The Role of Intrinsic Brain Functional Connectivity in Vulnerability and Resilience to Bipolar Disorder

Gaelle E. Doucet, Ph.D., Danielle S. Bassett, Ph.D., Nailin Yao, Ph.D., David C. Glahn, Ph.D., Sophia Frangou, M.D., Ph.D.

Objective: Bipolar disorder is a heritable disorder characterized by mood dysregulation associated with alterations in brain connectivity. Resting-state functional MRI (fMRI) studies in bipolar disorder have shown that disease mechanisms influence intrinsic connectivity, including that of the default mode, sensorimotor, and central executive networks (1–3). Imbalance between the functional connectivity of the sensorimotor and default mode networks has been directly linked with the clinical expression of bipolar disorder, as illustrated in a recent study (2) that found the sensorimotor and default mode networks showing opposite variability patterns during depressive and manic episodes.

Bipolar disorder is highly heritable (4), but the pathway from genetic risk to clinical symptoms is not fully understood. Siblings of patients have about a 10-fold higher risk than the general population, with the mean weighted prevalence of bipolar disorder (all subtypes included) in siblings estimated at 11.9% (5). Disease expression and familial risk for bipolar disorder influence the functional connectivity of brain regions involved mainly in the default mode network, the mesolimbic network, and the central executive network (1, 3, 6). These neural systems–level alterations in individuals with a familial risk of bipolar disorder are thought to occupy an intermediate location on the path from genetic risk to disorder (3, 7). However, despite harboring risk-related features, a significant proportion of relatives remain psychiatrically well. In addition, there is emerging evidence that some measures of brain functional (8–10) and structural connectivity (9, 11) appear to index the avoidance or delayed onset of bipolar disorder in unaffected siblings, suggesting that these measures may involve mechanisms that actively counteract risk. Unaffected relatives may develop psychiatric morbidity at some future point, but as long as they remain well, they may manifest protective changes in brain connectivity. We consider such measures as indicators of “resilience” in relation to avoidance or delayed disease onset.

Here we describe a graph theoretical approach that seeks to disambiguate brain features of risk, disease expression, and resilience to bipolar disorder. Graph theory models the brain as a graph with regions and their connections represented as nodes and edges; its advantage over conventional approaches is that it offers tools to evaluate brain connectivity at the global and regional levels in accordance with the multiscale nature of human brain architecture (12). We obtained resting-state fMRI data from patients with bipolar disorder, their unaffected siblings, and demographically matched unrelated

Method: Graph theoretical methods were used to examine global and regional brain network topology in head-motion-corrected resting-state functional MRI data acquired from 78 patients with bipolar disorder, 64 unaffected siblings, and 41 healthy volunteers.

Results: Global network properties were preserved in patients and their siblings while both groups showed reductions in the cohesiveness of the sensorimotor network. In the patient group, these sensorimotor network abnormalities were coupled with reduced integration of core default mode network regions in the ventromedial cortex and hippocampus. Conversely, integration of the default mode network was increased in the sibling group compared with both the patient group and the healthy volunteer group.

Conclusions: The authors found that trait-related vulnerability to bipolar disorder was associated with reduced resting-state cohesiveness of the sensorimotor network in patients with bipolar disorder. However, integration of the default mode network emerged as a key feature differentiating disease expression and resilience between the patients and their siblings. This is indicative of the presence of neural mechanisms that may promote resilience, or at least delay illness onset.

healthy individuals. This design enabled us to characterize trait-related changes in brain connectivity associated with vulnerability and disease expression in bipolar disorder. We focused on 1) global connectivity, assessed by measures of global efficiency and characteristic path length (two measures of network integration), clustering coefficient (a measure of network segregation), and small-worldness (a measure of the balance between segregation and integration); 2) mesoscale connectivity, assessed by network modularity over a range of spatial scales; and 3) regional connectivity, assessed by nodal degree (a measure of a region's putative influence on the network) and participation coefficient (a measure of the extent to which a given node connects to nodes in modules other than its own).

**METHOD**

**Sample**

Patients with bipolar I disorder (N=78), their unaffected siblings (N=64), and unrelated healthy volunteers (N=41) were recruited from psychiatric facilities and community advertisements in Hartford, Conn. (Further details on recruitment and assessment are provided in the data supplement that accompanies the online edition of this article.) Patients were included if they met DSM-IV criteria for bipolar I disorder based on the Structured Clinical Interview for DSM-IV disorders; had no current substance abuse or dependence; had no history of major medical or neurological conditions; had an IQ >80; and had a sibling willing to participate in the study. Eligibility criteria for siblings and unrelated healthy volunteers were identical to those for patients, with the exception of a personal diagnosis of bipolar or psychosis spectrum disorders. In addition, unrelated healthy volunteers could not have a family history of mood or psychotic disorders. The three groups were matched on sex, age, IQ, and head motion during scanning. Table 1 summarizes the participants' characteristics (for head motion, see Table S1 in the online data supplement). All participants provided informed consent as approved by the institutional review board at Hartford Hospital and Yale University. Given the pooled estimates of 11.9% (SD=4) for the prevalence of bipolar disorder in siblings of patients (5), three to 12 siblings might convert at some future point, within a 95% confidence interval. Moreover, most of the siblings in this sample have gone past the critical risk period because of their age, since the risk of bipolar disorder after age 30 is very low (13). In addition, siblings and patients have remained discordant for a mean period of 15 years, which further reduces the likelihood of disease transition in the healthy siblings (see the online data supplement for additional analyses assessing the resilience of the siblings).

**Neuroimaging**

All MRI scans were collected at the Olin Neuropsychiatry Research Center, Institute of Living, Hartford Hospital, using a research-dedicated Siemens Allegra 3-T scanner. Details of MRI acquisition and preprocessing, including motion correction and parcellation into regions of interest using a validated template (14, 15), are provided in the online data supplement. For each participant, the mean blood-oxygen-level-dependent time course of each region of interest was computed by averaging the time series of all voxels within that region. A matrix (620×620) was created for each participant by computing the Pearson correlation coefficients between time courses for each pair of regions of interest. Correlations were then Fisher r-to-z transformed.

Computation of global and regional connectivity measures. These measures were estimated using MATLAB code in the Brain Connectivity Toolbox (www.brain-connectivity-toolbox.net). To compute each measure, a series of binarized matrices were produced using different thresholds, ranging from the top 1% to 50% of all connections, in increments of 1%, because network measures are less prone to nonbiological artifacts and noise in this density range (16). Negative correlations were set to zero, excluding an average of 42% of the connections (range, 20%–49%).

Global network measures included global efficiency and characteristic path length, two measures of network integration; clustering coefficient, a measure of network segregation; small-worldness, a measure of the balance between integration and segregation; and network robustness to targeted and random attack. Regional measures included nodal degree, equal to the number of links between a node and other nodes; and participation coefficient, a measure of intermodule connectivity. To correct for movement artifacts, the averaged head motion was regressed out from the graph-metric values. Detailed definitions of each measure are provided in the online data supplement.

Functional data analysis was used to assess group differences (17). This analysis is a statistical method that treats a metric curve as a function of the connection density. For each significant metric, we computed the average curve for each group separately (with threshold density on the x-axis and graph metrics on the y-axis). We then computed the area between the two curves (associated with the two groups) by summing the differences between the y values (graph-metric values) of the two groups at each value of x (corresponding to the connection densities). The difference between the two groups was tested for significance using nonparametric permutation testing, whereby the group identity of each individual was randomly reassigned without replacement. Average curves for the two pseudo groups were determined, and the area between the two curves was estimated. This process was repeated 5,000 times to create a set of 5,000 curve differences values. The p value of the true group difference was defined as the number of times the random curve values were greater than the true curve value, divided by the number of iterations.

Computation of mesoscale measures (brain modularity). We used a validated Louvain-like locally greedy algorithm implemented in MATLAB (18) to partition the resting-state brain connectivity in vulnerability and resilience to bipolar disorder.
data of each participant into networks (i.e., groups of brain regions with dense functional interconnectivity) and extract the constituent modules. Details of the procedure and computations involved are provided in the online data supplement. For each individual, we extracted the number, size, and structure of the modules, and we computed the Z-score of the Rand coefficient, an index of topological similarity between each individual partition and the average normative partition (derived from the healthy volunteers) (19). Lastly, we calculated the within-module and between-module functional connectivity for each individual (20). Within-module connectivity is the mean strength of the functional connectivity within a module \(M\), and between-module connectivity is the mean strength of functional connectivity between a module and all other modules. To correct for movement artifacts, the averaged head motion was regressed out and the residuals were entered into Kruskal-Wallis tests to assess group differences for each measure.

For the global and mesoscale level analyses, we first tested for an effect of group (patients, siblings, healthy volunteers), setting the threshold for statistical significance at the 5% level using false discovery rate correction (21). When indicated, we conducted post hoc pairwise analyses to test for differences in connectivity metrics between the three groups at \(p<0.05\). For the regional level, the significant values were set at \(p<0.05\) following permutation testing. When pairwise differences were significant, we provided estimates of effect size (Cohen’s \(d\)).

All connectivity analyses were conducted twice, with and without regressing the effect of age and sex; additional analyses were undertaken to examine the effect of medication and clinical features. These calculations are described in detail in the online data supplement, as they did not have an impact on the results.

**RESULTS**

Global Connectivity

No significant group differences were observed in any of the global graph-theory metrics, even at an uncorrected \(p\) threshold of 0.05 (Figure 1), including network robustness to random and targeted attack (see Figure S2 in the data supplement).

Mesoscale Connectivity (Brain Modularity)

Consistent with previous research (20), we identified four major networks: the default mode network, the central executive network, the sensorimotor network, and the visual network (Figure 2D). There were no significant group differences in the number (Figure 2A), size (Figure 2B), or structure (based on the Z-rand similarity index) (Figure 2C) of the modules at any spatial scale tested (as titrated by the structural resolution

---

**TABLE 1. Demographic and Clinical Characteristics of Patients With Bipolar Disorder, Unaffected Siblings, and Healthy Volunteers in a Study of Brain Connectivity in Vulnerability and Resilience to Bipolar Disorder**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients With Bipolar Disorder (N=78)</th>
<th>Unaffected Siblings (N=64)</th>
<th>Healthy Volunteers (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52 67</td>
<td>37 58</td>
<td>28 68</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34 13</td>
<td>32 13</td>
<td>33 12</td>
</tr>
<tr>
<td>Age at illness onset (years)</td>
<td>19 7</td>
<td>15 12</td>
<td></td>
</tr>
<tr>
<td>Illness duration (years)</td>
<td>15 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (years)</td>
<td>14 2</td>
<td>15 2</td>
<td>15 2</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>105 17</td>
<td>104 20</td>
<td>108 17</td>
</tr>
<tr>
<td>Clinical measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale(^b)</td>
<td>32.7 8.7</td>
<td>25.7 2</td>
<td>24.6 1.2</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale(^b)</td>
<td>7.4 7.3</td>
<td>1.2 1.7</td>
<td>0.5 0.9</td>
</tr>
<tr>
<td>Young Mania Rating Scale(^b)</td>
<td>5.7 6.8</td>
<td>0.6 1.1</td>
<td>0.2 0.6</td>
</tr>
<tr>
<td>Non-bipolar diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous substance abuse</td>
<td>1 1</td>
<td>14 22</td>
<td>4 10</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>0 0</td>
<td>2 3</td>
<td>3 1</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>0 0</td>
<td>3 5</td>
<td>0 0</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>0 0</td>
<td>1 2</td>
<td>0 0</td>
</tr>
<tr>
<td>Medications(^c)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant</td>
<td>22 28</td>
<td>6 9</td>
<td>1 2</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>24 31</td>
<td>3 5</td>
<td>0 0</td>
</tr>
<tr>
<td>Mood stabilizer (lithium)</td>
<td>34 44</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Multiple agents (≥3)</td>
<td>12 15</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>None</td>
<td>15 19</td>
<td>57 89</td>
<td>40 98</td>
</tr>
</tbody>
</table>

\(^a\) No significant differences between groups except as otherwise noted.  
\(^b\) Significant difference between groups (<0.001), patients = siblings = healthy volunteers.  
\(^c\) Medication percentages do not add up to 100 because some participants were on multiple agents.
parameter), even at an uncorrected p threshold of 0.05. In contrast, there was a significant group effect for within-module connectivity for the sensorimotor network (Kruskal-Wallis post hoc test: H=13.1, p=0.01). Within-module connectivity reduction was associated with familial risk for bipolar disorder, as it was reduced both in individuals with bipolar disorder (H=−31.9, p=0.005, Bonferroni corrected; Cohen’s d=0.58) and their siblings (H=−35.8, p=0.002, Bonferroni corrected; Cohen’s d=0.57) compared with healthy volunteers (see Figure S3 in the data supplement).

**Regional Connectivity**

We found group differences in nodal degree and participation coefficient, primarily in regions that are part of the sensorimotor and default mode networks (Figure 3), as detailed in Tables S2 and S3 and Figure S4 in the data supplement. Specifically, disease expression was associated with connectivity changes that differentiated patients both from their siblings and healthy volunteers; patients showed 1) increased nodal degree in higher-order cortical regions (supplementary motor area, middle frontal gyrus, supramarginal gyrus) and the ventromedial prefrontal cortex (medial frontal gyrus) and 2) reduced participation coefficient of the ventromedial prefrontal cortex and the hippocampus. The connectivity changes that are common in patients and siblings were considered as evidence of shared familial risk that define a state of vulnerability to bipolar disorder but are not sufficient for disease expression. Both patients and their siblings showed 1) reduced nodal degree and increased participation coefficient in regions of the sensorimotor network (pre- and postcentral gyri, paracentral lobule) and 2) increased nodal degree in higher-order visual processing regions (inferior temporal cortex). Connectivity changes uniquely associated with resilience were observed within the default mode network.
regions (the ventral anterior cingulate cortex, the angular gyrus, and the precuneus), where siblings showed increased participation coefficient compared with both patients and healthy volunteers.

Because of the association between familial liability and change in functional connectivity in the sensorimotor network in patients and siblings, we tested whether this was also reflected in terms of motor control based on the Barratt Impulsiveness Scale (22) score. This scale is composed of 30 items clustered into three main factors: attentional, motor, and nonplanning. Each factor has two subdomains: attentional focus and cognitive instability; motor impulsiveness and motor perseverance; and self-control and cognitive complexity. We found that patients had significantly higher scores than both their siblings and the healthy volunteers across all factors. The only difference between siblings and healthy volunteers was that siblings had higher motor impulsiveness scores (see Figure S5 in the data supplement).

Additional analyses were conducted to test resilience in the siblings, correlation between the imaging metrics and psychopathology, effects of medications, and the reliability of the results. All are described in the data supplement.

**DISCUSSION**

We characterized the topological organization and network modularity of the brain during the resting-state condition in patients with bipolar disorder, their unaffected siblings, and unrelated healthy volunteers. We found that disease expression, risk, and resilience to bipolar disorder...
were associated with mesoscale and regional changes primarily in the default mode and sensorimotor networks, while global network properties appeared to be conserved both in patients and their siblings (Figure 4).

We found that global network properties in bipolar disorder were preserved in a manner consistent with previous studies examining the structural connectome topology (23) and the global resting-state fMRI signal power and variance in patients with bipolar disorder (24). This contrasts with findings in schizophrenia, where increased global signal variance and network randomization have been reported in patients (24) and their unaffected relatives (25). Although schizophrenia and bipolar disorder have overlapping clinical phenotypes and genetic risk factors (4, 26), preserved global brain organization in bipolar disorder may represent a major difference between the two disorders. This observation aligns with replicated reports of preserved premorbid and academic performance in patients with bipolar disorder (27) and superior academic performance in their relatives (28), which is not the case for schizophrenia (27, 28).

Our results suggest that mechanisms related to vulnerability to bipolar disorder affect brain organization at the mesoscale and at the regional level and that they particularly disrupt the connectivity of sensorimotor regions. Typically the sensorimotor network shows high within-system connectivity and relatively low integration with the rest of the brain (20). This connectomic signature is characteristic of “cohesive provincial” networks that are dedicated to the specialized processing of sensory stimuli and motor responses. In the present study, patients and relatives showed decreased within-module connectivity (indicative of reduced network cohesiveness) coupled with increased interaction of sensorimotor regions with regions outside their module (indicative of greater integration). In other words, the sensorimotor network in bipolar disorder behaves as an incohesive connector network which likely disrupts the processing of sensorimotor information within the brain. It is surprising that research to date has largely overlooked the evidence for sensorimotor dysfunction in bipolar disorder.
FIGURE 4. Schematic Model of Network Organization in Patients With Bipolar Disorder, Unaffected Siblings, and Healthy Volunteers*

A. Healthy Volunteers
B. Patients With Bipolar Disorder
C. Unaffected Siblings

*The figure shows the three major networks, demonstrating differences in topology between groups. Changes in integration are based on results from the participation coefficient and between-module functional connectivity; changes in cohesiveness are based on results from the nodal degree and within-module functional connectivity.

given that abnormalities in motor and sensory processing are included in the diagnostic criteria for manic and depressive episodes. Complementing our findings, a large recent study (29) has reported reduced intracortical myelination in patients with bipolar disorder predominantly in the sensorimotor regions. Further studies have found abnormally reduced motor coordination, sensory integration, sensory gating, and selective attention in patients with bipolar disorder and their unaffected relatives (30, 31). In our data, increased motor impulsiveness was also associated with disease expression and risk for bipolar disorder, consistent with the connectivity changes in the sensorimotor network observed in patients and siblings.

The findings of this study underscore the role of regional default mode network connectivity in disease expression and resilience to bipolar disorder. Regional connectivity was evaluated using nodal degree and participation coefficient. Nodal degree is a measure of general connectedness, and participation coefficient is a measure of intermodular integration of individual brain regions. Typically, the default mode network regions show high within-network cohesiveness (high nodal degree) coupled with high between-network integration (high participation coefficient) (20, 32). These properties allow the default mode network to act as a “cohesive connector” and thus support a wide range of brain functions (20, 32). Consistent with previous reports of default mode network dysconnectivity in bipolar disorder (33, 34), we found that patients had abnormally reduced intermodular integration of two core regions of the default mode network—the ventromedial prefrontal cortex and hippocampus. In healthy individuals, hippocampal-midbrain connectivity supports reward-based learning and memory, and hippocampal-amygdala connectivity underpins contextually appropriate assignment of affective value and behavioral response selection (35). A similar role is conventionally attributed to the ventromedial prefrontal cortex in the regulation of the evaluative, expressive, and experiential aspects of emotion (36). Reduction in the integrative role of the hippocampus and ventromedial prefrontal cortex likely leads to impairment in stimulus appraisal and in contextually appropriate response selection. Moreover, the reduction of the integrative role of the default mode network, when considered together with the findings of the sensorimotor network dysconnectivity described above, supports the study by Martino et al. (2), who found that the balance between activity patterns of the default mode and sensorimotor networks was altered during acute episodes, favoring the default mode network in depression and the sensorimotor network in mania. Our observations suggest that a dysfunction of the default mode and sensorimotor networks is also present during interepisode intervals. The characterization of the cellular correlates of reduced default mode network integration is beyond the resolution of fMRI. Nevertheless, the present results are congruent with impaired neuronal plasticity and may be causally linked to the reduction in GABAergic and glutamatergic receptors reported in postmortem studies of bipolar patients (37, 38).

In contrast to patients, siblings had high participation coefficients in multiple regions of the default mode network that were even higher than those of the healthy volunteers. We infer that enhanced integration of the default mode network may represent an adaptive response to the dysconnectivity of the sensorimotor network observed in siblings and may thus be conducive to resilience (or at least delayed illness onset). This interpretation is speculative pending confirmation by longitudinal studies. Although one might consider increased integration of the default mode network as a prodromal marker for bipolar disorder, this is unlikely given the low risk for conversion in siblings, as discussed earlier, and in greater depth in the data supplement.

We took great care in minimizing potential head motion artifacts based on strict inclusion criteria, in addition to regressing out the average head motion from all of our metrics. The construction of brain graphs from fMRI data requires multiple methodological choices. We confirmed the robustness of our key results using alternative approaches, as detailed in the data supplement (including in Figure S6). Longitudinal studies of high-risk individuals are needed to confirm the association between default mode network connectivity and resilience and to test whether the clinical symptoms of bipolar disorder arise as a result of failure to either develop or maintain enhanced default mode network integration.
In summary, we found that the pathophysiology of bipolar disorder is characterized by abnormalities in regional—and not global—network properties, mainly affecting the default mode and sensorimotor networks. Enhanced default mode network integration was observed in unaffected siblings, which may have mitigated the effects of risk-related dysconnectivity in the sensorimotor network. The latter observation has the potential to open up avenues toward uncovering protective neural mechanisms and thus inform novel interventions to prevent or modify the course of bipolar disorder. Studies in neurological patients (e.g., 39) and healthy individuals (e.g., 40) suggest that both the default mode and sensorimotor networks may be amenable to plasticity-enhancing interventions. Future empirical studies may help define the types of plasticity-dependent interventions that might prove useful in bipolar disorder based on the spontaneous adaptive changes seen in resilient relatives.

AUTHOR AND ARTICLE INFORMATION

From the Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York; the Department of Bioengineering and the Department of Electrical and Systems Engineering, University of Pennsylvania, Philadelphia; the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn.; and the Olin Neuropsychiatric Institute, Institute of Living, Hartford Hospital, Hartford, Conn.

Address correspondence to Dr. Frangou (sophia.frangou@msmu.edu).

Drs. Glahn and Frangou are joint senior authors.

Dr. Frangou received support from NIH grant R01 MH104284-01A1. Dr. Glahn received support from NIH grant R01 MH080912. Dr. Bassett acknowledges support from the John D. and Catherine T. MacArthur Foundation, the Alfred P. Sloan Foundation, the Army Research Laboratory and the Army Research Office through contracts W911NF-10-2-0022 and W911NF-14-1-0679, NIMH grant 2R01-DC-009209-11, National Institute of Child Health and Human Development grant 1R01HD086888-01, the Office of Naval Research; and grants BCS-1441502, BCS-1430087, and PHY-1554488 from the National Science Foundation.

The authors report no financial relationships with commercial interests.

Received Jan. 24, 2017; revisions received March 21 and May 2, 2017; accepted May 18, 2017.

REFERENCES


