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 episode 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), supplemented by the episode characterization of mania from the KSADS Present and Lifetime version. 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) and the Child Depression Rating Scale–Revised (CDRS-R). We used the Behaviour Rating Inventory of Executive Function (BRIEF), 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. 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, 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 spatiotemporal 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. Group ICA combined with dual regression has been shown to be an effective and reliable approach to exploratory analyses of resting state fMRI data. For each IC, we compared individual connectivity maps for voxel-wise differences between the PBD and control groups. We performed permutation testing (randomize, FSL) 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>
<thead>
<tr>
<th>Table 1: Demographic variables and clinical characteristics of children with bipolar disorder and healthy controls</th>
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<tr>
<td>Characteristic</td>
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<td>Age, yr†</td>
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<td>YMRS score</td>
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<td>CDRS-R score</td>
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<td>BRIEF overall score§</td>
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<td>Metacognition/executive domain</td>
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<td>Sex, no. (%)</td>
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<tr>
<td>Other</td>
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<td>Comorbidity, no. (%)</td>
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<td>ADHD</td>
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<td>ODD</td>
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<td>Other</td>
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ADHD = attention-deficit/hyperactivity disorder; BRIEF = Behaviour Rating Inventory of Executive Function; CSRS-R = Child Depression Rating Scale-Revised; ODD = oppositional defiant disorder; SD = standard deviation; YMRS = Young Mania Rating Scale. *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 independent 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 pediatric and adult populations. In group comparisons using 2 sample \(t\) tests \((p < 0.05, \text{corrected})\), 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 \((p < 0.05, \text{corrected})\). 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.](image-url)
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 remained significant, except for the emotional regulation index, when an outlier ($\pm 2$ 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
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. 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, incidental processing of emotional faces while estimating the age of the faces or emotional words during a colour matching task and evaluating the level of hostility in emotionally neutral faces. Diffusion tensor tractography studies have also found white matter tracts that connect the amygdala, OFC, ACC, insula and striatum. 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 subserve 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

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\begin{align*}
\text{BRIEF cognitive regulation} & \quad r = -0.448, \ p < 0.015 \\
\text{BRIEF emotional regulation} & \quad r = -0.389, \ p < 0.037 \\
\text{BRIEF behaviour regulation} & \quad r = -0.433, \ p < 0.017
\end{align*}
\]

Fig. 4: The association between hyperconnectivity in the right amygdala in the resting state affective network and Behaviour Rating Inventory of Executive Function (BRIEF) 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. 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 subserve executive functions, such as working memory. For example, these regions are reliably activated on fMRI studies involving the Stroop or Wisconsin Card Sorting Test. 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 animals and in humans, 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.

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, 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. Although motor inhibition is primarily 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. 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. 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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Competing interests: None declared.

Contributors: M. Wu and M.N. Pavuluri designed the study. J. Fitzgibbon acquired the data. M. Wu, L.H. Lu, A.M. Passarotti, E. Wegbreit and M.N. Pavuluri analyzed the data and wrote the article. All authors reviewed the article and approved its publication.

References


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**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.