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Dynamic structure–function coupling across three major psychiatric disorders

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Abstract

Background. Convergent evidence has suggested atypical relationships between brain structure and function in major psychiatric disorders, yet how the abnormal patterns coincide and/or differ across different disorders remains largely unknown. Here, we aim to investigate the common and/or unique dynamic structure–function coupling patterns across major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ).

Methods. We quantified the dynamic structure–function coupling in 452 patients with psychiatric disorders (MDD/BD/SZ = 166/168/118) and 205 unaffected controls at three distinct brain network levels, such as global, meso-, and local levels. We also correlated dynamic structure–function coupling with the topological features of functional networks to examine how the structure–function relationship facilitates brain information communication over time.

Results. The dynamic structure–function coupling is preserved for the three disorders at the global network level. Similar abnormalities in the rich-club organization are found in two distinct functional configuration states at the meso-level and are associated with the disease severity of MDD, BD, and SZ. At the local level, shared and unique alterations are observed in the brain regions involving the visual, cognitive control, and default mode networks. In addition, the relationships between structure–function coupling and the topological features of functional networks are altered in a manner indicative of state specificity.

Conclusions. These findings suggest both transdiagnostic and illness-specific alterations in the dynamic structure–function relationship of large-scale brain networks across MDD, BD, and SZ, providing new insights and potential biomarkers into the neurodevelopmental basis underlying the behavioral and cognitive deficits observed in these disorders.

Introduction

Major psychiatric disorders such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ) are the leading global causes of disability (Murray et al., 2012). About 100 million people in China suffer from various kinds of major psychiatric disorders, posing a substantial burden on families and society (Huang et al., 2019). While MDD, BD, and SZ, each have their distinct clinical diagnosis and unique symptom profile, there is a notable overlap in symptoms and cognitive impairments among them (Insel et al., 2010; Marshall, 2020). Genetically, they share polygenic risks, as evidenced by common risk loci identified in genome-wide association studies, underscoring their intertwined genetic underpinnings (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a, 2013b; Elvsashagen et al., 2021; Xie et al., 2023). Additionally, recent neuroimaging research has revealed both shared and unique brain connectome abnormalities across these three disorders (Chana, Landau, Beasley, Everall, & Cotter, 2003; McGuinness et al., 2022; Repple et al., 2023; Tu et al., 2019a; Tu et al., 2020a). Specifically, prior diffusion tensor imaging research shows

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that structural connectivity (SC) changes in SZ are similar to those in BD but different from those in MDD (Koshiyama et al., 2019; Wang et al., 2020). Comparatively, functional magnetic resonance imaging (fMRI) studies find common yet scale-dependent functional connectivity (FC) disruptions among SZ, BD, and MDD, with severity in the order of SZ > BD > MDD (Ma et al., 2020; Wei et al., 2018). These findings imply that various illnesses may have both shared and specific patterns of brain dysconnectivity (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Reinen et al., 2018; Yang et al., 2021a; Zalesky et al., 2011; Zhao et al., 2020b), shedding new light on the possible common and unique neurobiological mechanisms underlying these disorders (Chand et al., 2020; Drysdale et al., 2017; Wolfers et al., 2018). More importantly, all the evidence points to the need to study MDD, BD, and SZ with multimodal imaging analysis in a single study to understand these disorders' pathophysiology better.

In parallel, structural connections offer a framework for functional interactions among various brain regions at multiple scales (Bullmore & Sporns, 2009; Honey et al., 2009; Paus, Pesaresi, & French, 2014). SC–FC coupling, an index that reflects the relationship between brain structure and function, generally describes structural constraints on functional communication (Grayson et al., 2014; Zhao et al., 2020a, 2020b) and plays a crucial role in the development of higher-order cognitive functions such as working memory, mental flexibility, and inhibitory control (Kulik et al., 2022; Suarez, Markello, Betzel, & Misic, 2020; van den Heuvel et al., 2013). SC–FC coupling tends to be firmly linked in the unimodal cortex and dissociated in the transmodal cortex, reflecting a fundamental architectural principle of brain organization (Suarez et al., 2020; Vazquez-Rodriguez et al., 2019). In prior independent studies of MDD, BD, and SZ, disruptions in SC–FC coupling were frequently documented, ranging from individual connections to global brain networks (Collin, Scholtens, Kahn, Hillegers, & van den Heuvel, 2017; Cui et al., 2019; Jiang et al., 2019). This raises the possibility that there are common and/or unique SC–FC coupling patterns across these psychiatric disorders.

Moreover, most previous SC–FC coupling research on psychiatric disorders assumed that the relationship between structure and function was constant during the entire scan duration. It is well known that the human brain is highly dynamic (Calhoun, Miller, Pearlson, & Adali, 2014). Consequently, the dynamic SC–FC coupling, which represents the time-varying correspondence between structural and functional networks, is a more efficient method for elucidating how the anatomical wiring of the brain sculpts its functional connection in healthy and disordered conditions (Gu, Jamison, Sabuncu, & Kuceyeski, 2021; Zamani Esfahlani, Faskowitz, Slack, Misic, & Betzel, 2022). A few recent studies have begun investigating the time-varying properties of SC–FC coupling in the healthy brain. One intriguing dynamic SC–FC coupling investigation by Fukushima et al., demonstrated that structural connections could mediate functional segregation and integration proportions only when their corresponding functional profile reveals an integrated network topology (Fukushima et al., 2018). Another study involving 327 healthy young individuals showed that dynamic SC–FC coupling is regionally heterogeneous and associated with the distribution of its connection lengths (Liu et al., 2022). To our knowledge, no previous study has focused on how brain structure–function relationships change over time in psychiatric disorders. It is still unknown if and how the abnormal patterns of dynamic SC–FC coupling coincide and/or differ across multiple disorders.

In this work, we aim to investigate the transdiagnostic and/or illness-specific disruptions of dynamic SC–FC coupling across MDD, BD, and SZ. We recruited a large cohort comprised of newly diagnosed patients juxtaposed with unaffected control participants. We developed a quantitatively analytical framework to examine the dynamic SC–FC coupling in large-scale brain networks. Specifically, dynamic FC states were initially obtained, followed by the SC–FC coupling analysis within each identified state to analyze the group differences at three distinct network levels (e.g. global, meso-, and local levels). To investigate how the structure–function relationship facilitates functional information communication, we then correlated dynamic SC–FC coupling with the topological properties of functional brain networks. Finally, we correlated the dynamic SC–FC coupling with clinical symptomatic aspects of patients to determine how the supporting of structural constraints to functional communication shaped the severity of the disease.

Methods

Participants

A total of 778 participants (137 first-episode treatment-naïve SZ patients, 186 treatment-naïve MDD patients, 201 BD patients, and 254 unaffected controls) were studied. All patients were recruited from outpatient at West China Hospital, Sichuan University, Chengdu, China, from October 2014 to June 2018. Unaffected controls (UCs) were recruited from the local population through advertising. All participants involved were Han Chinese. Patients were evaluated using the patient version of the Structured Clinical Interview for Mental Disorders (SCID), Fourth Edition, and UCs were assessed using the non-patient version. All patients met the DSM-IV diagnostic criteria for MDD, BD, or SZ. Using the Annett Handedness Scale, all participants were found to be right-handed. Participants with neurological problems, personality issues, substance or alcohol addiction, serious physical diseases, or an IQ below 70 were eliminated. The HAMD, YMRS, and PANSS were also used to measure the symptom severity in patients with MDD, BD, and SZ, respectively. The HAMD and PANSS were also employed to assess the severity of BD patients' symptoms. After head motion exclusion, the remaining 452 patients (MDD/BD/SZ = 166/168/118) and 205 UCs were included in the subsequent analyses. Detailed demographic and clinical characteristics of the included participants are shown in the online Supplementary material. The basic flow of this study is depicted in Fig. 1.

MRI acquisition and preprocessing

The MRI scans of all participants were carried out in a 3-T MRI scanner (Verio; Siemens Medical) using a 32-channel head coil. Detailed information about acquisition parameters and data preprocessing are presented in the online Supplementary material.

Group independent component analysis

To identify the ICNs and their corresponding activation spatial maps, we decomposed the fMRI data into multiple independent components (ICs) using spatial group independent component analysis (GICA) with the GIFT toolbox (http://mialab.mrn.org/

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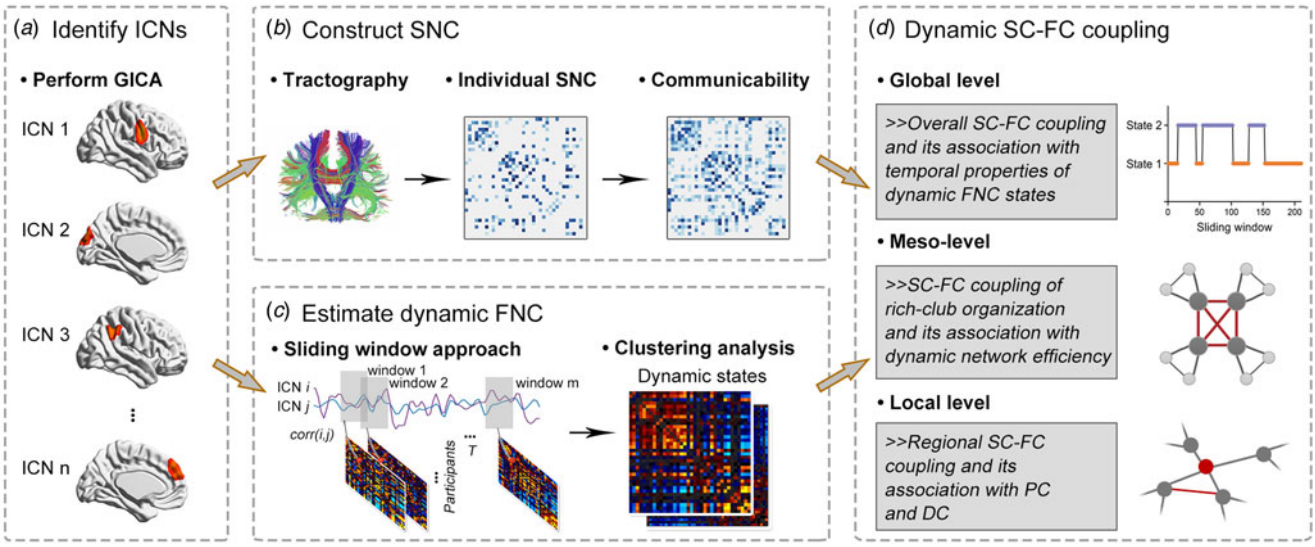


Figure 1. Analysis flowchart of studying dynamic structure–function coupling.Four major steps were included: (a) perform group independent component analysis (GICA) and select intrinsic connectivity networks (ICNs); (b) structural network connectivity (SNC) and communicability networks; (c) estimate dynamic functional network connectivity (FNC); and (d) examine dynamic SC–FC relationships in different network levels. ICN, intrinsic connectivity network; SNC, structural network connectivity; FNC, functional network connectivity; PC, participation coefficient; DC, degree centrality.

software/gift/). Note that we defined ICNs using GICA rather than anatomical brain atlases, as GICA may capture individual differences in real functional boundaries in the brain (Calhoun, Adali, Pearlson, & Pekar, 2001). A combination of the visual and spatial template-matching inspection was used to identify ICNs among ICs. The templates were created using the GICA analyses described in previous studies (Allen et al., 2014; Liu et al., 2017). Finally, 50 ICNs were identified and assigned to one of seven resting-state networks (RSNs). For details concerning the activation information and spatial maps of each ICN, see online Supplementary material.

Structural and dynamic functional network construction

Structural networks were constructed using deterministic streamline tractography, which has been demonstrated to be an appropriate technique for reconstructing the connectome (Khalsa, Mayhew, Chechlacz, Bagary, & Bagshaw, 2014). The edge between any two nodes (ICNs) was reconstructed using streamline density (s.d.) (Suárez, Richards, Lajoie, & Misic, 2021). A 50×50 weighted SC matrix was obtained as structural network for each participant. Notably, deterministic tractography produced a relatively sparse SC matrix, making it challenging to quantify SC–FC coupling due to the small number of non-zero edges in each connectome profile (Baum et al., 2020). Thus, each SC matrix's communicability were assessed by including direct and indirect connections between two nodes, resulting in a fully connected SC matrix (Crofts & Higham, 2009).

Dynamic functional networks were estimated using a previously validated sliding window approach (Allen et al., 2014; Kim et al., 2017; Tu et al., 2020a, 2020b). In brief, a tapered window with a length of 44 s was used to divide the time courses of ICNs across the entire scan into 209 windows with a 2s increment-step. A k-means clustering analysis was then applied to estimate the recurrent dynamic FC states, which represent the transient patterns of FC throughout time. We investigated the temporal properties of dynamic FC states by determining the occurrence rate and mean dwell time in each state and the number of transitions and transition likelihood from one state to another (Fiorenzato et al., 2019; Tu et al., 2019a, 2019b). To ensure that the results remained true across various sliding window sizes, we performed the dynamic FC analyses with different window sizes (36–52 s).

Network topological analysis

The topological organization of structural and functional brain networks was investigated using a theory-based graph technique. We investigated the anatomical rich-club organization for structural networks, which describes a set of interconnected anatomical hubs and serves as the core structural backbone for global brain communication (van den Heuvel, Kahn, Goni, & Sporns, 2012). Rich-club, feeder, and local edges were further classified based on whether they connected rich-club hubs, rich-club hubs and non-rich-club hubs, or non-rich-club hubs. Regional participation coefficient (PC), which assesses the diversity of intermodular interconnections of individual nodes, and degree centrality (DC), which quantifies the importance of individual nodes in functional integration, were calculated for functional networks in each dynamic state. Functional network efficiency (both globally and locally) was calculated for each dynamic state to characterize the parallel information transfer within the functional network.

Calculation of dynamic SC–FC coupling at three network levels

The level of SC–FC coupling was measured using the Spearman rank correlation between the connections of the SC matrix and the state-specific FC matrix (excluding the self-connection) (Gu et al., 2021). For each participant, we calculated SC–FC coupling at three distinct network levels (i.e. global, meso-, and regional) as follows: a global level calculation was performed for the brain network's overall connections; a meso-level calculation was focused on the anatomical rich-club organization and separately performed for three categories of connections, including rich-club, feeder, and local edges (van den Heuvel et al., 2012); and a regional level calculation was performed for the connections between one brain region to the remaining $N-1$ regions.

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Statistical analysis

The between-group differences in connection strength, temporal properties of dynamic FC states, SC–FC coupling, and graph metrics were investigated using a one-way analysis of variance (ANOVA) and a permutation test with 10 000 resamples. The relationships between SC–FC coupling and the temporal properties of dynamic FC states, as well as between SC–FC coupling and graph metrics, were investigated using a Spearman correlation analysis. Additionally, while controlling for age, gender, and mean FD, Spearman correlations between graph metrics and clinical symptom characteristics (e.g. HAMD, YMRS, and PANSS scores) were calculated. Statistical significance was established at $p < 0.05$ with false discovery rate (FDR) correction conducted for each experiment separately.

Results

Overall SC–FC coupling between structural and dynamic functional networks

Significant group effects on overall SC strength were found among the four groups ($p = 0.002$, FDR-corrected, $\eta^2 = 0.019$; Fig. 2a and b). The post hoc analyses revealed that compared to controls and patients with MDD, SZ patients exhibited a significant decrease in overall SC strength, indicating a prominent hypoconnectivity in the structural network of SZ. Fig. 2c depicts the cluster centroids corresponding to two distinct dynamic FC states across all participants. State 1 was characterized by a predominance of connections within the RSN, whereas State 2 displayed strong positive couplings among the AUD, VIS, and SM. We then analyzed the temporal properties of dynamic states and found significant group effects on transition likelihood. As shown in Fig. 2d, patients with SZ exhibited a higher switching probability from State 2 to State 1 than controls ($p = 0.007$, permutation test) and patients with BD ($p = 0.011$, permutation test), indicating less stable inter-network interactions in patients with SZ. Moreover, we calculated the SC–FC coupling between all connections of structural and functional networks for every state and discovered that the overall SC–FC coupling was similar across patients and controls (Fig. 2e). To determine how structure–function relationship facilitates dynamic state transition, we further assessed the associations between overall SC–FC coupling and transitional likelihood. We found that the probability of switching from State 2 to State 1 was significantly correlated with the overall SC–FC coupling in each group (Fig. 2f). We observed that these results were independent of different settings of the sliding window (see online Supplementary material), indicating that the SC–FC coupling in these major psychiatric disorders was preserved overall.

Dynamic SC–FC coupling of rich-club organization

We determined the anatomical rich-club organization of structural networks for each group individually and observed main effects of group in SC strength for rich-club ($p < 0.001$, FDR-corrected, $\eta^2 = 0.225$), feeder ($p < 0.001$, FDR-corrected, $\eta^2 = 0.397$), and local edge categories ($p < 0.001$, FDR-corrected, $\eta^2 = 0.094$; Fig. 3). Subsequent post hoc analyses unveiled a diminished SC density in both rich-club and local edges for each patient group, in contrast with the control group (all $p < 0.001$, permutation test). Conversely, each patient group exhibited an increased SC density in feeder edges when compared with the control group (all $p < 0.001$, permutation test). Next, we investigated dynamic SC–FC coupling for each connection category and observed significant group effects on the rich-club (State 1: $p = 0.003$, FDR-corrected, $\eta^2 = 0.023$; State 2: $p < 0.001$, FDR-corrected, $\eta^2 = 0.043$) and local edges (State 1: $p < 0.001$, FDR-corrected, $\eta^2 = 0.033$; State 2: $p = 0.042$, FDR-corrected, $\eta^2 = 0.017$) across both states (Fig. 3c and d). Post hoc analyses revealed that compared to the control group, in State 1, the level of SC–FC coupling was decreased in the rich-club edges for MDD and SZ groups but increased in the feeder edges for all patient groups (all $p < 0.05$, permutation test); in State 2, the level of SC–FC coupling was decreased in the rich-club edges for all patient groups but increased in the feeder edges for MDD and BD groups (all $p < 0.05$, permutation test). We also found that the SC–FC coupling of rich-club edges was negatively correlated with the PANSS total scores in State 1 in patients with SZ ($r = -0.25$, $p = 0.014$, FDR-corrected) and BD ($r = -0.20$, $p = 0.019$, FDR-corrected) and negatively correlated with the HAMD scores in State 2 in patients with MDD ($r = -0.24$, $p = 0.018$, FDR-corrected), indicating that the lower level of SC–FC coupling is associated with the greater disease severity (Fig. 3e–g). To explore how brain structure-function relationship facilitates functional information transfer, we assessed the dynamic network efficiency and correlated it with the SC–FC coupling of each connection category in each state. We found that the constraint of SC–FC coupling to network efficiency was modified for patient groups in a manner that depends on specific dynamic conditions (Fig. 4).

Dynamic regional SC–FC coupling

The previous sections focused on global and meso-level couplings between structure and function. Here, we investigated disorder-related differences in structure–function coupling at a local (regional) level. Fig. 5a and b depict each state's group average regional SC–FC coupling and show that the SC–FC coupling level varied considerably across cortical and subcortical regions for each state. Specifically, the SC–FC coupling of the VIS was greater than that of the other RSNs in State 1 ($p < 0.001$, FDR-corrected, $\eta^2 = 0.121$), whereas the CC had greater SC–FC coupling than the other RSNs in State 2 ($p < 0.001$, FDR-corrected, $\eta^2 = 0.186$). We then noticed state-specific group differences in regional SC–FC coupling (Fig. 5c and d). In State 1, patients with BD had higher coupling in the bilateral middle frontal gyrus (MFG) than controls but lower coupling in right supramarginal gyrus (SMG) than controls and patients with MDD; patients with SZ had higher coupling in bilateral MFG and paracentral lobule (PCL) than controls, but only in bilateral MFG compared to patients with MDD. In State 2, patients with SZ exhibited lower coupling in the bilateral inferior temporal gyrus (ITG) than controls, higher coupling in the left middle temporal gyrus (MTG) than patients with MDD, and lower coupling in bilateral ITG and precuneus (PCU) than patients with BD; patients with BD exhibited lower coupling in right SMG than patients with MDD. Finally, we explored the relationships between spatial variability of regional SC–FC coupling and the hierarchy of functional specialization (PC) and integration (DC). As shown in Fig. 5e and f, patients with SZ display lower association levels (SC–FC coupling ~ PC) in State 1 than the other groups (MDD $p = 0.010$, BD $p = 0.008$, UC $p = 0.007$, permutation test), while BD and SZ groups had a higher

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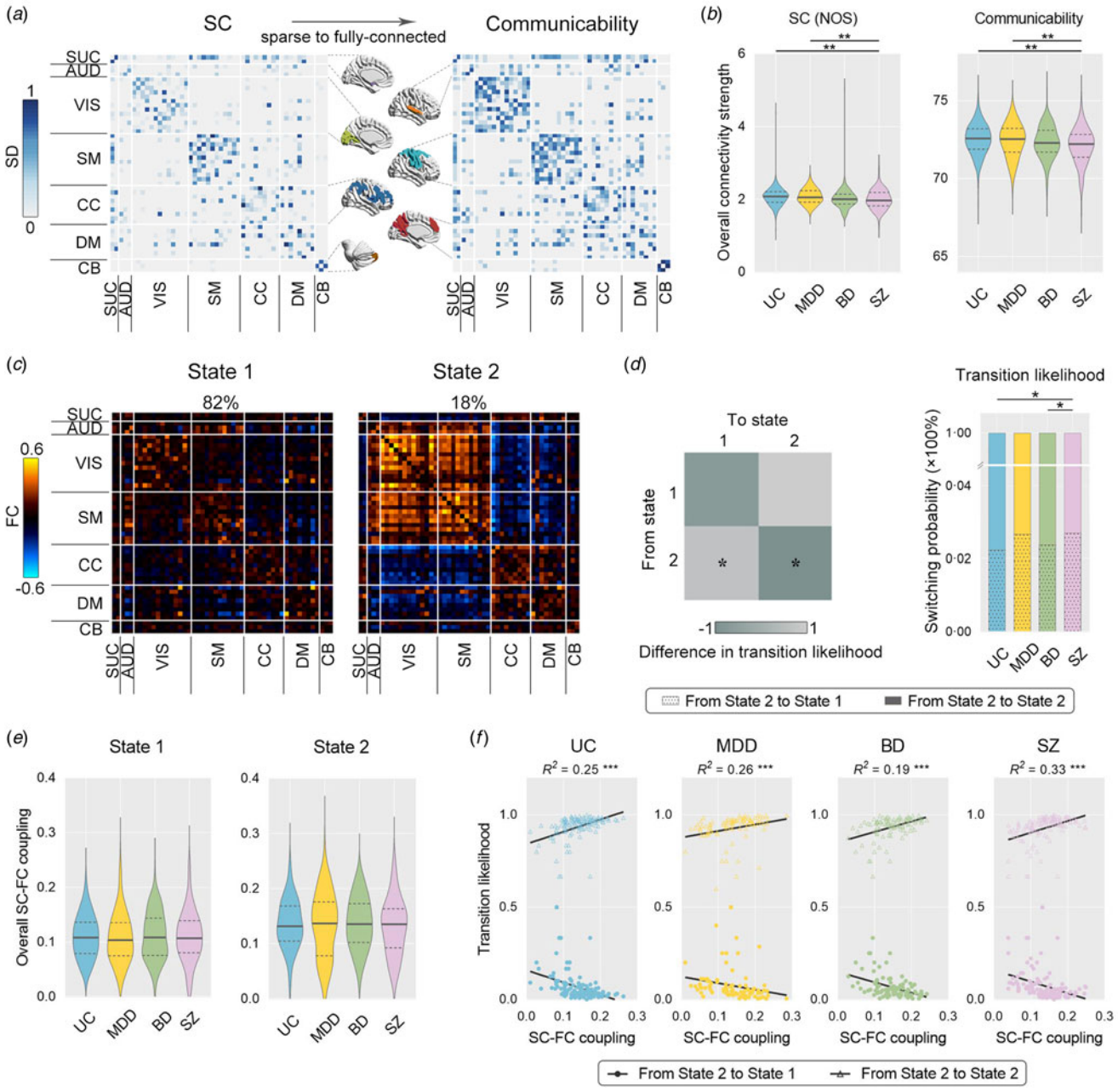


Figure 2. Overall SC–FC coupling of structural and dynamic functional networks. (a) Averaged structural network connectivity matrix and its communicability matrix across all participants. Fifty ICNs were identified by a group independent component analysis (GICA) and grouped into seven functional networks based on their anatomical and functional properties, including sub-cortical (SUC), auditory (AUD), visual (VIS), somatomotor (SM), cognitive control (CC), default mode (DM), and cerebellar (CB) networks. (b) Violin plots showing mean (s.d.) level values of overall SC strength per participant group. (c) Two discrete connectivity patterns (states) across all groups. The percentage of occurrences is listed above each cluster centroid. The color bar represents the *z*-value of FC. (d) Group differences in transition likelihood (TL). Bar plots showing mean level values of switching probability per participant group. (e) Violin plots showing mean level values of overall SC–FC coupling per participant group for each state. (f) Scatter plot showing the association between overall SC–FC coupling and TL with group differences. MDD, major depressive disorder; BD, bipolar disorder; SZ, schizophrenia; UC, unaffected control. *$p < 0.05$, ****$p < 0.0001$, with FDR-corrected.

association level (SC–FC coupling ~ DC) in State 2 than the control group (BD $p = 0.007$, SZ $p = 0.005$, permutation test).

Discussion

In this study, we performed a systematical dynamic SC–FC coupling analysis to investigate the shared and specific brain changes across MDD, BD, and SZ. We found that the coupling and its association with the topological properties of functional brain networks are preserved at the global network level for the three disorders but differed at the meso- (i.e. rich-club organization) and local (i.e. individual brain regions) levels, exhibiting both transdiagnostic and illness-specific alterations. These findings provide novel evidence for the common and distinct manifestations and etiologies of MDD, BD, and SZ, and highlight the potential of dynamic structure–function relationship of large-scale brain networks in the search for neurobiological biomarkers for psychiatric disorders.

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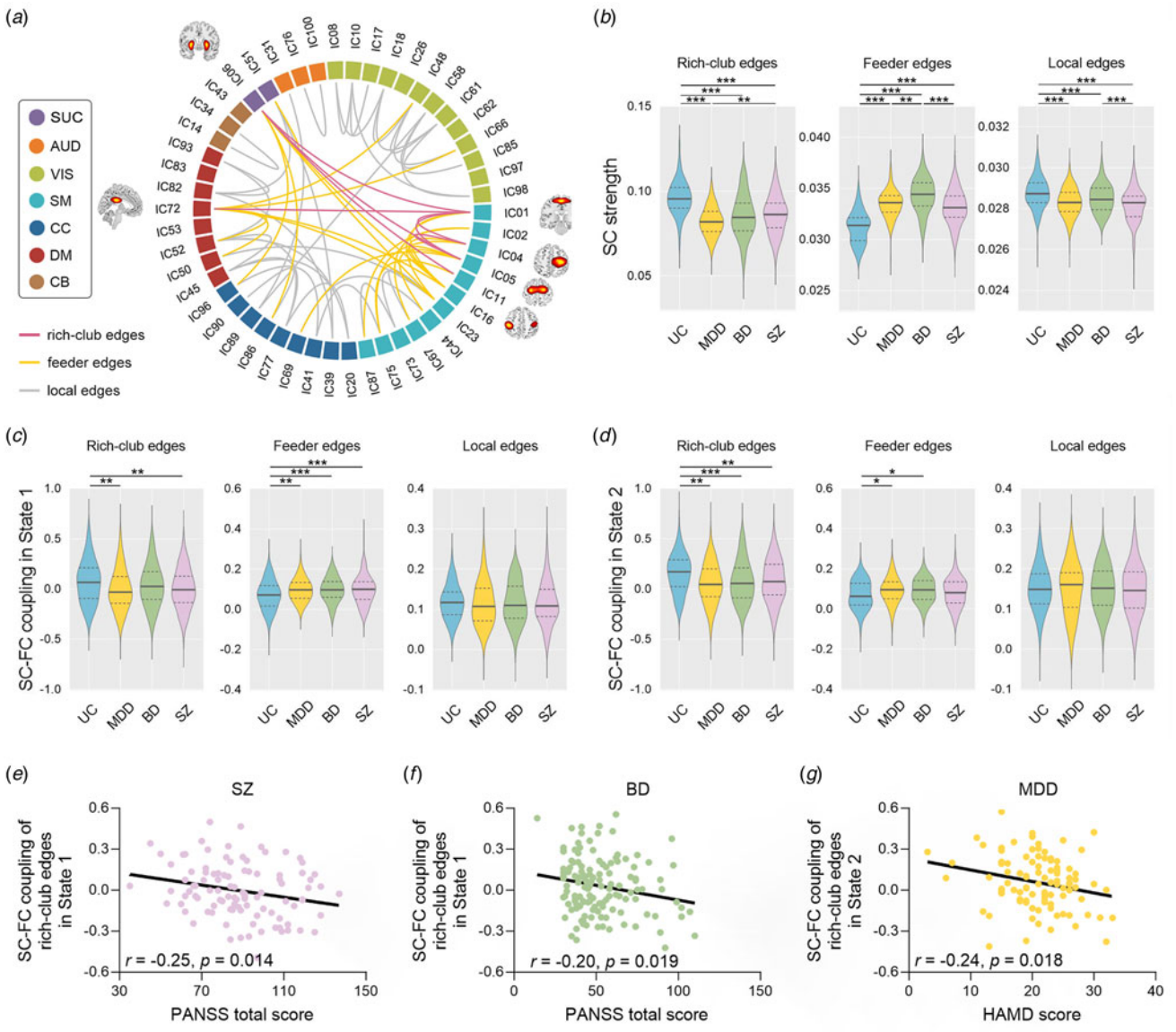


Figure 3. State-specific SC–FC coupling of the rich-club organization. (a) Group-specific anatomical rich-club organization (UC group). At a threshold of degree $k > 13$, rich-club hubs such as the bilateral paracentral lobule, precentral gyrus, postcentral gyrus, posterior cingulate cortex, and bilateral putamen were identified. (b) Violin plots showing mean level values of SC strength of rich-club, feeder, and local edges per participant group. (c) Violin plots showing mean level values of SC–FC coupling of rich-club, feeder, and local edges per participant group for State 1. (d) Violin plots showing mean level values of SC–FC coupling of rich-club, feeder, and local edges per participant group for State 2. (e) Scatter plot showing the association between SC–FC coupling of rich-club edges in State 1 and the positive and negative syndrome scale (PANSS) total score in patients with SZ. (f) Scatter plot showing the association between SC–FC coupling of rich-club edges in State 1 and the PANSS total score in patients with BD. (g) Scatter plot showing the association between SC–FC coupling of rich-club edges in State 2 and the Hamilton rating scale for depression (HAMD) score in patients with MDD. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, FDR-corrected.

Neuroimaging studies have shown that patients with psychiatric disorders exhibit both structural and functional brain network disruptions (Cui et al., 2019; Du et al., 2018; Reinen et al., 2018; Yang et al., 2021a, 2021b; Yao et al., 2019). Importantly, we discovered that SZ patients differed significantly more from healthy controls regarding global SC strength and the temporal properties of FC states than MDD and BD patients. Indeed, previous research has demonstrated that SZ may have the most severe white matter impairment and dynamic FC disruption when compared to MDD and BD (Huang et al., 2020; Rashid, Damaraju, Pearlson, & Calhoun, 2014; Sheffield et al., 2017). Collectively, our findings suggest that SZ is more vulnerable to disruptions in global network connectivity, which may be a factor in the disorder's more severe clinical symptoms. Despite the obvious abnormalities in each connection profile of SZ, we found no significant deficits in the overall SC–FC coupling for each state, corroborating prior static connectivity studies suggesting that whole-brain structure–function coupling in the early stages of SZ may be intact (Cui et al., 2019). However, it is also possible that global structure–function coupling indicators are insufficient for investigating potential transdiagnostic and illness-specific alterations in psychiatric disorders.

Our observations of altered SC–FC coupling of rich-club organization in patients are partially consistent with previous connectome research in clinical high-risk, first-episode, and chronic individuals for MDD, BD, and SZ (Collin et al., 2017;

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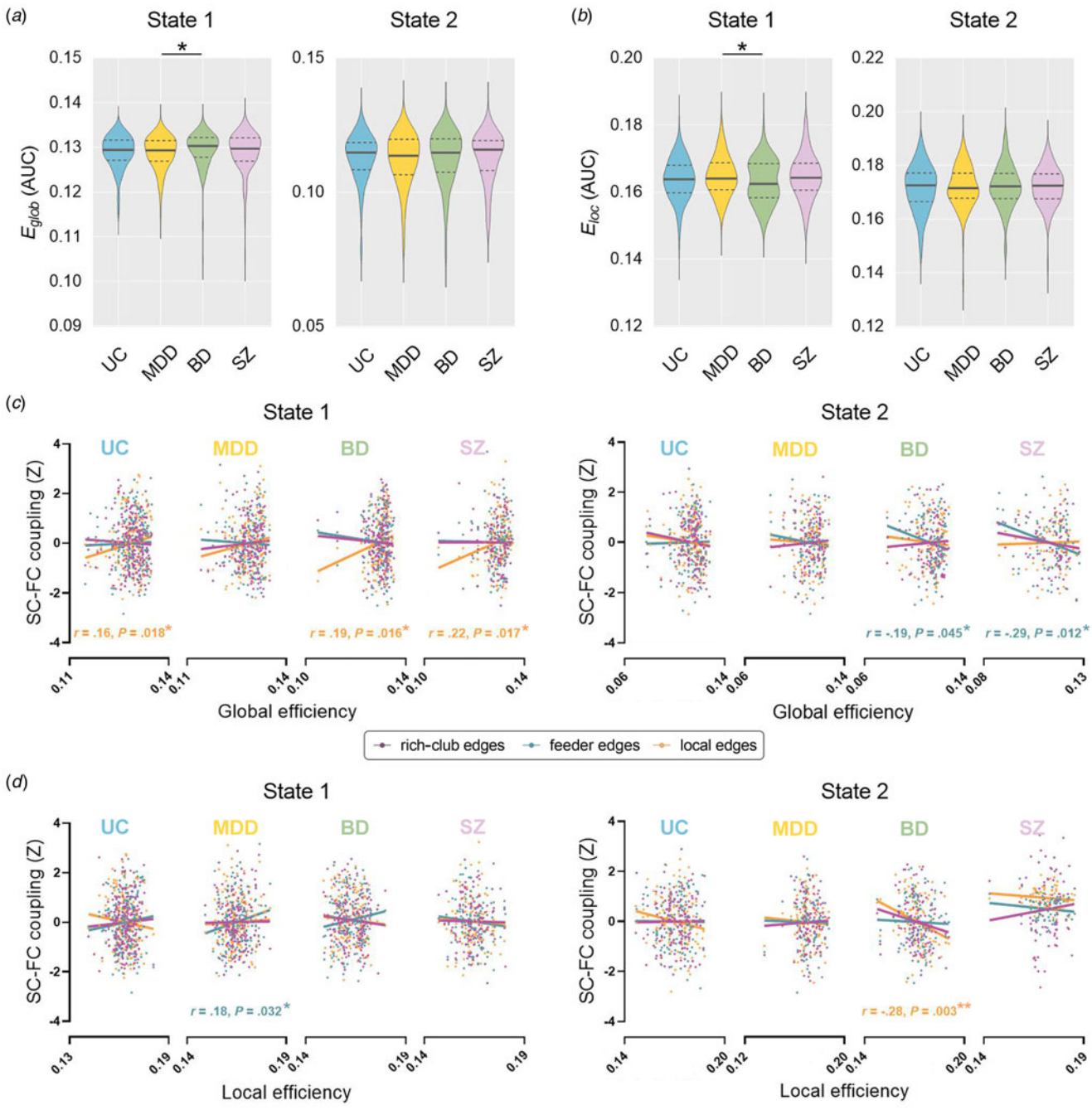


Figure 4. Dynamic network efficiency and its association with SC–FC coupling of rich-club organization. (a) Violin plots showing mean (s.d.) values of global efficiency per participant group for each state. (b) Violin plots showing mean (s.d.) values of local efficiency per participant group for each state. (c) Scatter plot showing the association between global efficiency and SC–FC coupling of rich-club, feeder, and local edges per participant group for each state. (d) Scatter plot showing the association between local efficiency and SC–FC coupling of rich-club, feeder, and local edges per participant group for each state. Note that for visualization purposes, the SC–FC coupling of each category was normalized by using the *Z*-transform. *$P < 0.05$, **$p < 0.01$, FDR-corrected.

Cui et al., 2019; Jiang et al., 2019; Liu et al., 2021; van den Heuvel et al., 2013). The rich-club organization has been shown to provide a crucial structural backbone for brain communication (van den Heuvel et al., 2012). Its disruption may indicate a selective influence of the key pathways between brain regions in these disorders. In addition, we revealed that the SC–FC coupling of certain connection categories, such as rich-club and feeder edges, was concurrently increased or decreased in patient groups for each state, indicating a transdiagnostic disturbance. Increased coupling in State 1, a segregated state, may indicate enhanced processing within distinct RSNs, which can result in RSN-constrained cognitive impairments (Whitfield-Gabrieli & Ford, 2012). At the same time, decoupling in State 2, an integrated state, may be indicative of less stable structural support for the global integration of functional brain networks, which has been associated with poorer cognitive performance in the attentive, memory, and visuospatial domains (Berman et al., 2016; McNabb et al., 2018; Misic et al., 2016; Vazquez-Rodriguez

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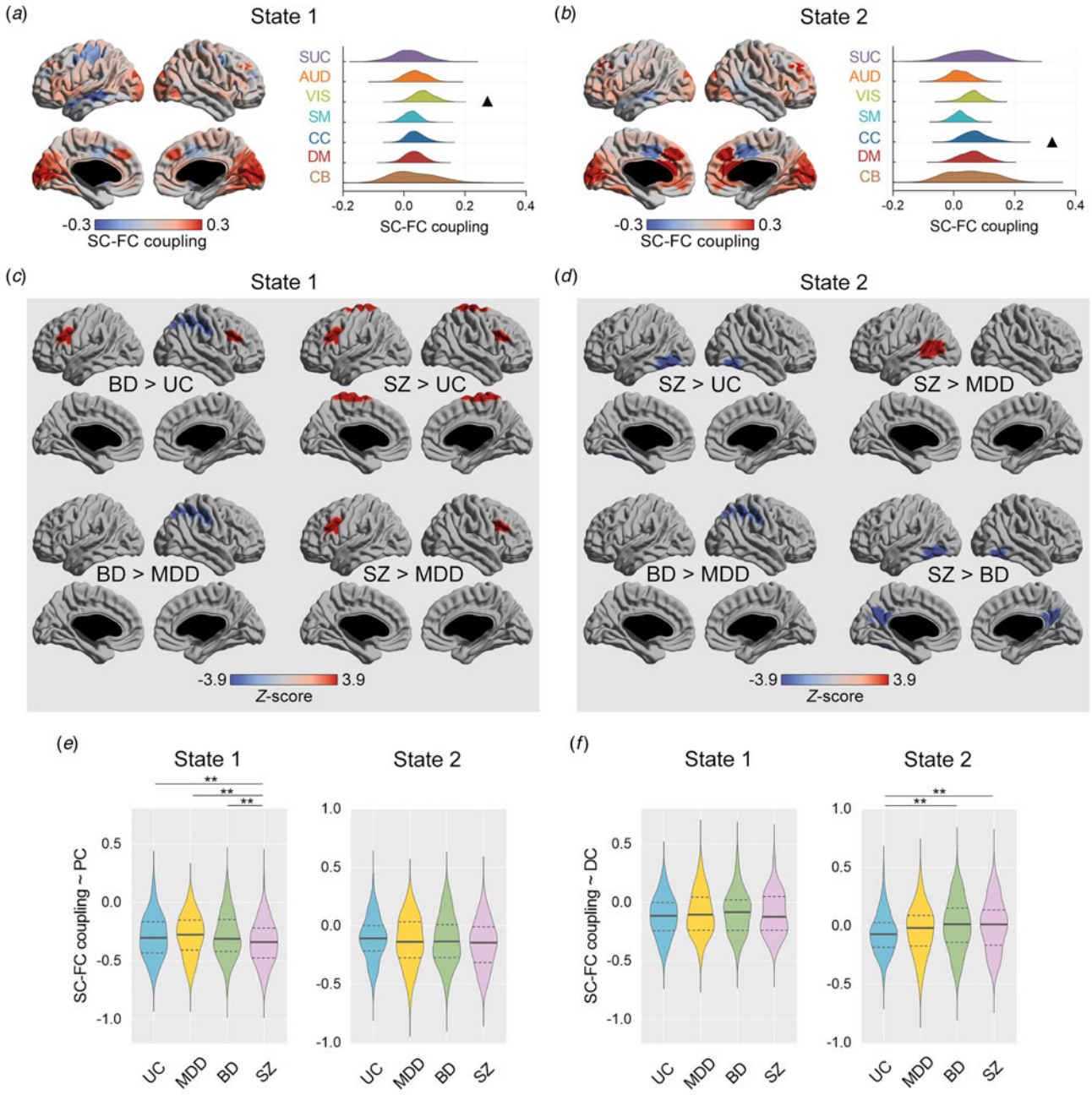


Figure 5. State-specific regional SC–FC coupling and its association with local topological properties. (a) Regional SC–FC coupling across all groups for State 1. (b) Regional SC–FC coupling across all groups for State 2. (c) Group differences in regional SC–FC coupling for State 1. (d) Group differences in regional SC–FC coupling for State 2. (e) Violin plots showing mean level values of association between regional SC–FC coupling and participation coefficient (PC) per participant group for State 1 and State 2. (f) Violin plots showing mean level values of association between regional SC–FC coupling and degree centrality (DC) per participant group for State 1 and State 2. The black triangle represents the RSN with the highest level of SC–FC coupling in each state. $^{*}p < 0.05$, $^{**}p < 0.01$, FDR-corrected.

et al., 2019). These are further supported by the clinical correlations identified in our study, in which a lower state-specific level of SC–FC coupling was associated with more severe clinical symptoms for SZ, BD, and MDD. It is noteworthy that we investigated the impairment of SC–FC coupling of rich-club organization in cohorts of patients with a short-term disease course, thereby reducing the potential influence of chronic disease on our findings and echoing the hypotheses regarding the neurodevelopmental origins of major psychiatric disorders (Delavari et al., 2021). Contemporary theories have suggested that the SC–FC coupling is continuously remodeled with age during childhood and adolescence, and its atypical development may contribute to the emergence of psychiatric disorders (Baum et al., 2017; Di Martino et al., 2014; Stephan, Baldeweg, & Friston, 2006). Myelination in highly interconnected fronto-parietal hubs has been shown to continue postnatally until the third decade of life, which overlaps with the common onset of the disease (Silbereis, Pochareddy, Zhu, Li, & Sestan, 2016). Consequently, our findings suggest that atypical myelination in microstructure content may transform into abnormal reorganizations in SC–FC

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coupling of rich-club organization during development, which in turn leads to a variety of psychosis symptoms corresponding to what has been termed 'Spatiotemporal Psychopathology' (Northoff & Duncan, 2016; Northoff et al., 2018). Further results demonstrated that the correlations between SC–FC coupling of rich-club organization and functional network efficiencies were altered in patient groups, indicating that the structure–function relationship no longer supports the efficiency of information transfer. Overall, our findings provide strong evidence that state-specific disruptions in SC–FC coupling of the core structural backbone are likely transdiagnostic characteristics of neurodevelopmental conditions associated with these disorders.

Several brain regions involved in the VIS, SM, CC, and DM networks exhibited significant between-group changes in regional SC–FC coupling. The morphological hierarchy of intracortical myelin and the laminar patterns of interareal projections have been shown to reflect functional and transcriptional specialization (Margulies et al., 2016; Wu et al., 2020). The cortical SC–FC coupling appears to be variable across the brain, with strong coupling in lower-order sensory areas (exhibiting higher cortical myelination and a larger SC node degree) and weak coupling in higher-order association areas (exhibiting lower myelination and a smaller SC node degree) (Gu et al., 2021; Suárez et al., 2021; Vazquez-Rodriguez et al., 2019). This study expands prior research into the temporal dynamic realm and demonstrates that the regional SC–FC coupling is partly driven by the brain's functional segregation and integration. Specifically, we discovered that greater regional coupling of the middle frontal gyrus (MFG) in State 1 was a neuroimaging characteristic shared by patient groups. The MFG is a crucial CC region concerned in integrating the external environment with internal representations that have been stored (Buckner, Andrews-Hanna, & Schacter, 2008). Investigations on MDD, BD, and SZ have demonstrated that the MFG is always disconnected from other high-order functional networks (e.g. DM), resulting in various executive control deficiencies in these disorders (Menon, 2011; Zhang et al., 2021). Meanwhile, SZ patients in State 2 exhibited higher SC–FC coupling in the middle temporal gyrus (MTG), a key VIS region (Rizzolatti & Matelli, 2003), than MDD patients. They showed lower coupling in the precuneus (PCU), the main hub node of the DM network (Cavanna & Trimble, 2006), than BD patients. It is believed that psychotic symptoms, such as visual hallucinations, are linked to aberrant MTG connectivity (Kim et al., 2019), and dysfunction in the PCU may lead to disruptions in self-reference processing (Whitfield-Gabrieli & Ford, 2012). More severe psychotic symptoms have been associated with larger disruptions in the two regions of SZ (Huang et al., 2020). Our results suggest that the structure-function coupling of the MTG and PCU may serve as possible biomarkers to differentiate MDD patients from SZ patients and BD patients from SZ patients, respectively. In addition, we observed a weaker correlation between regional coupling and PC in State 1 for the SZ group compared to other groups, as well as a stronger correlation between regional coupling and DC in State 2 for the SZ and BD groups compared to the control group, indicating an atypical contribution of SC–FC coupling to functional specialization and integration in these disorders. The tighter coupling of local hubs in segregated RSNs has been proven to reduce competitive interference between different RSNs, allowing the suppression of irrelevant cognitive activity while processing target brain input (Hampson, Driesen, Roth, Gore, & Constable, 2010). In contrast, reduced coupling in transmodal brain regions may facilitate functional flexibility and dynamic recruitment in response to varying task demands (Yeo et al., 2015). Therefore, the abnormal correlations we observed in these disorders may imply a decreased capacity to suppress irrelevant information during specialized cognitive processing and/or to balance multi-channel information related to various cognitive processes.

Several methodological considerations should be considered when interpreting our findings. First, head motion is a potential confound in the connectome estimation and should be carefully minimized to the greatest extent possible (Liu et al., 2022; Wang, Wu, Liu, & Lü, 2021). In addition to motion correction and global signal regression, we censored high-motion frames, which have been shown to mitigate these effects further, and incorporated motion as a covariable in the coupling analysis. Second, accurately reconstructing cortico-cortical white matter pathways from DWI remains difficult. Because streamlined tractography has been widely utilized to quantify the connectome in psychotic disorders, our findings of SC–FC coupling are comparable to those of previous research (Collin et al., 2017; Cui et al., 2019). Nevertheless, existing tractography algorithms frequently encounter difficulties detecting crossing fiber bundles, resulting in an underrepresentation of structural network connections and diminished connectome sensitivity (Jones, Knösche, & Turner, 2013). More advanced tractography algorithms will be required to reconstruct white matter fiber pathways in the future. Third, we opted to employ the Spearman rank correlation between the structural and functional connection profiles as a measure of structure–function coupling, enabling us to compare our results to previous research on psychiatric disorders. Other methods, however, such as multilinear models (Vazquez-Rodriguez et al., 2019; Zamani Esfahlani et al., 2022), statistical models (Misic et al., 2016), embedding models (Rosenthal et al., 2018), spectral decompositions (Becker et al., 2018), and deep learning (Suárez et al., 2021), may lead to high levels of structure–function coupling. Future research should examine additional strategies in greater detail.

In conclusion, we comprehensively demonstrated, for the first time, both transdiagnostic and illness-specific alterations in the dynamic SC–FC coupling of large-scale brain networks across MDD, BD, and SZ. Changes in SC–FC coupling and its association with functional topology properties were particularly dominated by two configuration states. These findings shed new light on the significance of brain structure–function relationships in the pathophysiology of psychiatric disorders.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003525.

Data availability statement. Not all participants gave their permission to share their data with the public. Some data are part of longitudinal studies that will generate more than one manuscript. The data will eventually be made available, with the permission of the participants, once these manuscripts are completed. Reasonable requests can be sent to the corresponding author (T.L.).

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Author contributions. Z.Z. designed the study, statistical analyses, drafted the manuscript, and approved the final manuscript as submitted. W.W. performed the MRI data acquisition and the neuropsychological assessment, drafted the manuscript, and approved the final manuscript as submitted. S.W., X.L., X.L., Q.W., H.Y., Y.Z., W.G., X.M., L.Z., W.D., and P.S. coordinated and carried out the data collection, revised the manuscript, and approved the final manuscript as submitted. Y.S. drafted the manuscript and approved the

final manuscript as submitted. T.L. conceptualized the study and approved the final manuscript as submitted.

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Competing interest. None.

Ethical standards. The Institutional Review Board of West China Hospital, Sichuan University authorized this study. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants or their legal guardians provided written informed consent to participate in the study.

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