State- and trait-related dysfunctions in bipolar disorder across different mood states: a graph theory study

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Introduction

Bipolar disorder (BD) typically features recurring cycles, with brief elevated mood periods followed by extended depressive episodes.1,2 Patients with BD display diverse patterns of progression, treatment response and clinical manifestations. Often, brief episodes of elevated mood in the early stages go unnoticed, resulting in delayed diagnosis and potentially inadequate treatment. Enhancing management requires a profound grasp of the neurobiology of BD and the development of early detection features. Certain features are linked to recurrent manic and depressive episodes, indicating their state-related presence during acute mood episodes. Conversely, some characteristics represent the trait of BD, manifested across various phases and among people at high genetic risk for BD.3–6

Conventional theories of brain function have traditionally centred on specialized domains responsible for cognitive and emotional functions,7 presuming BD emerges from aberrations within regions governing emotional regulation. Recent research, however, has expanded this understanding to include the role of large-scale circuits and networks.8–10 Anatomic wiring patterns in the brain are organized into networks, contributing to dynamic patterns of large-scale neural activity.11,12 These networks integrate sensory, associative and motor areas, supporting the complex features of human cognition and behaviour that span across different systems and modalities.13 Complex network analysis, known as graph theory, quantifies the topologies of network representations. It provides a rigorous mathematical framework for analyzing the topology of complex brain networks consisting of nodes...
The prevailing corpus of graph theory research related to BD lacks distinction regarding the particular mood states that define the expression of the disorder. Nonetheless, employing graph-theoretical methodologies on entire brain networks has unveiled a more intricate portrayal; BD has exhibited subtle reductions in network integration, as indicated by either the characteristic path length14 or equivalent global efficiency.3 However, the latter metric did not retain statistical significance under family-wise error correction.3 Disparities in whole-brain segregation, assessed through the clustering coefficient, have also been documented, albeit with contradictory trends (i.e., both diminished15 and elevated13 levels), potentially attributed to mixed emotional states. Specifically, Wang and colleagues16 found abnormal global properties in BD, including increased characteristic path length, and decreased global efficiency and local efficiency. Locally, patients with BD showed abnormal nodal parameters (e.g., nodal strength, nodal efficiency), predominantly in the parietal, orbitofrontal, occipital and cerebellar regions.16 The observed inconsistencies in global network patterns within BD research, stemming from the conflation of distinct affective states, may further underscore the potential vulnerability of BD’s global network properties to external modulatory factors.17 Some studies indicated that the subtle decreases in whole-brain integration observed in BD may reflect alterations to interhemispheric connectivity,3 as well as the disrupted connectivity of frontolimbic circuits.17,18

Given that emotional dysregulation is central to the phenomenological diagnosis of the illness, it is not surprising that contemporary neurobiological models of BD stress the importance of a frontolimbic network thought to serve affective processing.19–23 Several studies involving BD have implicated an abnormal constellation of regions in the frontolimbic circuit.24–28 Contemporary neurobiological theories propose that emotion is associated with frontolimbic regions — including the hippocampus and insula — that connect to anxiety and fear circuitry, such as the amygdala. These regions interact with cognitive control areas like the inferior frontal gyrus and anterior cingulate cortex.29,30 Supporting this notion, structural magnetic resonance imaging (sMRI) studies have identified morphological abnormalities in frontolimbic and subcortical structures.31–37 The agranular cortices proposed to embed interoceptive predictions comprise the prefrontal and limbic areas that are repeatedly implicated in BD.38–40

Studies on BD face numerous challenges, including the influence of various medication classes, comorbidity and potential secondary effects related to illness manifestation. Tackling these concerns can be accomplished through the examination of unaffected high-risk cohorts. Recent investigations of people at high genetic risk of BD report morphological differences in functionally related brain regions.4,34 Notably, studies on the structural network properties of those at high genetic risk of BD are scarce. One study found abnormal nodal properties in the global network among those at high genetic risk relative to healthy controls.41 However, this study had a small sample size. Furthermore, whether the frontolimbic circuit mediates the relationship between the underlying genetic vulnerability and the disease expression remains unknown. In addition, most studies have ignored the role of connections within the greater network by examining only a small subset of possible connections.

Few network studies have concurrently assessed diverse mood states to elucidate state- and trait-related aspects. Such clarity is pivotal for comprehending the disease’s pathophysiologym, neural attributes linked to susceptibility to and recovery from acute mood episodes, and markers of treatment response. We aimed to explore how this framework can integrate diverse connectomic disruptions among both patients with BD and those at high genetic risk of BD, encompassing local and large-scale connectivity alterations. We sought to use graph theory to probe the state- and trait-related attributes of BD among patients (including those experiencing manic [MBD], depressed [DBD] or euthymic [EBD] episodes), compared with healthy controls. We also sought to conduct further evaluations among those at high genetic risk to substantiate the manifestation of disrupted connectivity in this context, while considering potential confounding effects of medication.

**Methods**

**Participants**

We recruited patients with BD from the psychiatric inpatient unit of the Department of Psychiatry of the First Affiliated Hospital of China Medical University and Shenyang Mental Health Centre in Shenyang, China. Two trained clinical psychiatrists determined diagnoses according to the Structured Clinical Interview for DSM-IV Axis I Disorders. All patients met the diagnostic criteria of the DSM-IV for BD without any other Axis I disorder. On the day of the scan, the patients were rated using the Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAMA) and Young Mania Rating Scale (YMRS), with different thresholds for patients with DBD (HAM-D ≥ 20 and YMRS ≤ 5), MBD (YMRS ≥ 13 and HAM-D ≤ 7) or EBD (HAM-D ≤ 7 and YMRS ≤ 7).

We excluded people with BD in mixed episodes, those with substance or alcohol misuse or dependence; those with a concomitant major medical disorder; those with other Axis I disorders; those with substantial pathological changes (found via T1- and T2-weighted MRI); those with a history of head trauma with loss of consciousness for 5 minutes or longer; those with any neurologic disorder; those with any infectious disease, such as HIV/AIDS or severe acute respiratory syndrome; those with any MRI contraindications; and those with suboptimal imaging data quality.

We also recruited healthy controls without a diagnosis of BD, with the same exclusion criteria as that of the patients. We also recruited 27 first-degree relatives of patients with BD (i.e., at least 1 of their parents or children met the DSM-IV diagnostic criteria for BD). These participants must not have had previous or current DSM-IV Axis I disorders. In addition, we required both healthy controls and those at high genetic risk to have HAM-D and YMRS scores of 4 or less.
**MRI acquisition**

We performed MRI using a 3.0 T GE Sigma system (General Electric) with a standard 8-channel head coil at the First Affiliated Hospital of China Medical University. We acquired $T_1$-weighted images using a 3-dimensional fast-spoiled gradient echo sequence with a repetition time of 7.1 ms, echo time of 3.2 ms, image matrix of $240 \times 240$, field of view of $240 \times 240$ mm$^2$, 176 contiguous slices of 1 mm without gap and a voxel size of $1.0 \times 1.0 \times 1.0$ mm$^3$. We acquired diffusion tensor imaging (DTI) using a single short-spin echo-planar imaging sequence with a repetition time of 17 000 ms, echo time of 85.4 ms, image matrix of $120 \times 120$, field of view of $240 \times 240$ mm$^2$, 65 contiguous slices of 2 mm without gap and 25 noncollinear directions ($b = 1000$ s/mm$^2$), alongside an axial acquisition without diffusion weighting ($b = 0$) and a voxel size of $2.0 \times 2.0 \times 2.0$ mm$^3$.

**MRI preprocessing**

The DTI data set was preprocessed using PANDA. Data preprocessing included brain extraction, correction for eddy-current distortion and simple head motion, correction for the B-matrix, computation of the diffusion tensor and fractional anisotropy.

**Network construction**

We constructed the white matter network using PANDA. The procedure consists of 2 basic steps, the definition of nodes and the definition of edges.

**Network node definition**

We used an automated anatomic labelling atlas to parcellate the cortical and subcortical structures of the brain into 90 regions (excluding the pons and cerebellum). Each region represents a node in the white matter network. First, the structural image (i.e., $T_1$-weighted image) of each participant was coregistered to the b0 image in the native DTI space by linear transformation. Next, the coregistered image was non-linearly normalized to the $T_1$ template of ICBM152 in the Montreal Neurological Institute (MNI) space, resulting in a non-linear transformation. Finally, an inverse transformation was applied to warp the automated anatomic labelling template from the MNI space to each participant’s native DTI space. The frontolimbic circuit involves key brain regions such as the superior, middle and inferior frontal gyri (orbital parts), the olfactory cortex, the cingulate gyrus (anterior, middle and posterior), the hippocampus, the parahippocampal gyrus and the amygdala. These interconnected regions play a vital role in emotional processing, cognitive control and regulation, contributing to understanding of emotional experiences and behaviours. On this basis, we used 22 brain regions (11 in each hemisphere) of the frontolimbic circuit as nodes to establish the white matter structural subnetwork according to automated anatomic labelling (Figure 1).

**Network edge definition**

We implemented the reconstruction of whole-brain white matter tracts using a deterministic fibre assignment by continuous tracking algorithm. If the turn angle of a fibre tract was greater than 45° or if any voxel of a fibre’s fractional anisotropy was less than 0.2, the tracking procedure was terminated. We determined that an edge existed if at least 3 tracts had terminal points between 2 nodes. In this study, we defined the weight of the edges using the mean fractional anisotropy value (an index for evaluating fibre integrity of white matter) of the white matter fibres between 2 nodes. We reconstructed frontolimbic

![Figure 1: The schematic diagram of the frontolimbic circuit brain area.](image)
white matter tracts according to the same procedure. Using these criteria, we obtained 90 × 90 and 22 × 22 fractional anisotropy–weighted metrics in the whole brain and the frontolimbic circuit network for each participant.

We used PANDA to check the quality of the registrations, such as the registration of DTI to T1, T2 to MNI space, and DTI to MNI space. We used TrackVis (www.trackvis.org) to check the quality of deterministic fibre tracking.

**Network analysis**

We chose an array of graph metrics to examine the brain graphs in terms of global and nodal functional integration and segregation. The threshold value for individual participants’ connectivity matrices varied from 0.10 to 0.30 with steps of 0.01. We computed the topological metrics of the white matter network using graph theory. We used GREtna (www.nitrc.org/projects/gretna/) to calculate topological metrics.

**Graph metrics**

We calculated global efficiency, local network efficiency, clustering coefficient ($C_p$), shortest path length ($L_p$), normalized clustering coefficient ($\gamma$), normalized shortest path length ($\lambda$), and small worldness ($\sigma$) for all of the individual networks as global network properties. We also calculated the $C_p$ and $L_p$ in the frontolimbic circuit network. The characteristic path length is the average of all the $L_p$ values between each possible pair in the network. The global efficiency is the average inverse $L_p$.

The local network efficiency is described as the mean of the local efficiencies for all of the nodes in the network. The mean local efficiency across all nodes in the network is what defines the local network efficiency. Local network efficiency reflects the network’s overall resilience to faults and disruptions.

**Small-world properties**

To investigate the small-world topological characteristics of the networks, we contrasted the network’s $C_p$ and $L_p$ values, denoted as $C_p$(real) and $L_p$(real), respectively, with those from 100 randomly generated networks, denoted as $C_p$(rand) and $L_p$(rand), respectively. We established these random networks using the random rewiring approach, maintaining identical node and edge counts as the actual networks, along with the degree distribution, while redistributing the associated weights. We then computed the normalized clustering coefficient

\[
\gamma = \frac{C_p(\text{real})}{C_p(\text{rand})}
\]

and the normalized characteristic path length.

**Global efficiency**

In addition to the conventional small-world parameters, a more biologically sensible property of brain networks is the network efficiency that can be described in terms of global efficiency ($E_{\text{glob}}$). In a complex network, the shortest path length is defined as the smallest sum of the edges throughout all possible paths from nodes $i$ to $j$ in the graph. The average global efficiency of the network ($G$) is defined as the reciprocal of the average of the reciprocals of shortest path length between pairs of nodes within the network.

\[
E_{\text{glob}}(G) = \frac{1}{N} \sum_{i<j} E_{\text{nodal}}(i, j)
\]

**Statistical analysis**

We used 1-way analysis of covariance to compare demographic variables (except for sex, which was compared using the $\chi^2$ test) among the 4 groups (patients with EBD, DBD or MBD and healthy controls), followed by post hoc 2-sample $t$ tests. We used MATLAB (Mathworks) software for statistical evaluations. We performed analysis of variance for between-group comparisons of global, regional and nodal network parameters. We further evaluated statistical differences between 2 groups using post hoc 2-sample $t$ tests. When we compared group differences of those network parameters (global and regional nodal parameters), we considered age, sex and education years as nuisance covariates and regressed them out. We performed partial correlation analyses with age, sex and education years as covariates to investigate the relationship between white matter network metrics and clinical symptoms across all BD groups, with correction for false discovery rate (FDR). Statistical significance was set at $p < 0.05$ for the analysis of demographic and clinical characteristics as well as network metrics. For analyses involving nodal network metrics of the frontolimbic network, we applied an FDR correction for multiple comparisons ($n = 22$ tests; significance set to a corrected $p_{\text{FDR}} < 0.05$). For the secondary analysis, we have described detailed information in Appendix 1, available at jpn.ca/lookup/doi/10.1503/jpn.230069/tab-related-content.

**Ethics approval**

This study was approved by the Medical Science Research Ethics Committee of The First Affiliated Hospital of China...
We included 152 patients with BD — including 52 with DBD, 64 with EBD and 36 with MBD — and 75 healthy controls. All participants were right-handed, with ages ranging from 18 to 50 years. As shown in Table 1, most demographic variables were similar. However, there were significant differences in terms of education level and clinical measures among the 4 groups.

### Results

We observed statistically significant distinctions in global efficiency, local network efficiency and $\gamma$ across the EBD, DBD, MBD and control groups (Figure 2 and Figure 3). Subsequent post hoc analyses showed that both the DBD and MBD groups exhibited notably reduced levels of global efficiency compared with the EBD and control groups. Moreover, the local network efficiency was significantly lower in the DBD group than the MBD group. Remarkably, the DBD group displayed significantly diminished local

![Figure 2: Global (E_{glob}) and local (E_{loc}) network efficiency among patients with euthymic bipolar disorder (EBD), depressive bipolar disorder (DBD) or manic bipolar disorder (MBD), and healthy controls (HC). Each dot represents 1 participant. *p < 0.05.](image-url)
network efficiency and γ values compared with the other 3 groups. Conversely, no discernible differences in λ and σ were noted among the 4 cohorts.

Similar frontolimbic circuit topology

Figure 4 shows the topologies (Lp and Cp) of the frontolimbic circuit in the EBD, DBD, MBD and control groups. Post hoc comparisons showed that patients with EBD, DBD or MBD had significantly lower Lp values than healthy controls. There were no differences in Cp among the 4 groups. Figure 5 shows the brain regions with a significant group effect in the Lp among the 4 groups. We found a group effect in 6 regions, located in the bilateral orbital middle frontal gyrus, the left anterior and paracingulate gyrus, the left medial paracingulate gyrus, the left amygdala and the right lateral orbital superior frontal gyrus. Post hoc comparisons revealed that all these regions had a significantly lower Lp among patients with BD than among healthy controls.

Clinical correlates

We observed significant negative correlations between γ and the total score on the HAMD total (r = −0.269, p < 0.001) and HAMA (r = −0.237, p < 0.001). We also identified a positive correlation between γ and the severity of mania (r = 0.236, p = 0.025; Table 2); however, this association did not remain statistically significant after the FDR correction.

Cross-validation among people at high genetic risk of BD

In our primary analyses, all patients with BD across the 3 emotional states exhibited lower Lp values within the frontolimbic circuit than healthy controls. Our secondary objective involved detecting the diminished Lp levels among people at high genetic risk of BD to eliminate the drug influence. The comprehensive list of variables and clinical details for this group, patients with EBD and healthy controls can be found in Appendix 1.

Figure 4: Shortest path length (Lp) of the frontolimbic network among patients with euthymic bipolar disorder (EBD), depressive bipolar disorder (DBD) or manic bipolar disorder (MBD), and healthy controls (HC). Each dot represents 1 participant. *p < 0.05. γ = normalized clustering coefficient; λ = normalized shortest path length; σ = small worldness.
Discussion

Bipolar disorder is characterized by state-associated alterations in the overall structural connectomes, particularly trait-related irregularities within the frontolimbic circuit, across manic, depressed and euthymic states. Notably, the global efficiency among patients with DBD and MBD was significantly lower than among patients with EBD and healthy controls, with patients with DBD exhibiting the most pronounced reduction. In addition, patients with

Figure 5: (A) The brain regions with significant group differences in nodal shortest path length ($L_p$) in the frontolimbic network among patients with euthymic bipolar disorder (EBD), depressive bipolar disorder (DBD) or manic bipolar disorder (MBD), and healthy controls (HC), including the (B) left orbital middle frontal gyrus, (C) right orbital middle frontal gyrus, (D) right medial orbital frontal gyrus, (E) left anterior cingulate and paracingulate gyrus, (F) left medial cingulate and paracingulate gyrus and (G) left amygdala. *$p < 0.05$. Each dot represents 1 participant.
DBD demonstrated compromised local network efficiency and $\gamma$ values compared with other groups. At a global level, $\gamma$ was negatively correlated with the severity of depression and anxiety. However, the $L_p$ differences between healthy controls and patients with BD, across the mood states, were notably prominent within the frontolimbic circuit, reflecting variations in network parameters. The presence of these consistent findings across diverse mood states, including patients with euthymic BD and people at high genetic risk of BD, underscores the trait-related abnormalities inherent to the disorder.

Only global efficiency was low among patients with MBD and DBD, which suggests, in part, that most global indices such as $\lambda$ and $\sigma$ remain intact in BD, aligning with previous literature.\textsuperscript{17} The disruption of extensive structural networks in BD reveals subtle attributes, primarily localized to specific regions and subnetworks within the frontal and limbic areas.\textsuperscript{17} The subtle decrease in comprehensive whole-brain integration potentially reflects perturbations in interactions within the prefrontal-limbic circuitry. Compared with the conspicuous disruptions observed in schizophrenia,\textsuperscript{50,51} the fundamental structural framework of the connectome remains largely preserved in BD. This is consistent with the cardinal differences in the phenotypes, specifically the relative interepisode preservation of cognition in BD.\textsuperscript{52}

Within the conventional neuroscientific understanding of brain network architecture, there is often an emphasis on the inherent stability of white matter structural networks, positing their resilience to external perturbations.\textsuperscript{53} However, our empirical investigation, which delved into the intricate interplay of brain networks across varying emotional states, found discernible variations in the overall network properties. Beyond the conventional small-world parameters ($C_p$ and $L_p$), an even more biologically relevant feature of brain networks is the sensitivity of the network efficiency, which encompasses global efficiency;\textsuperscript{54} although sensitivity maintains a relationship with $L_p$, this association is not strictly linear, which could be why global efficiency decreased in DBD and MBD. On the other hand, Lavagnino and colleagues\textsuperscript{55} found a reduced posterior corpus callosum volume among females with late-stage type I BD, compared with early-stage type I BD and healthy controls, after controlling for other confounding factors except episode frequency. Substantial evidence shows that white matter changes seem to be altered over the course of BD, and are especially associated with the number of episodes and severity.\textsuperscript{56–58} It is conceivable that participants in depressive or manic states may exhibit a higher propensity for mood cycling, or a distinct ratio of manic-to-depressive episodes, in contrast to participants who are in a euthymic state during the scan. In such a scenario, one could postulate that the observed variations in global efficiency may be attributed to the cumulative impact arising from the number of depressive or manic episodes throughout the course of the illness. Regrettably, we lacked data regarding the number of mood episodes, but this could be a prospective avenue for future investigation. Moreover, in this study, $\gamma$ was negatively correlated with the symptoms of depression, which suggests that the impairment of global brain network segregation may be associated with the severity of depressive symptoms in BD, further corroborating the aforementioned hypothesis. This departure from the conventional supposition prompts a reconsideration of the intricate dynamics governing the relationship between emotional states and the structural underpinnings of brain global connectivity.

The human brain functions as a dynamically interconnected system, governed by 2 key organizational principles, namely segregation, denoted by $C_p$, and integration, evident through reduced $L_p$.\textsuperscript{59,59} Striking a harmonious balance between these attributes enhances the efficiency of higher-level cognitive processes.\textsuperscript{86} The decreased $L_p$ of frontolimbic regions in mood-dysregulated BD indicates reductions in segregation and integration of the brain structure. This

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Table 2: Correlations between the normalized clustering coefficient ($\gamma$) and clinical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>$r$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic anxiety factor</td>
<td>$-0.319$</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Psychic anxiety factor</td>
<td>$-0.138$</td>
<td>0.006</td>
</tr>
<tr>
<td>Core depressive factor</td>
<td>$-0.211$</td>
<td>0.007</td>
</tr>
<tr>
<td>Anorexia factor</td>
<td>$-0.286$</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Total</td>
<td>$-0.269$</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>HAMA total</td>
<td>$-0.237$</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>YMRS total</td>
<td>0.236</td>
<td>0.025</td>
</tr>
</tbody>
</table>

HAMA = Hamilton Anxiety Rating Scale; HAMD = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.
reduction in the length of morphological network pathways could potentially restrict long-range functional integration within brain networks. Disrupting the equilibrium between segregation and integration in the brain’s connectome results in diminished modularized information processing (i.e., reduced capacity to integrate distinct modules in the network) and decreased resilience of brain networks. Imbalanced functional separation and integration capabilities can result in modular information processing and fault tolerance. Compared with healthy controls, patients with BD in different mood states showed a decrease in $L_p$ in the frontolimbic circuit. Similar to our results, Yang and colleagues reported a significant decrease in $L_p$ among patients, suggesting that this decrease limits the integration of long-distance connections in the brain network. In line with our observations, Zhang and colleagues documented reduced $L_p$ among patients with major depressive disorder, compared with controls. A recent study also reported that $L_p$ was significantly lower among patients with BD with mania and depression; however, $C_p$ did not change significantly and was not related to disease severity. In addition, some studies have shown that patients with BD have abnormal white matter structures in the limbic system under different emotional states, further supporting our findings. Given that emotional disorders are at the core of the phenomenological diagnosis of BD, the importance of frontolimbic neural networks is self-evident. The loss of the balance of separation and integration abilities of the frontolimbic network in BD is reflected in the non-optimization of the brain network topology and is unrelated to the emotional state of the disease.

Traditionally, the amygdala has held a pivotal role in conceptual frameworks concerning emotion regulation within the brain, primarily owing to its involvement in appraising threatening and other emotionally important stimuli. Nevertheless, responses to emotional stimuli are contingent on higher-order neural systems that govern affective regulation, characterized by prefrontal cortex regions. As extensively documented, the prefrontal cortex underpins an array of cognitive control and executive functions. In BD, functional underactivation has been observed within several prefrontal cortex regions — including the dorsolateral, ventrolateral, ventromedial, inferior frontal, and subgenual areas — during both emotional and cognitive control tasks. Conversely, heightened activation has been noted in the anterior cingulate cortex, although this may be contingent on task and mood dynamics, with instances of underactivation observed during cognitive control tasks among euthymic patients with BD. Parallel models of BD suggest that malfunctions within these frontolimbic neural circuits are at the core of the emotional and cognitive dysregulation that defines the disorder.

Interestingly, the frontolimbic circuit of patients with BD and adolescents at high genetic risk have been reported to have impaired structural networks. In recent years, studies of candidate genes and genome-wide association studies have received extensive attention. Notably, the insights provided by a meta-analysis support the heritability of neuroimaging abnormalities found in first-degree relatives of patients with BD. Specifically, genetic imaging studies on single-risk variants of BD consistently found that loci near the CACNA1Z, ANK3, 5-HTTLP, NGR1, and BDNF genes had significant effects on the frontolimbic structure. In summary, the low $L_p$ in the frontolimbic circuit of patients with BD and people at high genetic risk of BD, compared with healthy controls, suggests that the imbalance of the separation and integration ability of the frontolimbic circuit is an important factor in the occurrence of disease and is a relatively stable characteristic related to disease.

**Limitations**

Most of the patients in this study were taking medication. We did not collect the precise dose of medication taken by patients with BD on the day of the scan, although we conducted secondary analyses for people at high genetic risk of BD to account for the potential influence of medication. The effects of medication on brain white matter networks in BD are minimal. Interestingly, Hafeman and colleagues found that medication appeared to influence many sMRI studies, but had minimal impact on DTI findings. Most studies show no significant effect of medication status (e.g., class, dose, number) on fractional anisotropy. Future research should also include patients with nonmedicated BD. We lacked sufficient data on the frequency of mood episodes. Addressing this gap presents an opportunity for future research to delve into a crucial aspect of the disorder and its potential implications. We conducted a cross-sectional study without a longitudinal observation. Longitudinal follow-ups of patients with BD and people at high genetic risk of BD should be conducted in the future.

**Conclusion**

In summary, both the DBD and MBD groups displayed notably reduced global efficiency compared with the EBD and healthy control groups, with the DBD group exhibiting the lowest global efficiency. Furthermore, patients with DBD exhibited compromised local efficiency and $\gamma$, and $\gamma$ exhibited a negative correlation with depression and anxiety severity. Patients with BD across various mood states exhibited abnormal $L_p$ within the frontolimbic circuit compared with healthy controls, a pattern also observed among people at high genetic risk of BD, underscoring the intrinsic trait-related anomalies inherent in the disorder. Identifying mood-specific changes throughout the entire brain in BD could potentially provide biomarkers for transitioning between emotional states. In addition, these findings add to the accumulating evidence of enduring frontolimbic circuit disruptions linked to traits, possibly indicating fundamental pathophysiological mechanisms in BD.
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Competing interests: None declared.

Contributors: Yifan Chen, Xizhe Zhang, Yanqing Tang and Fei Wang contributed to the conception and design of the work. Pengfei Zhao, Chunyu Pan, Miao Chang, Jia Duan and Yange Wei contributed to data acquisition, analysis and interpretation. Yifan Chen and Fei Wang drafted the manuscript. All of the authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Funding: The authors were supported by research grants from the National Science Fund for Distinguished Young Scholars (no. 81725005 to Fei Wang), National Natural Science Foundation of China (no. 81571311 to Yanqing Tang, no. 81573131 to Fei Wang), National Key Research and Development Program (no. 2018YFC1511694 to Yanqing Tang, no. 2016YFC1306900 to Yanqing Tang, no. 2016YFC0904300 to Fei Wang), National High Tech Development Plan (no. 863; 2015A020531 to Fei Wang), Liaoning Science and Technology Project (no. 2015222018 to Yanqing Tang), Liaoning Education Foundation (Pandeng Scholar to Fei Wang), Innovation Team Support Plan of Higher Education of Liaoning Province (no. LT2017007 to Fei Wang), Major Special Construction Plan of China Medical University (no. 31101107059 to Fei Wang).

Data sharing: The authors are committed to the principles of transparency and openness within the scientific community. To that end, they pledge to provide all data and materials related to this study to enable replication and further analysis by peers.

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References

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