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Episode-specific cortical functional connectome reorganization and neurobiological correlates in bipolar disorder: a cross-sectional study

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Abstract

Background Bipolar disorder (BD) is a heterogeneous psychiatric condition characterized by distinct episodes: manic (BipM), depressive (BipD), mixed (mBD), and remission (rBD). Current evidence indicates alterations in brain functional connectivity in BD, yet a comprehensive understanding across all episodes remains incomplete.

Methods Here, to investigate how different BD episodes alter brain functional organization, we calculated the sensory-association axis using diffusion map embedding on the functional connectome matrix and compared this axis between the four BD groups and neurotypical controls. Then, we employed regression dynamic causal modeling to investigate the directional information flow along the reorganized sensory-association axis across different BD episodes. Furthermore, we applied Nested Spectral Partitioning to decode functional integration and segregation along the same axis. Finally, we compared the reorganization patterns with normative maps of clinical symptomatology, cellular composition, and receptor distribution to elucidate symptom-related and molecular-level associations.

Results Compared to healthy controls, we observed sensory region expansion and association region compression in BipM, BipD, and rBD. The mBD showed expanded visual and prefrontal regions but compressed motor and precuneus regions. Analyzing neural information flow revealed reduced connectivity in association regions for BipM and BipD, indicating association dominance in functional reorganization. Conversely, mBD exhibited heightened bidirectional signal flow between sensory and association regions, emphasizing increased integrative processing. Network analyses further revealed increased integration and decreased segregation across unipolar episodes, with the highest integration in mBD. Clinical correlations highlighted that emotional fluctuations primarily related to association region reorganization, suggesting potential biomarkers for mood episode detection. Moreover, these functional reorganizations spatially correlated with serotonin transporter, gamma-aminobutyric acid type A receptor, alpha-4-beta-4 nicotinic acetylcholine receptor, and specific cortical neuron layers (layer 4 and layer 5 excitatory neurons).

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Conclusions Our findings propose functional reorganization as both a biomarker and a simplified neural phenotype framework for systematically quantifying BD-related neural abnormalities.

Keywords Bipolar disorder, Episode states, Functional gradients, Functional integration and segregation, Signal flow, Receptor and cellular maps

Background

Bipolar disorder (BD) is a psychiatric condition characterized by extreme mood fluctuations, presenting as manic (BipM), depressive (BipD), mixed episodes (mBD), and remission episodes (rBD) [1–4]. The clinical symptoms of dynamic episodes, such as emotional imbalances, may be associated with various cognitive and behavioral abnormalities and brain function [5, 6]. Among the various episode types, mBD are clinically distinct due to the concurrent presence of manic and depressive symptoms. Compared to pure manic or depressive episodes, mBD is associated with greater functional impairment, higher suicide risk, and poorer treatment response [7–9]. This co-occurrence of opposing affective states may reflect a unique pattern of brain functional organization, particularly involving disruptions in systems supporting emotional and cognitive integration. The current measurement of brain functional alterations primarily relies on functional magnetic resonance imaging (fMRI) [10–12], which detects the regional blood-oxygen-level-dependent (BOLD) signal across continuous time points and offers the spatiotemporal dynamics related to brain function. Resting-state fMRI studies have indicated that emotional dysregulation and cognitive impairments in individuals with BD are linked with disrupted inter-regional connectivities [10, 13]. Utilizing graph theory, studies have found that BD is associated with alterations in brain modularity [14, 15]. However, prior investigations have largely been confined to localized regions or discrete networks, resulting in a fragmented understanding of functional reorganization across the full spectrum of BD episodes [16–18].

Brain organization emphasizes the spatial patterns of integrating and segregating inter-regional information [19], such as functional network communities [20] and continuous gradients of functional spectrum [21]. Functional gradients provide a new insights into smooth transitions between sensory and association regions rather than separate communities, representing the low dimensionality of the regional functional connectome [19]. Association regions are covered by default mode and frontoparietal networks, which support integrative, abstract, and flexible cognitive functions [21]. Furthermore, gradients in brain organization have been studied in multiple psychiatric conditions and demonstrate high sensitivity and robustness [22, 23]. In BD, applying a gradient-based framework may uncover systematic, spatially continuous disruptions along the sensory-association axis—extending beyond localized abnormalities towards a more integrated understanding of global functional architecture. Furthermore, the primary functional gradient in health has been found closely related to neurobiological substrates, including cortical morphology, superficial white matter microstructure, structure–function coupling [24], and genetic patterns [25], highlighting the microstructural and cellular underpinnings of the sensory-association axis of cortical functional organizations [26]. Understanding how the sensory-association gradient is distorted across BD episodes may reveal biologically tractable targets for treatment and etiological studies.

Extending the low-dimension representation approach, advances in dynamic information flow methods (e.g., regression dynamic causal model (rDCM) [27]) have further clarified directional interactions between sensory and association regions, elucidating dominant dynamics among functional regions. For instance, via rDCM and resting state fMRI, a previous study revealed temporal lobe epilepsy showed atypical signal flow among various functional reorganization regions [28]. Even though low-dimensional representation captures the continuous functional variations across the cortical surface, brain functional connectome is highly dimensional, hierarchically organized, and supports nested segregation and integration across multiple spatial scales [29, 30]. While high-dimensional approaches reveal the hierarchical organization and topographical patterns among different brain regions [20], further emphasizing the balance between functional integration and segregation as a uniform framework to understand functional reorganization and cognition flexibility [30, 31]. A recent study has developed the Nested Spectral Partitioning (NSP) method [32] to determine the hierarchical functional reorganization based on segregation and integration balance from the whole high-dimension human networks [33].

Together, functional reorganization, especially functional integration and separation, offers a unified and simplified representation of neural phenotype to quantify mental abnormality of different BD episodes systematically. Functional integration reflects enhanced coordination between brain regions, supporting the

execution of higher-order cognitive tasks, while functional separation ensures the independence of brain regions, maintaining sensory processing and basic functional stability [34–37]. Disruptions in this balance impair the ability to switch between cognitive tasks or emotional states, exacerbating deficits in cognitive flexibility [2, 4, 5, 17, 38]. For instance, excessive integration within the default mode network (DMN) may enhance self-referential thinking, manifesting as rumination and hyper-introspection during depressive episodes [10, 38] while reduced integration between the central executive network and other functional networks during manic episodes can lead to impulsive behaviors and impaired executive function [39]. Also, cumulative evidence has shown that the vulnerability of BD is associated with resting-state cohesiveness of the sensorimotor network and resilience of patients is linked to integration of the default mode network [40]. Notably, these functional reorganizations in BD are underpinned by significant molecular and biological mechanisms [41]. Although these findings highlight the critical role of functional imbalances between primary sensory and higher-order cognitive networks in BD, the exact mechanisms by which these abnormalities serve as a shared etiology across different episodes remain unclear. Developing a unified model to quantify these brain functional changes is essential for advancing cross-episode diagnostics and comorbidity-targeted therapies.

Therefore, in the present study (Fig. 1), we first examine the functional reorganization along the sensory-association axis by contrasting this primary functional gradient between BD and healthy controls (HC). We delineate distinct reorganization patterns among various episodes by further comparing these functional reorganization measures across rBD ($n=37$), mBD ($n=38$), BipD ($n=42$), BipM ($n=38$) and HC ($n=35$) groups. Then, the directional information flows in the reorganized sensory-association axis of different BD episodes are probed via rDCM [27], and the separate integration and segregation in the same axis are decoded via NSP [31]. Finally, the reorganization patterns are compared with clinical symptoms and normative maps of cellular and receptor profiles to investigate the symptomatic and molecular associations.

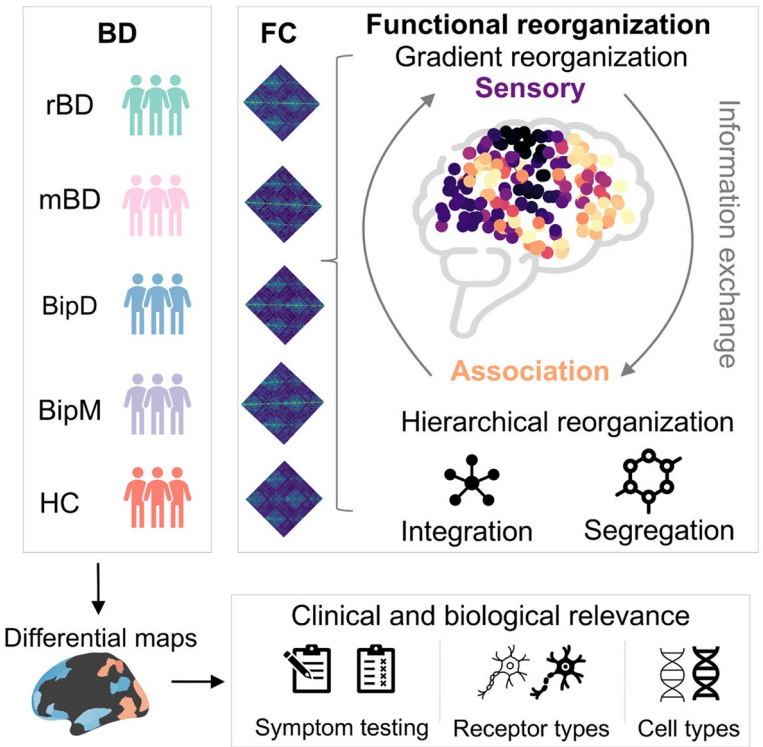

Fig. 1 Overall framework in this study is to understand functional reorganization of four episodes of BD, including rBD, mBD, BipD, BipM, and HC. Here, in this study, we firstly delineate functional reorganization via low dimension representation along the cortex and emphasize information exchange between sensory and association regions. Next, we build Nested Spectral Partitioning (NSP) to summarize functional reorganization across spatial scale. Finally, we associated the functional reorganization patterns with clinical and biological relevance, including receptor and cell types. Note that rBD, mBD, BipD, BipM represent remission episodes,mixed episodes, depressive episodes, and manic episodes, respectively

Methods

The present study received ethical approval from the Ethics Committee of Renmin Hospital, Wuhan University (Approval No. WDRY22022-K195). Prior to participant enrollment, comprehensive information outlining the study's aims, methodology, and potential risks was thoroughly communicated to all participants and, where applicable, their legal guardians—particularly in cases involving individuals with diminished decision-making capacity. Informed consent was obtained only after confirming that participants and their families had fully understood the nature and implications of the research. Written documentation of consent was then secured. Furthermore, the study was prospectively registered with both the National Medical Research Registration Information System and the Chinese Clinical Trial Registry (ChiCTR2200064938).

Clinical symptoms and cognitive assessment

The Young Mania Rating Scale (YMRS) is a clinical assessment tool designed to evaluate the severity of manic symptoms. It comprises 11 items, with scores ranging from 0 to 4 for items 1, 2, 3, 4, 7, 10, and 11, and from 0 to 8 for items 5, 6, 8, and 9 [42]. Clinicians assess each item based on patient responses, and the total score guides the understanding and management of manic symptoms. The Hamilton Anxiety Scale (HAMA) objectively assessed anxiety symptoms. It includes 14 items, each scored from 0 to 4, representing levels of symptom severity: None (0), Mild (1), Moderate (2), Severe (3), and Very Severe (4). Anxiety factors are categorized into somatic and psychic, and scores are analyzed accordingly [14]. The Hamilton Depression Rating Scale (HDRS) is widely used to assess the severity of depression [43]. The HDRS-17 is a newer version that categorizes disease severity, with lower scores indicating milder conditions and higher scores indicating more severe cases. HDRS is divided into seven factors: Anxiety/Somatization, Weight, Cognitive Disturbances, Diurnal Variation, Retardation, Sleep Disturbances, and Desperation. The Perceived Disability Questionnaire (PDQ) assesses the degree of impairment in daily life, work, social, and leisure activities. It consists of 20 items, each scored on a 5-point scale from 0 (no difficulty) to 4 (extremely difficult). The questionnaire covers various functional activities such as concentration, work completion, social interaction, and household chores.

Imaging dataset

Initial screening of research participants was conducted using the Chinese version of the Mini-International Neuropsychiatric Interview (MINI) [44]. All participants were diagnosed by two experienced psychiatrists following the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria for BD [45]. Inclusion and exclusion criteria for the BipM group [2] are as follows: Age 18–45; DSM-5 diagnosis of BD, YMRS > 8, and HDRS < 7; First episode and untreated or first-time undergoing treatment. The criteria for the BipD group [46] were HDRS −17 > 12 and YMRS < 7; inclusion criteria for the rBD group are as follows:: Age 18–45; DSM-5 diagnosis of BD, HDRS < 7, and YMRS < 7; inclusion criteria for the mBD group are as follows:: Age 18–45; DSM-5 diagnosis of BD, HDRS > 12, and YMRS > 8; Patient-initiated discontinuation for more than 14 days. Exclusion criteria are as follows:: MRI contraindications; Organic brain diseases; Other mental illnesses; History of psychotropic medication use or administration of electroconvulsive therapy; Left-handedness; Unstable physical illnesses; Substance abuse history; Pregnancy or lactation; Concurrent other brain function disorders. HC were recruited through community, university, and Hubei Provincial People's Hospital posters, with age and gender matching to the patient group; right-handedness. Exclusion criteria for HC are as follows:: MRI contraindications; Organic brain diseases; Substance abuse history; Pregnancy or lactation; Family history of neurological or psychiatric disorders. All participants had withdrawal and termination criteria: Withdrawal criteria included voluntary withdrawal of informed consent and researcher judgment of unsuitability to continue. Termination criteria involved non-cooperation leading to data invalidation, exclusion from final data analysis, and discontinuation of further investigation.

MRI images were acquired using an Achieva 3 T MRI scanner (GE, SIGNA Architect) equipped with a 48-channel head coil. Participants were instructed to stay awake, remain motionless, relax, and keep their eyes closed during the scanning procedure. To minimize head movement and reduce scan noise, foam padding and soft earplugs were provided. All scans were performed by two licensed MRI technicians with intermediate professional titles in the MRI room. T1_3D data sets were acquired with a maximum TR, minimum TE, a NEX of 1, a layer thickness of 2 mm, and a field of view of 256 × 256 mm^2. Scan time = 7 min. For rs-fMRI, a TR of 2000 ms, a TE of 30 ms, a FOV of 220 mm × 220 mm, a flip angle of 90°, a matrix of 64 × 64, a resolution of 3 × 3 × 3, a slice thickness of 36, and 240 time points were acquired, scan time = 9 min.

The demographics are shown in Table 1. And the quality control could be seen in S-Fig. 1 in Additional File.

HDRS Hamilton Depression Rating Scale, *YMRS* Young Mania Rating Scale, *PDQ* Perceived Disability Questionnaire, *HAMA* Hamilton Anxiety Scale, *rBD* remission

Table 1 Demographics

	Age	Sex(M/F)	Handness (R/L)	HDRS	YMRS	PDQ	HAMA
rBD	24.3 ± 6.5	17/20	37/0	3.54 ± 3.09	3.5 ± 2.7	34.78 ± 8.97	12.18 ± 4.75
BipD	21.9 ± 5.2	15/27	42/0	22.6 ± 3.3	3.24 ± 3.09	45.43 ± 13.25	24.88 ± 7.81
BipM	24.9 ± 6.4	21/17	38/0	5.6 ± 0.8	16.90 ± 6.70	31.25 ± 12.17	17.87 ± 6.97
mBD	17.5 ± 4.1	15/23	38/0	32.32 ± 6.20	11.42 ± 3.15	------	------
HC	26.7 ± 7.3	14/21	35/0	------	------	------	------
F values	0.0307	0.0054	------	321.05	111.61	15.67	35.67
p values	0.96	0.98	------	< 0.001	< 0.001	< 0.001	< 0.001

of bipolar disorder, *BipD* depressive episode of bipolar disorder, *BipM* manic episode of bipolar disorder, *mBD* mixed episode of bipolar disorder, *HC* healthy control.

Data preprocessing and functional connectome

For all datasets, raw DICOM files were converted to Brain Imaging Data Structure (BIDS) [47] format using HeuDiConv v0.13.1. The structural and functional preprocessing of both bipolar individuals was performed with fMRIPrep 23.0.2 [48], which is based on Nipype 1.8.6 [49]. The main anatomical data preprocessing steps include intensity normalization, brain extraction, tissue segmentation, surface reconstruction, and spatial normalization. The main functional data preprocessing steps include head motion correction, slice-time correction, and co-registration. For original preprocessing details generated by fMRIPrep, the derived functional time series were parcellated into the Schaefer 200 × 7 atlas and underwent a confound removal process implemented in Nilearn [50]. The confound removal process adopted the "simple"'strategy from [51], including high-pass filtering, head motion (threshold was 2 mm) and tissue signals removal, detrending, and z-scoring. Functional connectivity matrices were then estimated for each subject using zero-lag Pearson correlation coefficient and Fisher's r-to-z transformation.

Functional organization gradients

We initially generated cortex-wide functional connectome gradients utilizing BrainSpace (version 0.1.10; https://github.com/MICA-MNI/BrainSpace) with default parameters. Consistent with prior study [21], we retained the top 10% of weighted connections per region following z-transformation of the data to return more robust gradient loadings [19]. To capture the similarity in connectivity profiles between regions, we constructed an affinity matrix using a cosine similarity. We employed diffusion map embedding, a robust non-linear manifold learning technique to identify low-dimensional representations from high-dimensional functional connectome for each individual [21]. We extracted the first 10 components but used the first one in this study to focus on the sensory-association axis. Then, individual-level gradient maps were aligned to template gradients generated from 100 unrelated healthy adults from the human connectome project database using Procrustes rotation [52].

To estimate functional reorganization across various BD episodes, we implemented one-way ANOVA to compare the functional organization pattern between rBD/BipD/BipM and HC, respectively. The age and sex were considered covariates and regressed out before group-comparison analysis. Then False Discovery Rate (*FDR*, $q < 5\%$) was used to consider the multiple comparisons correction. Furthermore, post hoc analysis with Tukey's Honest Significant Difference (HSD) was implemented to clarify the multiple comparisons among various episodes.

Cognition decoding for functional reorganization

We then further estimated the cognition relevance of functional reorganization patterns among different episodes of bipolar disorder using *NeuroSynth* [53]. We used twenty cognition maps from a previous study [19] and correlated them with functional gradient difference maps between BD episodes and HC via *Pearson's* correlation. Finally, we visualized cognition terms according to these correlation values.

Information exchange in functional reorganization regions across various episodes of bipolar disorder

To further examine the directional functional flow in reorganization regions, we employed rDCM to parcellation preprocessed time sequence of each subject. rDCM is a computationally efficient framework expanding upon classical dynamic causal modeling (DCM) framework. Compared with the original DCM, rDCM was designed to be more data-driven and implemented a linear hemodynamic response function and mean-field approximation among various regions. A more detailed description of rDCM could be found elsewhere [27, 54]. Specifically, we fit parcellation-level time series

from preprocessed rs-fMRI via TAPAS (https://www.tnu.ethz.ch/de/software/tapas) to obtain whole-brain effective connectome estimation (200×200 matrix) for each individual. To simplify directional information of resting state on the whole cortex, we estimated the weighted outward and weighted inward degrees, reflecting outward and inward signal flows from specific regions, respectively. To simplify the interpretation of cortical flow across functional reorganization regions, we further averaged the weighted outward and inward degree in previous significant regions in sensory regions and association regions respectively and compared them via *one-way ANOVA*, regressing out of age and sex.

Functional integration and separation of cortex-wide connectome

We applied the NSP [30] based on the eigenmodes method to detect hierarchical modules as well as quantify capacity for functional segregation and integration in FC networks. Differing from clustering and modularity-maximization methods, the NSP method is based on a physical principle where regions with the same eigenvector sign are considered cooperatively activated, and regions with different signs are considered oppositely activated [30]. Specifically, using spectral graph theory, the Laplacian matrix of the whole-brain functional connectivity matrix is computed, and its eigenvalues and eigenvectors are utilized to perform an initial partition of the whole-brain functional network. This spectral partitioning minimizes the cut edges between regions, defining the initial functional modules. Based on this initial partitioning, each subnetwork is further partitioned in a nested manner, recursively continuing this process until a predetermined partitioning scale or other termination criteria are met. At each level of partitioning, the strength of connections within each subnetwork (reflecting segregation) and between subnetworks (reflecting integration) is calculated [30, 31]. These metrics quantify the segregation and integration of the brain's functional network at different hierarchical levels. It is noteworthy that the NSP method is influenced by the length of the signal used to construct functional connectivity. However, in this study, the resting-state data collection duration for each subject was consistent.

Finally, we evaluated the segregation and integration coefficients of whole-brain functional connectivity for each individual and used a *one-way ANOVA* and post hoc analysis to compare those coefficients' differences between the disease group and the healthy control group with age and sex as covariates.

Functional reorganization and clinical symptom association

To explore clinical symptoms of functional reorganization, we further linked functional gradient values to clinical symptom estimation. We averaged functional gradient values in previous significant regions in sensory regions and association regions respectively. Then, we calculated *Pearson's* correlation between gradient alteration in BipM, rBD, BipD with YMRS, HRSD, HAMA, and PDQ, respectively, age and sex as covariates.

Molecular mechanism of functional reorganization

Functional reorganization and receptor maps

Receptor densities were assessed through the utilization of PET tracer investigations encompassing a total of 18 receptors and transporters spanning nine neurotransmitter systems. This data, recently shared by Hansen and colleagues (https://github.com/netneurolab/hansen_receptors) [55]. The neurotransmitter systems include dopamine (D1, D2 DAT), norepinephrine (NET), serotonin (5-HT1A, 5-HT1B, 5-HT2, 5-HT4, 5-HT6, 5-HTT), acetylcholine $\alpha4\beta_2$, M1, VAChT), glutamate (mGluR5), GABA (GABAa), histamine (H3), cannabinoid (CB1), and opioid (MOR) [55]. Volumetric PET images were aligned with the MNI-ICBM 152 nonlinear 2009 (version c, asymmetric) template. These images, averaged across participants within each study, were subsequently parcellated into the Schaefer 200 template. Receptors/transporters exhibiting more than one mean image of the same tracer (5-HT1B, D2, VAChT) were amalgamated using a weighted average [55].

Functional reorganization and cellular maps

Here, we further correlated patterns observed in three episodes of bipolar disorder with 24 cellular maps from a previous study [26]. The molecular signature profiles of all cell classes were constructed from snDrop-seq samples provided by [56]. Then cell type fractions were deconvolved from microarray samples downloaded from the Allen Human Brain Atlas (AHBA; http://human.brain-map.org/) [57]. The 24 cell types are Lamp5, Pax6, Vip, Sncg, Lamp5, Lhx6, L5ET, L5/L6 NP, L6 CT, L6b, Astro, VLMC, Endo, Micro/PVM, Oligo, OPC, L2/3 lT, L6 lT Car3, L4 lT, L6 lT, L5 lT, Chandelier, Pvalb, Sst, and Sst Chodl, as detailed in [26].

Null model

In our study, we aimed to explore the topographic correlations between functional reorganization patterns and other notable features. To infer these correlations, we implemented a null model that systematically disrupted the relationship between two topographic maps while

maintaining their spatial autocorrelation [58]. Initially, we shuffled receptor maps or cellular maps and examined their relationship with functional reorganization patterns. The resulting spatial coordinates provided the basis for generating null models through a process of randomly sampled rotations and reassignment of node values based on the nearest resulting parcel [55]. This process was iterated 1000 times. Importantly, the rotation was first applied to one hemisphere and then mirrored onto the other. The threshold value was determined by the 95th percentile of shuffling occurrence frequencies derived from spatial null models.

Results

Functional reorganization across various episodes

We applied diffusion map embedding [21, 59] to cortex-wide functional connectomes derived from resting-state fMRI for each individual and investigated the alteration of functional organization gradients for each episode state compared to healthy controls. Note that compression refers to gradient values becoming more centralized along the gradient axis, whereas expansion denotes a shift toward the extremes. Figure 2a shows the variability of the functional gradient across various episodes.The average principal functional gradient maps across rBD, BipD, BipM, and HC demonstrated a continuous spatial transition from sensory regions to association regions in all groups (S-Fig. 2 in Additional File), accounting for 15.00% ± 0.70%, 15.14% ± 0.92%, 15.30% ± 0.78%, and 15.14% ± 0.83% of total variance respectively and aligning with previous study (Margulies et al., 2016). Notably, for 3 unipolar episodes, we found rBD, BipD, and BipM exhibited markedly higher gradient values in sensory regions and significantly lower gradient values in association regions (all $p_{FDR} < 0.05$, shown in Fig. 2b and S-Fig. 3 in Additional File). The common reorganization regions across the three unipolar episodes included the visual network, dorsal attention network posterior, orbitofrontal cortex in limbic, lateral prefrontal and medial prefrontal in the control network, as well as cingulate cortex in the control network according to Yeo atlas [20]. More specifically, those networks included temporal regions, parietal regions, prefrontal regions, precuneus/posterior cingulate cortex, dorsal prefrontal cortex/medial prefrontal cortex, and visual regions (Fig. 2c). The specific functional reorganization regions for various unipolar episodes are displayed in S-Fig. 4 in Additional File. Note that we did not observe any statistically significant relationship among the three episodes after correction**.** Those results showed functional reorganizations were similar across all episodes and implied it as a common principle to reveal potential shared mechanisms for unipolar episodes. Next, we further compared the functional reorganization of mixed episodes with unipolar episodes. mBD exhibited markedly higher gradients in motor regions and precuneus regions of association anchor, and lower gradient values in visual regions and prefrontal regions of association anchor, shifting from sensory toward association anchor. To further clarify the annotation of functional reorganization, we linked those cortical maps to *NeuroSynth* [53]. We chose 20 terms from [19] and associated them with functional reorganization patterns (shown in S-Fig. 5). mBD reorganization patterns as well as three unipolar episodes were especially related to high-order cognition (e.g., emotion inhibition, autobiographical memory, and social cognition), confirming three unipolar episodes and mBD showed similar brain functions. In all, we observed that expansion in sensory regions and compression in association were general functional reorganization principles of three unipolar episodes. Expansion in visual regions and prefrontal regions, compression in motor regions, and precuneus regions were functional reorganization for mixed episodes, in contrast to HC. However, the three unipolar episodes did not differ from each other.

Information flow in reorganization regions across various episodes

After identifying functional reorganization regions in various episodes, we further explored how information flows clarified dominance between sensory and association regions (Fig. 3a) and implemented rDCM to estimate the cortex-wide effective connectome for each participant (seen in S-Fig. 6 in Additional File). Here, we calculated outward and inward degree centrality in both sensory and association regions to represent information flow across regions in both unipolar episodes and mixed episodes. To simplify the analysis, we averaged outward and inward degrees in the significant sensory and association regions respectively and focused on the significant comparison in Fig. 2b. Via one-way analysis of variance (ANOVA), we found there was a significant difference in outward ($F_{(4,186)} = 5.58$, $P = 0.0003$) and inward ($F_{(4,186)} = 4.34$, $P = 0.0022$) degrees in both association regions and sensory regions between rBD/mBD/BipD/BipM and HC (Fig. 3b and c). Specifically, the post hoc analyses revealed that both the average inward degree and outward degree of rBD, mBD, BipD, and BipM are significantly higher in association regions compared to HC ($P_{HSD} < 0.05$). However, we did not find any statistical difference in both average outward and inward degrees in sensory regions between episodes and healthy controls ($p_{HSD} > 0.05$), indicating the information flow differences were specific to association regions. Then, we found that the average inward degree in both association regions and sensory regions for rBD, BipD, and BipM, compared

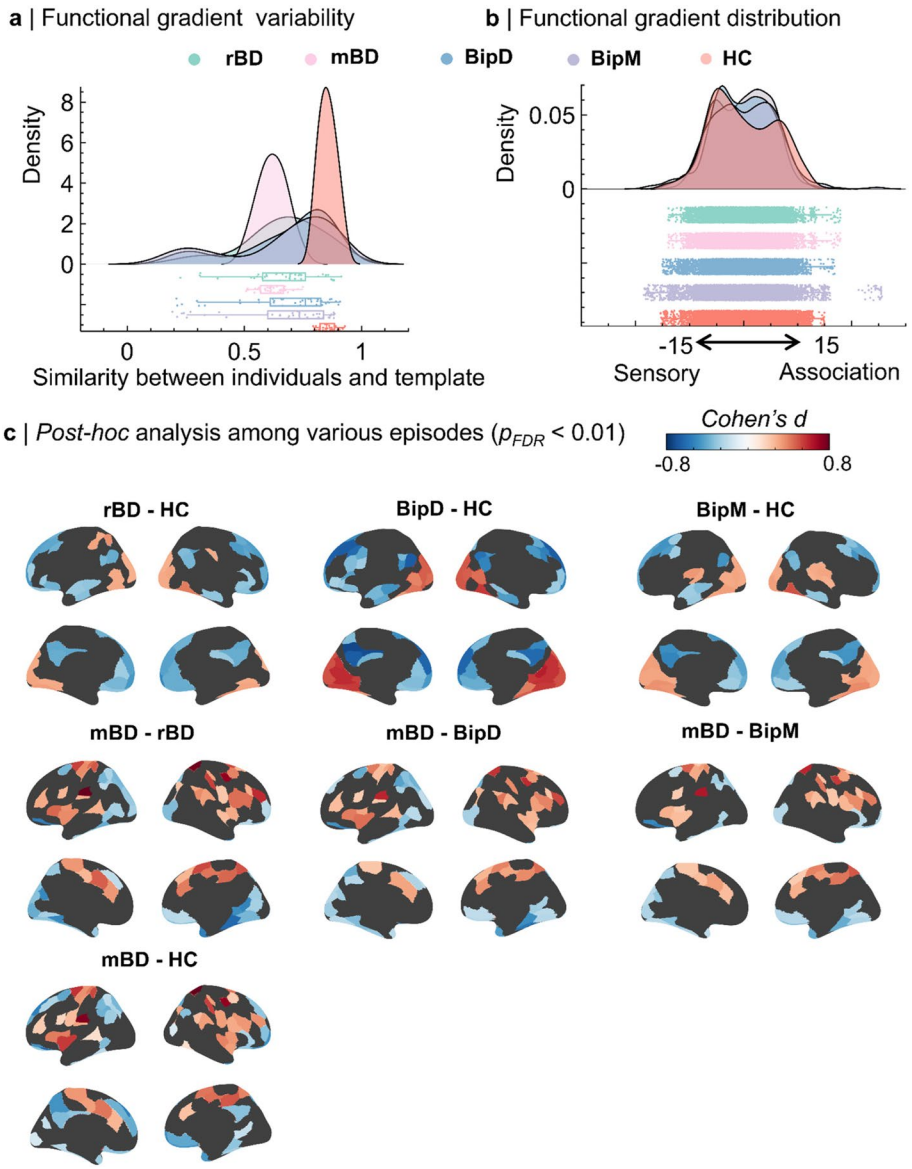

Fig. 2 Functional reorganization in flow dimension space in various episodes, including rBD ($N=37$), mBD ($N=38$), BipD ($N=42$), BipM ($N=38$), and HC ($N=35$) groups. **a** Variability of functional gradient across different BD episodes. Note that variability represents the similarity between individual functional gradient maps and templates. **b** Distribution of functional gradients from various episodes. **c** The comparison of functional gradients among rBD, mBD, BipD, BipM, and HC

to mBD ($P_{HSD}<0.05$). Those results further clarified that association regions dominated the functional reorganization along the cortex continuously in unipolar episodes, while both association regions and sensory regions were affected in mixed episodes.

Functional integration and separation in high-dimensional approaches among various episodes

Although functional gradients offer a perspective to detect both integration and segregation along the cortex continuously, high-dimensional approaches summarize the hierarchical organization and topographical patterns across various spatial scales. Therefore, we explored the separate functional integration and segregation across various episodes via NSP (Fig. 4a). We observed that the first component of NSP was significantly positively related to the functional gradient map ($r=0.51$, $p<0.001$) in S-Fig. 7, suggesting NSP revealed similar information as functional gradient. To further explore the association between NSP values and functional reorganization,

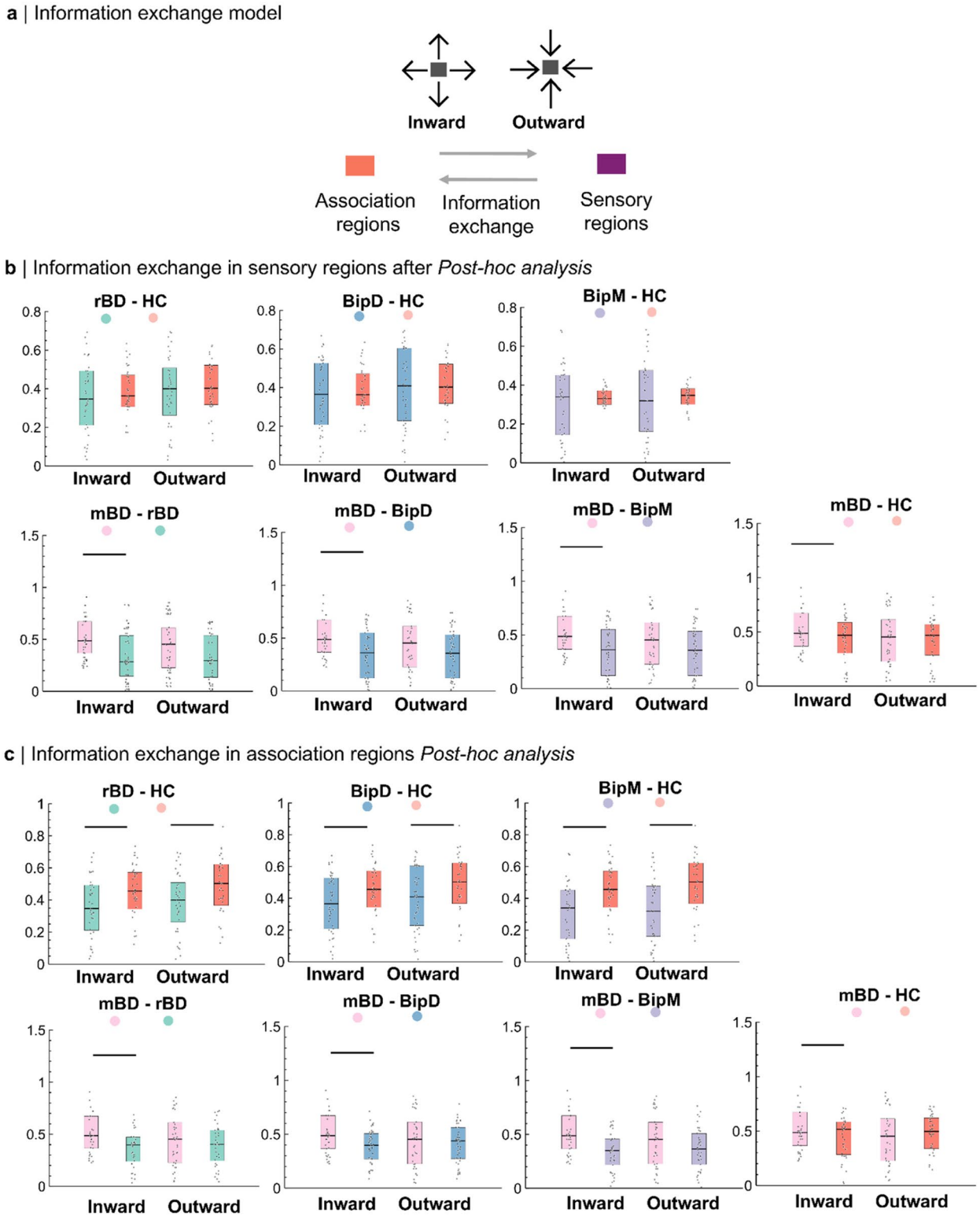

Fig. 3 Outward and inward degree in the sensory and association regions. **a** Outward and inward of functional reorganization regions across rBD, mBD, BipM and BipD via one-way ANOVA and post hoc analysis. Note that the arrows represent information exchange among sensory regions and association regions via inward and outward degree. **b** The abnormal information flows in various episodes in sensory regions ($P_{HSD} < 0.05$). Note that → means significant after post hoc analysis and HSD. **c** The abnormal information flows in various episodes in association regions ($P_{HSD} < 0.05$)

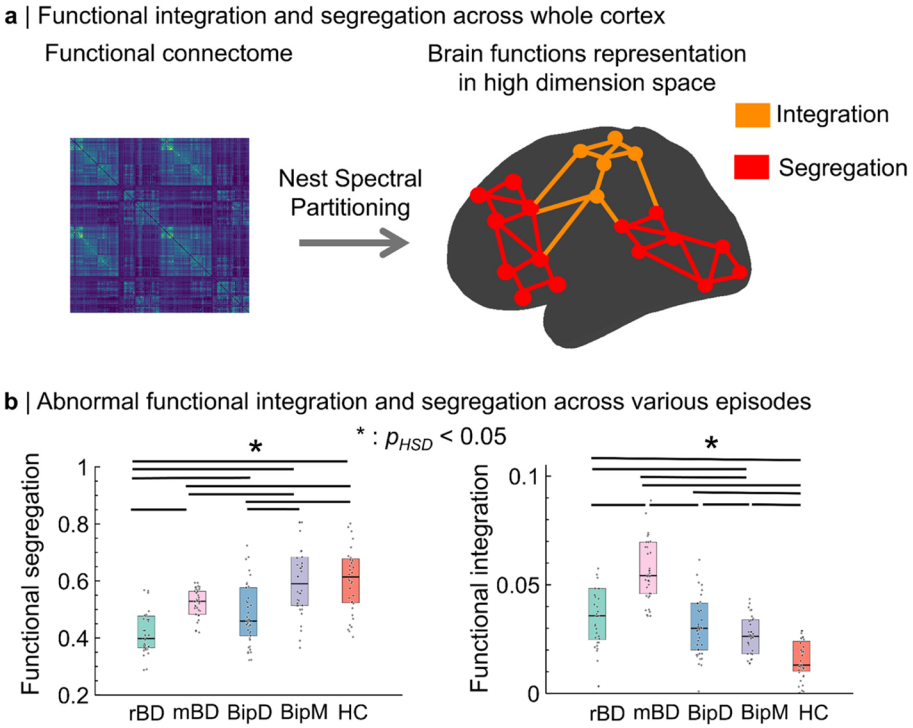

Fig. 4 Functional separation and integration across the whole cortex among rBD, mBD, BipD, and BipM. **a** Whole cortex functional integration and functional segregation. **b** Whole cortex functional integration and functional segregation among rBD, mBD, BipD, and BipM (* means $p_{HSD} < 0.05$ after *post-hoc* analysis)

integration scores defined by NSP were positively correlated with sensory reorganization ($r = -0.19$, $p < 0.05$) and segregation scores were negatively correlated with association reorganization regions ($r = 0.20$, $p < 0.05$) in S-Fig. 8. This suggests that the reorganization of sensory regions is more related to functional integration, while the reorganization of association regions is more associated with functional segregation. Functional separation significantly increased ($F_{(4,186)} = 15.24$, $p < 0.001$) while functional integration significantly decreased from rBD, BipD, and BipM ($F_{(4,186)} = 34.76$, $p < 0.001$) (Fig. 4b). For unipolar episodes, post hoc analyses showed rBD had significantly lower functional separation than BipD ($t = -2.37$, $p_{HSD} < 0.05$), BipM ($t = -5.69$, $p_{HSD} < 0.05$) and HC ($t = —6.32$, $p_{HSD} < 0.05$) while BipD had significantly lower functional separation than BipM ($t = -3.82$, $p_{HSD} < 0.05$) and HC ($t = -4.32$, $p_{HSD} < 0.05$). In contrast, rBD had significantly higher functional integration than BipM ($t = 3.27$, $p_{HSD} < 0.05$) and HC ($t = 5.95$, $p_{HSD} < 0.05$), BipD had significantly higher functional integration than BipM ($t = 2.20$, $p_{HSD} < 0.05$) and HC ($t = 5.28$, $p_{HSD} < 0.05$). And BipM also had higher functional integration than HC ($t = 4.15$, $p_{HSD} < 0.05$). These results further emphasize that the dynamic changes in integration and segregation during functional reorganization in unipolar episodes may reflect a progression of functional imbalance from rBD to BipD, BipM, and finally to HC. For mixed episodes, we found functional segregation in mBD was significantly higher than rBD ($t = 4.00$, $p_{HSD} < 0.05$) but significantly lower than BipM ($t = -3.57$, $p_{HSD} < 0.05$) and HC ($t = -4.15$, $p_{HSD} < 0.05$), while its functional integration was significantly higher than other episodes (rBD: $t = 20.11$, $p_{HSD} < 0.05$; BipD: $t = 25.01$, $p_{HSD} < 0.05$; BipM: $t = 24.73$, $p_{HSD} < 0.05$; HC: $t = 25.04$, $p_{HSD} < 0.05$). In summary, these findings highlight integration and segregation as holistic principles for understanding functional reorganization in BD. They suggest that from rBD to BipD and BipM, the capacity for functional integration progressively weakens, indicating a gradual decline in integrative capacity along this trajectory in unipolar episodes. Also, mixed episodes showed the strongest functional integration capacity across all episodes.

Functional reorganization and clinical symptom in various episodes

Next, we probed the clinical association with neuroimaging findings (Fig. 5) to further confirm functional gradient as a biomarker to quantify functional abnormality of various episodes of BD. Specifically, the analysis also revealed a positive correlation between the HDRS score

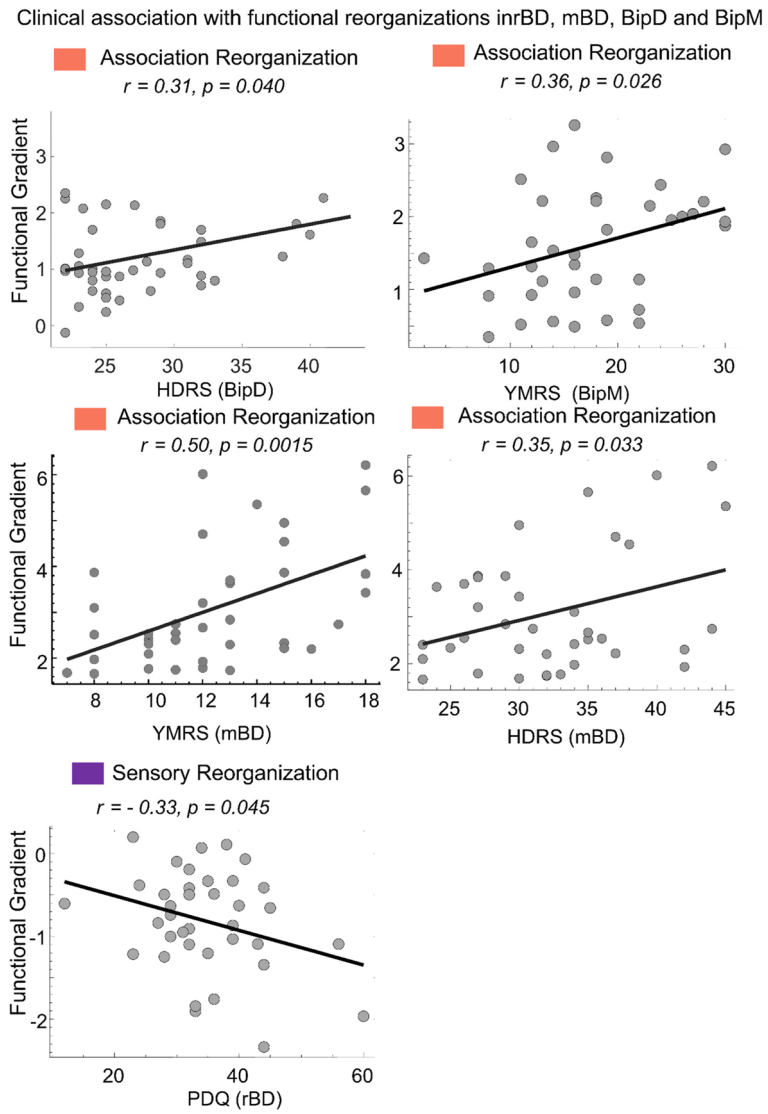

Fig. 5 Functional reorganization in association as well as sensory regions and clinical symptoms across various BD episodes. Association reorganization was positively related with HDRS both in BipD ($r=0.32$, $p=0.038$) and mBD ($r=0.50$, $p=0.0015$) and with YMRS both in mBD ($r=0.35$, $p=0.033$) and BipM ($r=0.43$, $p=0.006$). Also, the sensory reorganization in rBD was negatively related with PDQ scores ($r=-0.33$, $p=0.045$). Note that HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; PDQ, Perceived Disability Questionnaire

and the reorganization of the association areas in BipD ($r=0.32$, $p=0.038$), and between the YMRS score and the reorganization of the association areas ($r=0.43$, $p=0.006$) in BipM. For mBD, sensory reorganization (visual regions) was negatively associated with YMRS ($r=-0.36$, $p=0.003$) and association reorganization (precuneus regions) was positively associated with HDRS ($r=0.35$, $p=0.033$). However, we did not find any significance between the functional reorganization in association areas and YMRS in BipD($r=-0.18$, $p=0.26$), HDRS in BipM($r=0.17$, $p=0.34$) and both YMRS ($r=0.1$, $p=0.87$) and HDRS ($r=-0.21$, $p=0.22$) in rBD (S-Fig. 10 in Additional File). There is no significance between sensory reorganization and YMRS and HDRS in various episodes $p>0.05$). These results suggest that extreme mood changes are mainly related to functional reorganization in association regions, which may be used as specific and sensitive biomarkers to detect mood changes in different episodes. Also, we observed a significantly negative correlation between the PDQ score and the functional reorganization of sensory areas in rBD ($r=-0.33$, $p=0.045$). More specifically, the extension of functional gradient in sensory areas may exacerbate difficulties or impairments in perception for these patients. These findings

confirmed the clinical relevance of the functional reorganization for various BD episodes and further revealed that functional reorganizations may be caused by emotion alternation.

Molecular underpinnings functional reorganization

Next, we further tested the biological association of functional reorganization patterns and focused on common regions across 4 episodes. We conducted spatial correlation analyses between the molecular or cellular maps and functional reorganization maps for each episode, including unipolar episodes and mixed episodes. The molecular and cellular maps are from *Neuromaps* [26, 55], which provides normative maps for various neurotransmitter systems and cellular systems. Here, the spatial correlation reflects which receptor and cellular types association aligned spatially with the sensory-association reorganization axis across various episodes. Specifically, negative association values showed higher cell or neurotransmitter density more related to sensory reorganization, while positive correlation showed more related to association reorganization. Notably, Fig. 6a shows that the reorganization of sensory areas in unipolar episodes was correlated with Paired box gene-cell (Pax6), Synuclein (Sncg), Astrocyte (Astro), and Layer 5 thick-tufted (L5IT), and reorganization of association areas was correlated with L4IT (Layer 4 thick-tufted). The functional reorganization of association for mixed episodes was associated with Layer 5 Extra Telencephalic neurons (L5-ET), Endothelial cells (Endo), Layer 6 Intra Telencephalic neurons expressing Car3 (L6-IT-Car3), and Layer 2/3 Intro Telencephalic neurons (L2/3 IT). These associations suggest that specific genes and cell types may have distinct contributions and mechanisms in the process of functional reorganization and adaptation in different brain regions. This indicates that functional changes in different brain areas may depend on specific molecular and cellular characteristics. At the cellular level, we also found that the reorganization of association areas in unipolar episodes was correlated with the Serotonin Transporter (5 HTT), Dopamine Transporter (DAT), and Gamma-Aminobutyric Acid Type A Receptor (GABAa), whereas the reorganization of sensory areas was correlated with the Alpha4Beta4 Nicotinic Acetylcholine Receptor Subtype (α4β4), Cannabinoid Receptor Type 1 (CB1), and Vesicular Acetylcholine Transporter (VAChT) (shown in Fig. 6b). The association functional reorganization was associated with 5-Hydroxytryptamine receptor 2 A (5HT2a) and 5-Hydroxytryptamine receptor 4 (5HT4) and sensory functional reorganization was associated with Dopamine receptor D1 (D1) and Norepinephrine transporter (NET) in mixed episodes. These findings suggest that the functional reorganization of different brain regions may rely on distinct neurotransmitter and receptor signaling mechanisms, which in turn influence their functional performance under specific pathological or adaptive conditions. Together, these findings suggest that the functional reorganization pattern across various BD episodes aligned topographically with the cortical distribution of chemical neuromodulator systems and implied their potential molecular biomarker.

Discussion

In the present study, we uncovered functional connectome reorganization characteristics of multiple episodes in BD. Specifically, we identified a dichotomy in reorganization: sensory regions expanded and association regions compressed in unipolar episodes. Whereas, functional reorganization in mBD showed predominantly from sensory to association regions. Regional activity propagation revealed reduced outward and inward flows in association regions during unipolar episodes, highlighting their dominant role in functional reorganization. In contrast, mBD exhibited more frequent inward flows, reflecting enhanced sensory-association interactions. A network integration-segregation analysis showed increased integration and reduced segregation in unipolar episodes, with mBD displaying the highest integration levels across all episodes. Furthermore, clinical relevance analysis suggests that emotional changes were mainly related to association functional reorganization, which may be a specific and sensitive biomarker for different episodes. Molecular correlates of these reorganizations included serotonin transporter, gamma-aminobutyric acid type A (GABA_A) receptor, alpha-4-beta-4 nicotinic acetylcholine receptor, and cellular profiles of Layer 4 and Layer 5 thick-tufted cells.

The expansion of sensory regions and compression of association regions suggests a significant reconfiguration of brain network architecture in unipolar episodes. Previous studies have also found compression of functional gradients in the association regions of BD [60] and gradients in sensory regions [61]. Functional reorganization from sensory to association in mBD further revealed there may be greater reliance on sensory regions for processing external information and self-regulation, while association regions may be due to heightened emotional conflict and cognitive burden, reducing their functional influence as emotional fluctuation [62–65]. It suggests that association may be a common marker for network reorganization in psychiatry [66] such as autism spectrum disorder [67], major depression disorder [68], and schizophrenia [69]. Our findings also suggest that such reorganization is a common marker for episodes in BD, though there is no statistical difference between unipolar episodes. The functional gradient reflects both global

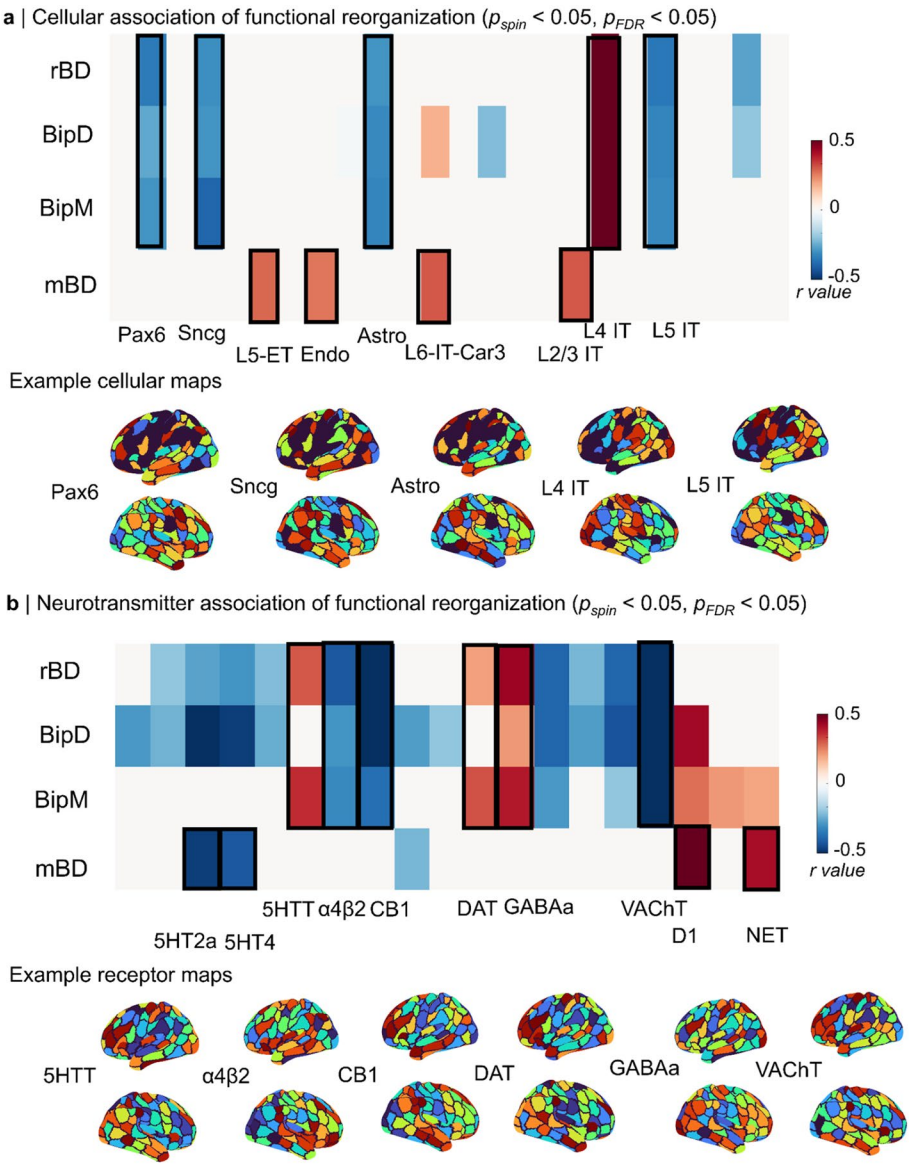

Fig. 6 Molecular mechanism of functional reorganization among rBD, mBD, BipD, and BipM (p_{spin} < 0.05, p_{FDR} < 0.05). **a** Cellular mechanism of functional reorganization. We found sensory reorganization correlated with Pax6, Sncg, Astro, L4IT, and L5IT, and association reorganization correlated with L4IT in unipolar episodes. And association functional reorganization in mixed episodes was associated with L5-ET, Endo, L6-IT-Car3, and L2/3 IT. **b** Receptor mechanism of functional reorganization. Specifically, association reorganization correlated with 5HTT, DAT, GABAa, and sensory reorganization correlated with α4β4, CB1, and VAChT for unipolar episodes. The association functional reorganization was associated with 5HT2a and 5HT4, and sensory functional reorganization was associated with D1 and NET in mixed episodes. Note that Pax6, Sncg, Astro, L4IT, L5IT, L5-ET, Endo, L6-IT-Car3, L2/3 IT, 5HTT, DAT, GABAa, α4β4, CB1, VAChT D1 and NET means Paired box gene, Synuclein, Astrocyte, Layer 4 thick-tufted, Layer 5 thick-tufted, Layer 5 Extratelencephalic neurons, Endothelial cells, Layer 6 Intratelencephalic neurons expressing Car3, Layer 2/3 Intratelencephalic neurons, Serotonin Transporter, Dopamine Transporter, Gamma-Aminobutyric Acid Type A Receptor, Alpha4Beta4 Nicotinic Acetylcholine Receptor Subtype, Cannabinoid Receptor Type 1 and Vesicular Acetylcholine Transporter, dopamine receptor and Norepinephrine Transporter

integration and segregation [19]. In this study, functional reorganization in three unipolar episodes indicated that sensory and motor areas, which are primarily responsible for processing external stimuli, become more prominent, while association regions involved in higher-order cognitive functions lose their functional influence [70]. Such reorganization could be a compensatory mechanism where the brain reallocates resources to maintain basic sensory and motor functions at the expense of higher-order cognitive processes. This finding

is consistent with previous studies that have reported reduced connectivity within the DMN [71] and affective networks during acute episodes but not in remitted states of BD.

Our study also highlights the significant role of aberrant association information interaction in unipolar episodes of BD, compared with sensory regions. We found that the signal outward flow and inward flow of association regions were significantly lower in three unipolar episodes of BD compared to healthy individuals. A widely accepted mechanism underlying bipolar disorder is the early developmental disruption in brain networks that regulate emotional behavior (e.g., white matter connectivity and prefrontal pruning), leading to reduced connectivity between the ventral prefrontal network and limbic brain regions [72]. Those regions consist of association regions, and their reduced connectivity suggests a core dysfunction in BD that transcends symptomatic episodes, contributing to the cognitive and emotional dysregulation observed in BD [73]. Also, we found inward flow in both sensory regions and association regions in mBD was highest across all episodes. Indeed, the mBD is often characterized by extreme emotional and behavioral states, with heightened emotional conflict and cognitive burden, leading to enhanced functional integration and information exchange within association regions [74, 75]. Specifically, the enhanced bidirectional signal flow may reflect both a compensatory mechanism, where sensory regions become hyper-responsive to external stimuli, and elevated demands placed on association regions due to increased emotional and cognitive processing needs. Furthermore, abnormal connectivity between these two domains could exacerbate the integrative demands, resulting in a pronounced functional imbalance along the sensory–association axis unique to mBD. Our findings are aligned with the previous assumption and further clarified association regions were dominated in the functional reorganization across various episodes of BD.

Using large-scale functional connectivity modeling, we observed a significant increase in the brain's integration capacity and a decrease in its segregation capacity during BipM, BipD, and rBD. While mBD had the highest integration capacity among all episodes, compared to HC. These alterations suggest a shift towards a more globally connected but less modular brain network organization in BD. A normally functioning brain at rest maintains a balance between segregation and integration, allowing for efficient communication both locally and globally. This balance is associated with the integration of primary sensory information and emotion regulation [76]. Previous studies have indicated that imbalances in this functional segregation and integration may be related to functional abnormalities in various brain disorders [31]. In this study, we further emphasize that the hierarchical structure of integration-segregation may underlie the emotional abnormalities and consequent behavioral anomalies observed across different BD episodes. Increased integration capacity may reflect compensatory mechanisms attempting to maintain cognitive function, while decreased segregation capacity could indicate a loss of specialized processing within distinct functional domains. This shift in network organization is consistent with findings from studies comparing functional connectivity patterns between unipolar and bipolar depression, which have shown altered connectivity in prefrontal and limbic networks [77].

Finally, our study identifies sensory-association functional reorganization anchors across BD episodes, which are strongly associated with specific receptors and cell types. Sensory reorganization correlated with Pax6, Sncg, Astro, and L5IT, while association reorganization was linked to L4IT. At the cellular level, association reorganization was associated with 5HTT, DAT, and GABAa, whereas sensory reorganization correlated with α4β4, CB1, and VAChT. These findings highlight that the functional properties of the human brain are influenced by the diverse cell types in the cortex, with cellular spectra aligning with the macroscopic organization of functional gradients and networks [26]. 5HT4 receptors modulate serotonin signaling, crucial for mood regulation and cognition [78], while 5HTT receptors regulate serotonin availability [79]. CB1 receptors, part of the endocannabinoid system, influence mood and synaptic plasticity [80]. Higher GABA receptor density in association regions may enhance inhibitory control, thereby reducing long-range excitatory drive and promoting local functional specialization—manifesting as increased segregation and gradient compression in these areas [81]. In sensory regions, elevated alpha-4-beta-4 nicotinic receptor expression, particularly in thalamocortical pathways, may enhance sensory gain and cholinergic signaling, supporting excitation and integration with higher-order areas and contributing to gradient expansion in specific bipolar conditions [82]. mGluR5 receptors contribute to synaptic plasticity and excitatory neurotransmission [83]. Our results suggest that these receptors modulate synaptic plasticity and firing patterns, impacting large-scale brain network integration and segregation. These abnormalities likely reflect the molecular basis of emotion-driven brain function and behavioral disruptions in BD. Similarly, Pax6 [84], Snc [85] and L5IT single-cell [86] spectra are indicative of specific cell types and their gene expression profiles, which are intricately linked to the observed changes in brain network organization. The differential expression and action of these receptors and cell types across cortical gradients may thus serve as mechanistic

links between molecular architecture and the episode-specific functional topographies of BD. Together, these findings strengthen the rationale for linking multiscale brain organization—from gene expression to network dynamics—as a framework for understanding the biological heterogeneity of BD.

Limitations

Several limitations warrant consideration in this study. Firstly, our sample was sourced from a single site, and the relatively small sample size may constrain the reliability and generalizability of our findings. Future research will focus on multicenter studies with larger samples to address these limitations. Such an approach will enhance the external validity of our research, facilitating the extrapolation of findings to a broader patient population. Secondly, our study included both initial BipM patients and those with rBD beyond the medication washout period to gain a comprehensive understanding of the imaging features of BD. Even though we included the first episode participants in this study, it is important to acknowledge the potential impact of medications on brain function as a limitation, though this is a common challenge in BD research [87], and an ideal solution has yet to be identified. Lastly, the receptor maps and cellular maps utilized in our study were derived from group-averaged results of previous research, without accounting for individual differences. Future studies will need to validate these findings by considering individual variability.

Conclusions

In summary, our study systematically elucidates brain functional reorganizations during various BD episodes. We argued functional reorganization may serve not only as a specific biomarker for detecting mood changes across different episodes of bipolar disorder but also as a unified and simplified neural phenotype framework for systematically quantifying mental abnormalities across these episodes. The identified patterns of sensory expansion and association compression suggest a reconfiguration of brain network architecture that aligns with compensatory mechanisms and core dysfunctions in BD. However, these findings are limited by the cross-sectional study design, and longitudinal studies recording the episodes of BD are necessary to verify the connectome changes in the brain in the future. The associations with specific receptors and cell spectra further highlight the molecular basis of these changes, offering preliminary evidence linking function to biology. These findings underscore the importance of integrating genetic, molecular, and functional imaging data to understand multilevel changes related to various episodes of BD.

Abbreviations

HDRS	Hamilton Depression Rating Scale
YMRS	Young Mania Rating Scale
PDQ	Perceived Disability Questionnaire
HAMA	Hamilton Anxiety Scale
rBD	Remission of bipolar disorder
BipD	Depressive episode of bipolar disorder
BipM	Manic episode of bipolar disorder
mBD	Mixed episode of bipolar disorder
HC	Healthy control
fMRI	Functional magnetic resonance imaging
BOLD	Blood-oxygen-level-dependent
DMN	Default mode network
rDCM	Regression dynamic causal model
NSP	Nested Spectral Partitioning
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
BIDS	Brain Imaging Data Structure
FDR	False Discovery Rate
D1	Dopamine receptor D1
D2	Dopamine receptor D2
DAT	Dopamine transporter
NET	Norepinephrine transporter
5-HT1A	5-Hydroxytryptamine receptor 1A
5-HT1B	5-Hydroxytryptamine receptor 1B
5-HT2	5-Hydroxytryptamine receptor 2
5-HT4	5-Hydroxytryptamine receptor 4
5-HT6	5-Hydroxytryptamine receptor 6
5-HTT	Serotonin transporter
5HT2a	5-Hydroxytryptamine receptor 2A
5HT4	5-Hydroxytryptamine receptor 4
α4β2	Alpha4Beta2 nicotinic acetylcholine receptor subtype
α4β4	Alpha4Beta4 nicotinic acetylcholine receptor subtype
M1	Muscarinic acetylcholine receptor M1
VAChT	Vesicular acetylcholine transporter
mGluR5	Metabotropic glutamate receptor 5
GABAa	Gamma-aminobutyric acid type A receptor
H3	Histamine receptor H3
CB1	Cannabinoid receptor type 1
MOR	Mu-opioid receptor
Pax6	Paired box gene 6
Sncg	Synuclein gamma
Astro	Astrocyte
L5IT	Layer 5 intratelencephalic neurons
L4IT	Layer 4 intratelencephalic neurons
L5-ET	Layer 5 extratelencephalic neurons
Endo	Endothelial cells
L6-IT-Car3	Layer 6 intratelencephalic neurons expressing carbonic anhydrase 3
L2/3 IT	Layer 2/3 intratelencephalic neurons

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04277-7.

Additional file 1: Supplementary material

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Authors' contributions

Xiaobo Liu (1,2) and Bin Wan (3,4) jointly conceived and designed the study, supervised the implementation of the research framework, and drafted the initial manuscript. Xi-Han Zhang (5) supported data acquisition and technical troubleshooting, contributing significantly to the Methods and Results sections. Ruifang Cui (6) coordinated data collection, performed preliminary statistical analysis, and assisted with data visualization. Siyu Long (2) provided experimental operations and aided in data preprocessing. Ruiyang Ge (7)

offered algorithmic support for data postprocessing, verifying the reliability and reproducibility of the main findings. Lang Liu (8) facilitated experimental resource management, suggested improvements to measurement protocols, and reviewed the final manuscript. Jinming Xiao (5) co-managed hardware/instrumentation with Xi-Han Zhang and composed technical supplements relevant to the experimental platform. Zhen-Qi Liu (2) carried out statistical modeling, wrote portions of the Results section, and collaborated closely with the main authors on paper structure. Jiadong Yan (2) implemented additional behavioral protocols, broadened theoretical perspectives, and responded to reviewer comments during revision. Ke Xie (2) provided network analysis and data-integration support, ensuring computational reproducibility. Meng Yao (5) led participant recruitment and ethics approvals, contributing to methodological background and final figure polishing. Xin Wen (9) developed key software functionalities, maintained data integrity, and assisted with references and formatting. Sanwang Wang (10) contributed interdisciplinary perspectives for interpreting findings and shaping the paper's narrative flow. Finally, as the corresponding author, Yujun Gao (1) provided overall guidance throughout the project—from conceptualization to data analysis and manuscript preparation—reviewed and approved all content, and was responsible for final submission.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The present study received ethical approval from the Ethics Committee of Renmin Hospital, Wuhan University (Approval No. WDRY22022-K195). Informed consent was obtained only after confirming that participants and their families had fully understood the nature and implications of the research. Written documentation of consent was then secured. Furthermore, the study was prospectively registered with both the National Medical Research Registration Information System and the Chinese Clinical Trial Registry (ChiCTR2200064938).

Consent for publication
The participants in this study have signed a consent for publication form to allow their anonymized medical data and potentially a photograph of them to be used in a research paper.

Competing interests
The authors declare no competing interests.

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