Shared and Distinct Dysfunction of Dynamic Connectivity Networks across Schizophrenia, Bipolar Disorder and Major Depression Disorder

Chao Li, M.D., Ph.D. [b, c#]; Ke Xu, M.D., Ph.D.[b, c#;]; Yange Wei, M.D., Ph.D.[a, c]; Jia Duan, M.D., Ph.D. [a, c]; Shaoqiang Han, Ph.D.[e, f]; Ruiqi Feng, M.D., Ph.D. [b, c]; Yifan Chen, M.D., Ph.D.[a, c]; Luheng Zhang, M.Phi[a, c]; Xiaowei Jiang , M.D., Ph.D.[a, b, c]; Shengnan Wei, M.D., Ph.D. [a, b, c]; Huafu Chen, Ph.D. [e, f]; Yanqing Tang, M.D., Ph.D. [a, c]; Fei Wang, M.D., Ph.D.[a, b, c, d*]

[a] Department of Psychiatry, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning, PR China

[b] Department of Radiology, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning, PR China

[c] Brain Function Research Section, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning, PR China

[d] Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut, USA

[e] The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China, Chengdu, China

[f] School of life Science and technology, center for information in medicine, University of Electronic Science and Technology of China, Chengdu, China.

[#]The two authors contributed equally to this work.

[*]To whom correspondence should be addressed:

Fei Wang, M.D., Ph.D., Department of Psychiatry and Radiology. The First Affiliated Hospital, China Medical University, 155 Nanjing North Street, Shenyang 110001, Liaoning, PR China, and Department of Psychiatry, Yale University School of Medicine, New Haven CT 06511, USA; Phone/Fax: 8624-83283405, email: fei.wang@cmu.edu.cn; fei.wang@yale.edu

Abstract. Converging evidence indicates that each nominally distinct psychiatric disease entity have both broadly shared and distinct risk genes, clinical symptoms, and brain structural and functional disruption. Many studies used the static (time-averaged) functional connectivity to examine the similarities and differences in functional brain networks in psychiatric disorders. However, little is known about the similarities and differences in dynamic functional connectivity (FC) networks across multiple major psychiatric disorders. A total of 655 participants (125 with schizophrenia (SZ), 121 with bipolar disorder (BD), 192 with major depressive disorder (MDD), and 217 demographically matched healthy controls (HC) completed resting-state functional magnetic resonance imaging at a single site. We used sliding-window approach to construct dynamic FC networks, and used k-means clustering to obtain four dissociated networks by different states. We identified shared and distinct dysconnectivity across these psychiatric disorders compared with HC in each state. We found dysconnectivity in psychosis were state-specific, rather than a time-invariant global abnormality. SZ, BD and MDD shared decreased intra-network FC (especially frontoparietal control network (FPN)), whereas increased inter-network FC (especially between visual network (VN) and both default mode network (DMN) and FPN). Almost all dysconnectivity in BD and MDD were included in those in SZ, with SZ had distinct dysconnectivity that preferentially involving inter-network dysconnectivity between high-level cognitive networks. Many dysconnectivity were not detected by static FC. These findings shed new light on the current transdiagnostic knowledge, and advocate future researches use dynamic methods to study psychiatric disorders, besides use static methods.

Introduction

Modern mainstream view of psychiatry holds the idea that major psychiatric disorders

are separate diagnostic categories with distinct etiologies and clinical presentations. According to the DSM-V, the major psychiatric disorders are divided into three separate diagnostic categories, i.e., schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD). However, existing diagnostic categories are not clearly associated with distinct neurobiological abnormalities(1, 2), which may hinder the search for biomarkers in psychiatry(3). Major psychiatric disorders have common abnormalities in many aspects, including genetic risk and etiology (4, 5), neural alterations (6-8), and clinical symptoms (9-11). In addition, co-morbidity among psychiatric disorders is very common, with 22% carried 2 diagnoses and 23% carried 3 or more diagnoses (12). Above mentioned findings together argue that there are no clear-cut boundaries between the different mental disorders. In contrast, each distinct psychiatric disorder entity is hypothesized to have both broadly shared and distinct etiologies and mechanisms among multiple psychiatric disorders (13, 14). Transdiagnostic studies are necessary due to they focus on fundamental processes underlying multiple disorders, help to explain co-morbidity among disorders, and may lead to more effective assessment and treatment of disorders (15-17).

An important way to apply transdiagnostic models of psychopathology is to uncover shared (or common) and distinct (or specific) neurobiological abnormalities across several psychiatric disorders. The vast majority of previous studies, however, have only compared one specific group of psychiatric disorder with healthy controls (HC). In a small number of transdiagnostic studies, many of them are meta-analyses that were based on individual studies using different methodologies (6, 8, 18, 19). Recently, a few but rapidly growing original transdiagnostic researches have been conducted to directly investigate the shared and distinct abnormalities in brain structure and functional connectivity (FC) across multiple mental-disorders (20-25). For example, a previous study reported disruptions within the frontoparietal control network (FPN) may be a shared feature across both SZ and affective psychosis (20), which was validated and extended by a recent study (25). In addition, a recent study

found that higher p factor scores and associated risk for common mental illness maps onto hyperconnectivity between visual association cortex and both FPN and default mode network (DMN) (23).

Despite the contribution of advancing the transdiagnostic research, with regard to the studies using FC, these studies assumed that the brain functional properties during the entire fMRI scan were static but not dynamic. In fact, interactions among large-scale brain networks are highly dynamic, time-averaged or static connectivity provides limited information about the functional organization of neural circuits (26, 27). Therefore, using time-varying or dynamic method to investigate shared and distinct dysfunction of large-scale FC networks across major psychiatric disorders may provide more information about their psychopathology. Follow this idea, a few transdiagnostic studies used dynamic FC to investigate the dynamic functional architecture of the brain network in healthy young adults or neurobiological abnormalities of the psychiatric disorders (28-32). For example, a previous study showed that dynamic FC can found connectivity abnormalities that are not observed in the static FC, which suggests dynamic FC is more sensitive than static FC (31). Recently, another transdiagnostic study demonstrated that dynamic FC are quite reliable within participants (within and across visits), and can act as a fingerprint, identifying specific individuals within a larger group (28). Although these studies that using dynamic FC are very important, either their sample size is relatively small (especially the patient's groups) or they only studied two diseases (i.e., SZ and BD, or MDD and bipolar depression).

Here, we used a widely used sliding-window approach (26, 27, 33, 34) to characterize dynamic FC networks among SZ, BD, MDD and HC (N = 655). Then, we applied k-means clustering to cluster these dynamic networks into 4 network states. In each

state, we identified shared and distinct dysconnectivity across these psychiatric disorders compared with HC. We found state-specific, intermittent shared and distinct disruptions of connectivity. These dysconnectivity tend to only occur in state 1 and state 2, rather than state 3 and 4. In general, shared dysconnectivity across these 3 psychiatric disorders marked by decreased intra-network connectivity (especially within FPN), while increased inter-network connectivity between most networks (especially between visual network (VN) and both FPN and DMN). In addition, interestingly, almost only SZ has distinct dysconnectivity, and almost all of the distinct dysconnectivity are between high-level cognitive networks (i.e., between DMN, SN, FPN and dorsal attention network (DAN)). In respect of time-averaged or static connectivity, however, we detect only a few significant results compared with dynamic connectivity.

Results

Dynamic Connectivity State. We used sliding-window approach constructed dynamic connectivity network. Then, we identified four dynamic connectivity network states using k-means clustering method. Dynamic connectivity matrices in four states are shown in Figure 1 (the top row). All nodes were grouped into brain networks to which they belong according functional atlas of Yeo et al. (35). Note that not all subjects have dynamic windows that are assigned to every state (26, 31, 34, 36). HC and psychiatric patients had similar network connectivity patterns in the four states. In state 1, which accounts for the largest proportion (47%) of all time windows, the network configuration was similar to static network configuration, which presented both weak positive and weak negative connectivity. In contrast to state 1, both positive and negative connectivity in state 3 was strong. In state 2, connectivity between VN and most nodes in FPN as well as that between VN and DMN was strongly negative, and connectivity between VN and sensorimotor network (SMN) was relatively strongly positive. Connectivity pattern in state 4 was seems to between

state 1 and 3.

Shared Dynamic Dysconnectivity Across Psychiatric Disorders. Figure 2 shows the results of ANCOVA and post-hoc two-sample t-tests for dynamic connectivity. In state 3 (both positive and negative connectivity was strong), no connectivity showed differences between groups. Based on the statistical results in state 1, 2 and 4, we identified the shared and distinct dysconnectivity across the three diseases. The first column in Figure 3 showed the shared dysconnectivity (see Figure S8 and Table S2 in Supplementary Materials for the unique identification number and name of each node).

In state 1, interestingly, all within-network dysconnectivity were hypoconnectivity, but almost all of the between-network connectivity were hyperconnectivity, with exception of a few pairs of connectivity between SN and other networks (i.e., FPN, DMN and SMN) and between FPN and DAN. Specially, in state 1, SZ, BD and MDD shared hypoconnectivity within FPN, SN, VN and SMN, whereas hyperconnectivity between most networks.

In state 2, shared dysconnectivity across the three diseases was marked by hyperconnectivity between VN and other networks (i.e., FPN and DMN). On the contrary, all within-VN connectivity were hypoconnectivity across the three groups. Besides, in state 2, we also found shared hyperconnectivity between SN and both DAN and SMN, but hypoconnectivity between SN and FPN. In state 4, we only detected one hyperconnectivity between DMN and FPN.

Distinct Dynamic Dysconnectivity among Psychiatric Disorders. In terms of the quantity of dysconnectivity, only the SZ had obvious distinct dysconnectivity. BD and MDD almost had no distinct dysconnectivity (the last 3 columns in Figure 3), which means that almost all of the dysconnectivity in BD and MDD were shared by at least two of patients' groups.

In state 1, almost all of the distinct dysconnectivity in SZ were between higher-order cognitive networks (i.e., DMN, SN and DAN). Specifically, SZ mainly showed hyperconnectivity between DMN and SN, while hypoconnectivity between DMN and DAN.

In state 2, also almost all of the distinct dysconnectivity in SZ were between higher-order cognitive networks (i.e., DMN, SN, DAN and FPN). Specifically, SZ mainly showed hypoconnectivity between DMN and DAN, and between SN and FPN. In addition, we also observed five pairs of hyperconnectivity between SN and DAN, which was significantly more than the quantity of shared hyperconnectivity between these two networks in the same state.

In state 4, SZ mainly showed hyperconnectivity between SN and other networks (i.e., DMN, VN and SMN).

Gradient in the Extent of Shared Dynamic Dysconnectivity across Psychiatric Disorders. Figures S3-S7 display the mean z values of all dysconnectivity in state 1, 2 and 4 for 4 groups. In state 1, the extent of abnormality in SZ is the greatest in most (23/38) shared dynamic dysconnectivity. In most (25/38) shared dynamic

dysconnectivity, the extent of abnormality in BD was greater than that in MDD. Consequently, a gradient in the extent of abnormality was SZ>BD>MDD in most shared dynamic dysconnectivity in state 1.

In state 2, however, the extent of abnormality in BD is the greatest in most (13/22) shared dynamic dysconnectivity. In most (14/22) shared dynamic dysconnectivity, the extent of abnormality in MDD was greater than that in SZ. Consequently, a gradient in the extent of abnormality was BD>MDD>SZ in most shared dynamic dysconnectivity in state 2.

In state 4, a gradient in the extent of abnormality was SZ>BD>MDD in dysconnectivity between control and default mode network.

Discussion

The present study is the first to examine the dynamic FC in three major psychiatric disorders, SZ, BD, and MDD, at relatively large sample size in a single site. We explored dynamic FC patterns using sliding-window approach and k-means clustering. Our study had four main findings. (1) Patients showed significant dysconnectivity only in state 1 and 2, rather than state 3 and 4. (2) Shared dysconnectivity that cross traditional diagnostic categories were that overall decreased intra-network connectivity, especially those within FPN, while increased inter-network connectivity, especially those between VN and both FPN and DMN. (3) Among the three psychiatric disorders, only SZ had significant distinct dysconnectivity, and all these distinct dysconnectivity were between high-level cognitive networks, i.e., DMN, SN, FPN and DAN. (4) Most of the dysconnectivity cannot be detected by time-averaged FC. Collectively, these results support and advance current knowledge regarding

transdiagnostic findings across psychiatric disorders, and strongly advocate the application of time-varying or dynamic methods to explore the dysfunction of FC in psychiatric disorders.

State-specific and Network-specific Dysconnectivity. State-specific and transient dysfunction of large-scale cortical networks in psychiatric disorders was also found by previous studies and these dysconnectivity preferentially evident during the expression of particular network configurations (28, 31, 34). In the present study, as shown in Figure 3 and Figure S1, there was almost no difference between psychiatric patients and HC in state 3 and state 4. All the dysfunction of connectivity in patients was only manifested in state 1 and state 2. In addition, the pattern of abnormal connectivity between state 1 and state 2 was also obviously different, expressed as network specificity in specific state. In state 1, which accounts for the largest proportion (47%) of all time windows and in which the connectivity pattern resemble those of static FC, dysconnectivity were widely distributed. However, in state 2, in which the VN had both strongest positive and negative connectivity with other networks, dysconnectivity were very limited that almost only between VN and other networks, e.g. FPN and DMN. Together with previous studies, the present study suggests that FC disruptions in psychosis may be an intermittent disruption, rather than a time-invariant global abnormality during a whole resting-state scan.

Advantages of a Dynamic Analysis. Our viewpoint was supported by previous studies advocating advantages of a dynamic approach (28, 31, 34, 37). In fact, intrinsic fluctuations are a hallmark of neural activity, which emergent over time scales spanning milliseconds and tens of minutes (26). Previous research has established that individuals freely engage in various states of mental activity during the measurement period, e.g. resting-state scan (38). In the present study, we clustered the interaction between brain regions into four states according to the whole-brain

dynamic connectome. Many dysconnectivity that found by dynamic analysis were not found by time-averaged analysis. A speculative explanation is that in the present study the connectivity in normal mental states (i.e., state 3 and 4) may "neutralize" those at abnormal mental states (state 1 and 2), making the time-averaged or static connectivity shows no abnormal. Future researches need to test this hypothesis.

Decreased Intra-network and Increased Inter-network Connectivity May be an Important Transdiagnostic Characteristic. Overall, in present study, the dysfunction of dynamic connectivity across these three psychiatric disorders manifested as decreased intra-network but increased inter-network connectivity. The decreased intra-network connectivity was mainly expressed in state 1, in which the abnormality of FPN was the most obvious. This finding is consistent with that of previous studies which found decreased FC within FPN in multiple psychiatric disorders (25, 39) as well as in SZ (40-42), BD (43, 44) and MDD (45-47). The FPN is the core hub for cognitive control, adaptive implementation of task demands and goal-directed behavior (48-51). Reduced intra-network integration (or intra-network modularity(52)) in FPN may be responsible for cognitive dysfunction, one of the most prominent transdiagnostic characteristics of psychiatric disorders (8, 16).

Although the abnormality of FPN is the most obvious, SN, VN and SMN also showed transdiagnostic decreased intra-network connectivity in state 1. These findings also match those observed in earlier studies that found abnormality in salience (6, 53), VN and SMN (22, 23, 54) in psychiatric disorders. Together, these findings suggest that the intra-network integration is decreased in patients with psychiatric disorders, at least within FPN, SN, VN and SMN.

In contrast, most inter-network dysconnectivity were increased, especially between VN and both FPN and DMN. These disruptions were almost only expressed in state 2 in which the negative connectivity between VN and both FPN and DMN was strongest. While the dysconnectivity between VN and other networks are not often thought of as primary to dysfunction in psychopathology by early researches, this finding was in line with that of a recent work (23). This study performed a novel connectome-wide association study (CWAS) of the p factor (a single general transdiagnostic factor associated with risk for all common forms of mental illness) using multidimensional matrix regression (MDMR) in 605 university students (133 met criteria for substance abuse or a mental illness). They found that hyperconnectivity between the visual association cortex and the heteromodal FPN and DMN was correlated with higher p factor scores. Considering that the patients' groups of the present study were all psychiatric patients, our finding support and expand the recent study, suggesting that the more effortful or less efficient integration of bottom-up visual sensory information with attentional demands and executive control processes not only in those at higher risk for psychiatric disorders, but also in those already suffering from psychiatric disorders. This represents the possibility of a trait in multiple psychiatric disorders.

SZ had the Most Distinct Dysconnectivity that were Inter-network Dysconnectivity between High-level Cognitive Networks. In the present study, we found SZ not only had almost all dysconnectivity that BD and MDD had, but also had dysconnectivity that BD and MDD did not have. When integrating the information in Figure 3 and Figure S1 which shown the shared dysconnectivity across the three disorders and any two of the diseases respectively, our findings further illustrated that dysconnectivity in BD and MDD seem to be two similar but not identical parts that all were divided up from those of SZ. This finding was partially supported by previous studies (21, 22, 30) that reported psychiatric disorders have more shared but less

distinct brain abnormality and SZ has the most obvious abnormality. Together with previous studies, this finding support the idea that SZ, BD and MDD may be a transdiagnostic continuum of major endogenous psychoses (55), with SZ have more dysconnectivity.

Intriguingly, almost all these distinct dysconnectivity in SZ were between high-level cognitive networks. The distinct dysconnectivity was characterized by hypoconnectivity between DMN and DAN, whereas hyperconnectivity between DMN and SN networks. The DMN supports internally oriented attention and self-monitoring, among other functions, whose activity is high when the brain system is engaged in autobiographical memory retrieval, envisioning the future, and conceiving the perspectives of others, while low when the brain system is engaged in specific behavioral tasks on the external environment (56-58). In contrast to DMN, the SN and DAN are responsible for control attentional processes in relation to bottom-up sensory stimulation and top-down goals respectively (59, 60). Given the functions of the three networks mentioned above, this finding may reflect that the inappropriate communication of internal and external cognition is more likely to be a distinct/specific feature of SZ. These findings are consistent with previous studies found psychosis was correlated dysconnectivity between the DMN and task-positive networks (i.e., SN, DAN, and FPN) (2, 61).

Conclusion. We performed, to our knowledge, the first time-varying functional connectivity analyses in HC, SZ, BD and MDD in a single study at relatively large sample size. We used the same scanner and acquisition sequence for all participants, ensuring comparability of the data across multiple psychiatric disorders. We highlight the following three key findings. First of all, FC disruptions in psychosis may be state-specific and intermittent, rather than a time-invariant global abnormality at least during a scan. Secondly, both decreased intra-network integration and decreased inter-network segregation (especially within FPN and between VN and both DMN

and FPN) may be the important transdiagnostic substrate across the three psychiatric disorders. Lastly, almost all dysconnectivity in BD and MDD were contained in those in SZ, with SZ had more dysconnectivity that only involving inter-network dysconnectivity between high-level cognitive networks. These findings support and shed new light on the current knowledge about transdiagnostic findings, and strongly advocate that future researches should use dynamic methods to study psychiatric disorders, besides use static methods.

Materials and Methods

Participants. The study was approved by the Institutional Review Board of China Medical University. All participants provided written informed consent after receiving a detailed description of the study. Demographics, clinical characteristics, and cognitive function of included participants are summarized in Table S1. Six hundred and seventy-eight individuals participated in this study. We finally included 655 participants (see Data Preprocessing section for detail; ages 13–45 years), including 125 with SZ, 121 with BD, 192 with MDD, and 217 healthy controls. The study was approved by the Institutional Review Board of China Medical University. All participants provided written informed consent after receiving a detailed description of the study. All participants with SZ, BD, and MDD were recruited from the inpatient and outpatient services at the Shenyang Mental Health Center and the Department of Psychiatry, the First Affiliated Hospital of China Medical University, Shenyang, China. Healthy controls participants were recruited from the local community by advertisement.

The presence or absence of Axis I psychiatric diagnoses was determined by two trained psychiatrists using the Structured Clinical Interview for Diagnostic and

Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I Disorders for the participants 18 years and older, while using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-present and Lifetime Version (K-SADS-PL) for participants younger than 18 years. Patients with SZ, BD, or MDD must met the DSM-IV diagnostic criteria for SZ, BD, or MDD, respectively, and no other Axis I disorders. Healthy controls did not have a current or lifetime history of an Axis I disorder or a history of psychotic, mood, or other Axis I disorders in first-degree relatives, as determined from a detailed family history. Participants were excluded for (1) lifetime substance/alcohol abuse or dependence, (2) the presence of a concomitant major medical disorder, (3) any MRI contraindications, (4) a history of head trauma with loss of consciousness ≥5 minutes or any neurological disorder, and (5) any abnormality identified by T1-and T2-weighted image. Symptoms and cognitive measures were obtained using the Brief Psychiatric Rating Scale (BPRS), Hamilton Depression Rating Scale (HAMD), Hamilton Anxiety Rating Scale (HAMA) and Young Mania Rating Scale (YMRS), and Wisconsin Card Sorting Test (WCST).

MRI Acquisition. MRI data were acquired using a GE Signa HD 3.0-T scanner (General Electric, Milwaukee, WI) with a standard 8-channel head coil at the First Affiliated Hospital of China Medical University. Functional images were collected using a gradient-echo planar imaging (EPI-GRE) sequence. The following parameters were used: interleaved scanning, repetition time = 2000 ms, echo time = 30 ms, flip angle = 90 °, field of view = 240 mm × 240 mm, and matrix = 64 × 64, slice thickness = 3 mm without a gap, number of slices = 35. The scan lasted 6 minutes and 40 seconds, resulting in 200 volumes. Participants were instructed to rest and relax with their eyes closed but to remain awake during scanning.

Data Preprocessing. All images were preprocessed using SPM12 (www.fil.ion.ucl.ac.uk/spm/) and DPABI (62), like previous studies. Volumes at the

first 10 time points were discarded. The subsequent preprocessing steps included slice time correction and head motion correction. During head motion correction, 23 subjects (9 with SCZ, 6 with BD, 4 with MDD, and 4 healthy controls) were excluded from subsequent analyses due to excessive head motion, based on a criterion of 3 mm or 3 °. No significant differences in mean framewise displacement (FD) were observed among these groups (P = .151). The corrected functional images were spatially normalized to the Montreal Neurological Institute space using the EPI template in SPM12, and resampled to 3 mm × 3 mm × 3 mm isotropic voxels, and further smoothed via a Gaussian kernel with a 4-mm full-width at half-maximum. Then we performed linear detrending and temporal band-pass filtering (0.01–0.01 Hz) to reduce low-frequency drift and high-frequency noise. Next, several confounding covariates, including the Friston-24 head motion parameters, white matter, cerebrospinal fluid, and global signals, were regressed from the BOLD time series for all voxels. Finally, BOLD series were despiking by replaced the outliners (detected based on the median absolute deviation) with the best estimate using a third-order spline fit to clean the portions of time course implemented in 3dDespike (http://afni.nimh.nih.gov/afni).

Dynamic Connectivity Analysis. Average BOLD time series of 114 nodes within the 17-network functional atlas of Yeo et al. (35) were extracted. Dynamic Connectivity was estimated with a widely used sliding-window approach. Pearson's correlation coefficients were calculated between each pair of nodes using segments of the time series within a time window. The window had a width of 17 TRs (i.e., 34 s) and slide on time with a time step of 1 TR (i.e., 2 s). Previous study (63) suggests that a sliding-window width range of 30–60 s is appropriate for dynamic connectivity analyses. This previous study also revealed consistent state solution stability across varying sliding-window sizes of 33–63 s. Consequently, 17 TRs (i.e., 34 s) width were chosen in order to maximize signal estimates, while still capturing properties of

transient functional connectivity. Then, for each participant, we obtained a total of 174 windows, each of which had (114×113)/2 = 6,441 unique functional connectives. Finally, Fisher r-to-z transformation was performed for all functional connectivity.

Clustering Analysis. K-means algorithm can identify sets of time-varying network configurations in different windows with common features, grouping them into clusters that are more similar to each other than to configurations in other clusters. A previous (28) study applied k-means clustering to identify possible dissociable network configurations in solutions from 2 to 20 brain states in healthy people. Their results indicate relative stability in state solutions from 2 to 8, with 2-, 4-, 5-, and 8-state solutions showing points of increased stability, and they chose the four-state solution for following analyses due to the stability of the associated clustering solution and the relatively high within-participant reliability. According to previous study, we first apply k-means clustering to cluster these dynamic connectivity networks into 4 network states. Our k-means clustering used the city distance (L_1 distance) function with 100 times to repeat clustering using new initial cluster centroid positions to increase chances of escaping local minima. We selected k (k = 4) seeds by implementing the k-means++ algorithm for cluster center initialization for each iteration of the 100 times repeat clustering. The input of k-means clustering were a n_instances-by-n_fc matrix, where n_instances was equal to the number of sliding windows (n = 174) multiplied by the sample size (n = 655), and n_fc was equal to the 6,441 unique functional connectivity. The resulted cluster medians (centroid) were regarded as FC states in group level. For each participant, each state was regarded as the median of those windowed FC networks that had the same cluster index (index = 1, 2, 3 or 4). Given that we propagated group cluster indices to the subject level, not all subjects have dynamic windows that are assigned to every state (26, 31, 34, 36).

Static Connectivity Analysis. Average BOLD time series of 114 nodes within the 17-network functional atlas of Yeo et al. (35) were extracted for each individual by averaging the whole time series throughout all voxels in each node. Static functional connectivity between each pair of nodes was calculated using Pearson's correlation analysis, producing (114×113)/2=6,441 unique functional connectives for each subject. Fisher r-to-z transformation was performed for all functional connectives (correlation coefficients) to improve the normality of the correlation coefficients. See Supplementary Materials for results of static analyses.

Statistical Analysis. Group effects on each pair of static and dynamic connectivity were examined using one-way analysis of covariance (ANCOVA), with age and gender as covariates. Post hoc analyses two-sample t-tests were performed for significant group effects in the ANCOVA to determine the shared and distinct dysconnectivity across the SZ, BD, and MDD groups, which were applied in pair-wise fashion with the HC group as the common comparison. We used false-discovery rate (FDR) to perform multiple comparison correction for both the ANCOVA and post-hoc analyses ($q < 0.05$). Shared dysconnectivity were thought to be those where all three patients' groups have either hypoconnectivity or hyperconnectivity compared with HC. Besides, we also identified the shared dysconnectivity across any two of the diseases (Supplementary Figure S1). Distinct dysconnectivity of one patient group were thought to be those where only one patient group have abnormal compared with HC. Finally, we count the quantity of dysconnectivity in which each node or network involved in all states with dysconnectivity (see Figure S10).

Effects of Medication on FC. Considering that most patients have been treated with medications, an important question was whether medications influenced functional

connectivity. We compared the functional connectivity between medicated and un-medicated patients using ANCOVA, with age and gender as covariates (false-discovery rate (FDR), $q < 0.05$; comparison times = 6441). Because of the low sensitivity of static connectivity analysis (Figure S2) in the present study, our focus was on dynamic connectivity. Consequently, we only analyzed the effect of medications on dynamic connectivity. We found no statistical difference in dynamic connectivity in state 1, 2 and 4 between the medicated and un-medicated patients (because no statistical difference among the four groups in dynamic connectivity in state 3, we discarded the analysis of state 3). Figure S9 displays the F value map.

Validation Analysis. First, we also used width of 18 TRs (i.e., 36 s) to construct dynamic connectivity network. We also cluster these dynamic connectivity networks into 4 network states using as the same methods and parameters as those of 17 TRs. Then we calculated the Pearson's correlation coefficients in FC values between 20 TRs and 17 TRs. The best coefficient range from 0.9983 to 0.9999, showing very good consistency and robustness (see Supplementary Figure S11).

Data availability. The data used in the present study can be accessed upon request to the corresponding authors. All analysis code is available here: https://github.com/lichao312214129/lc_rsfmri_tools_matlab.

Acknowledgements

This study was funded by National Science Fund for Distinguished Young Scholars (81725005 to F.W.), National Natural Science Foundation of China (81571311 to Y.T., 81571331 to F.W.), National Key Research and Development Program (2018YFC1311604 to Y.T., 2016YFC1306900 to Y.T., 2016YFC0904300 to F.W.), National High Tech Development Plan (863) (2015AA020513 to F.W.), Liaoning

Science and Technology Project (2015225018 to Y.T.), Liaoning Education Foundation (Pandeng Scholar to F.W.), Innovation Team Support Plan of Higher Education of Liaoning Provience (LT2017007 to F.W.), Major Special Construction plan of China Medical University (3110117059 to F.W.).

References

1. Insel TR, Cuthbert BN (2015): Brain disorders? Precisely. *Science*. 348:499-500.

2. Xia CH, Ma Z, Ciric R, Gu S, Betzel RF, Kaczkurkin AN, et al. (2018): Linked dimensions of psychopathology and connectivity in functional brain networks. *Nature communications*. 9:3003.

3. Singh I, Rose N (2009): Biomarkers in psychiatry. *Nature*. 460:202.

4. Consortium C-DGotPG (2013): Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *The Lancet*. 381:1371-1379.

5. Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, et al. (2013): Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature genetics*. 45:984.

6. Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, et al. (2015): Identification of a common neurobiological substrate for mental illness. *JAMA psychiatry*. 72:305-315.

7. McTeague LM, Huemer J, Carreon DM, Jiang Y, Eickhoff SB, Etkin A (2017): Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *American Journal of Psychiatry*. 174:676-685.

8. Sha Z, Wager TD, Mechelli A, He Y (2019): Common Dysfunction of Large-Scale Neurocognitive Networks Across Psychiatric Disorders. *Biological psychiatry*. 85:379-388.

9. Levit-Binnun N, Davidovitch M, Golland Y (2013): Sensory and motor secondary symptoms as indicators of brain vulnerability. *Journal of Neurodevelopmental Disorders*. 5:26.

10. Barch DM, Sheffield JM (2014): Cognitive impairments in psychotic disorders: common mechanisms and measurement. *World Psychiatry*. 13:224-232.

11. Lee R, Hermens D, Naismith S, Lagopoulos J, Jones A, Scott J, et al. (2015): Neuropsychological and functional outcomes in recent-onset major depression, bipolar disorder and schizophrenia-spectrum disorders: a longitudinal cohort study. *Translational psychiatry*. 5:e555.

12. Kessler RC, Chiu WT, Demler O, Walters EE (2005): Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry*. 62:617-627.

13. Lahey BB, Zald DH, Hakes JK, Krueger RF, Rathouz PJ (2014): Patterns of heterotypic continuity associated with the cross-sectional correlational structure of prevalent mental disorders in adults. *JAMA psychiatry*. 71:989-996.

14. Cuthbert BN, Insel TR (2013): Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC medicine*. 11:126.

15. Nolen-Hoeksema S, Watkins ER (2011): A heuristic for developing transdiagnostic models of psychopathology: Explaining multifinality and divergent trajectories. *Perspectives on Psychological Science*. 6:589-609.

16. Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, Israel S, et al. (2014): The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science*. 2:119-137.

17. Husain M (2017): Transdiagnostic neurology: neuropsychiatric symptoms in neurodegenerative diseases. *Brain*. 140:1535-1536.

18. Wise T, Radua J, Via E, Cardoner N, Abe O, Adams T, et al. (2017): Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. *Molecular psychiatry*. 22:1455.

19. Brandl F, Avram M, Weise B, Shang J, Simões B, Bertram T, et al. (2019): Specific Substantial Dysconnectivity in Schizophrenia: A Transdiagnostic Multimodal Meta-analysis of Resting-State Functional and Structural Magnetic Resonance Imaging Studies. *Biological psychiatry*. 85:573-583.

20. Baker JT, Holmes AJ, Masters GA, Yeo BT, Krienen F, Buckner RL, et al. (2014): Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. *JAMA psychiatry*. 71:109-118.

21. Chang M, Womer FY, Edmiston EK, Bai C, Zhou Q, Jiang X, et al. (2017): Neurobiological commonalities and distinctions among three major psychiatric diagnostic categories: a structural MRI study. *Schizophrenia bulletin*. 44:65-74.

22. Xia M, Womer FY, Chang M, Zhu Y, Zhou Q, Edmiston EK, et al. (2018): Shared and distinct functional architectures of brain networks across psychiatric disorders. *Schizophrenia bulletin*. 45:450-463.

23. Elliott ML, Romer A, Knodt AR, Hariri AR (2018): A connectome-wide functional signature of transdiagnostic risk for mental illness. *Biological psychiatry*. 84:452-459.

24. Gong Q, Scarpazza C, Dai J, He M, Xu X, Shi Y, et al. (2019): A transdiagnostic neuroanatomical signature of psychiatric illness. *Neuropsychopharmacology*. 44:869.

25. Baker JT, Dillon DG, Patrick LM, Roffman JL, Brady RO, Pizzagalli DA, et al. (2019): Functional connectomics of affective and psychotic pathology. *Proceedings of the National Academy of Sciences*. 116:9050-9059.

26. Allen EA, Damaraju E, Plis SM, Erhardt EB, Eichele T, Calhoun VD (2014): Tracking whole-brain connectivity dynamics in the resting state. *Cereb Cortex*. 24:663-676.

27. Calhoun VD, Miller R, Pearlson G, Adalı T (2014): The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. *Neuron*. 84:262-274.

28. Reinen JM, Chen OY, Hutchison RM, Yeo BTT, Anderson KM, Sabuncu MR, et al. (2018): The human cortex possesses a reconfigurable dynamic network architecture that is disrupted in psychosis. *Nat Commun*. 9:1157.

29. Pang Y, Chen H, Wang Y, Long Z, He Z, Zhang H, et al. (2018): Transdiagnostic and diagnosis-specific dynamic functional connectivity anchored in the right anterior insula in major depressive disorder and bipolar depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 85:7-15.

30. Wang J, Wang Y, Huang H, Jia Y, Zheng S, Zhong S, et al. (2019): Abnormal dynamic functional network connectivity in unmedicated bipolar and major depressive disorders based on the triple-network model. *Psychological medicine*.1-10.

31. Rashid B, Damaraju E, Pearlson GD, Calhoun VD (2014): Dynamic connectivity states estimated from resting fMRI Identify differences among Schizophrenia, bipolar disorder, and healthy control subjects. *Front Hum Neurosci*. 8:897.

32. Han S, He Z, Duan X, Tang Q, Chen Y, Yang Y, et al. (2019): Dysfunctional connectivity between raphe nucleus and subcortical regions presented opposite differences in bipolar disorder and major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 92:76-82.

33. Hutchison RM, Womelsdorf T, Allen EA, Bandettini PA, Calhoun VD, Corbetta M, et al. (2013): Dynamic functional connectivity: promise, issues, and interpretations. *Neuroimage*. 80:360-378.

34. Damaraju E, Allen EA, Belger A, Ford JM, McEwen S, Mathalon D, et al. (2014): Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia. *NeuroImage: Clinical*. 5:298-308.

35. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. (2011): The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 106:1125-1165.

36. Liu F, Wang Y, Li M, Wang W, Li R, Zhang Z, et al. (2017): Dynamic functional network connectivity in idiopathic generalized epilepsy with generalized tonic-clonic seizure. *Hum Brain Mapp*. 38:957-973.

37. Rashid B, Arbabshirani MR, Damaraju E, Cetin MS, Miller R, Pearlson GD, et al. (2016): Classification of schizophrenia and bipolar patients using static and dynamic resting-state fMRI brain connectivity. *Neuroimage*. 134:645-657.

38. Delamillieure P, Doucet G, Mazoyer B, Turbelin M-R, Delcroix N, Mellet E, et al. (2010): The resting state questionnaire: an introspective questionnaire for evaluation of inner experience during the conscious resting state. *Brain research bulletin*. 81:565-573.

39. Baker JT, Holmes AJ, Masters GA, Yeo BT, Krienen F, Buckner RL, et al. (2014): Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. *JAMA Psychiatry*. 71:109-118.

40. MacDonald III AW, Carter CS, Kerns JG, Ursu S, Barch DM, Holmes AJ, et al. (2005): Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in never-medicated patients with first-episode psychosis. *American Journal of Psychiatry*. 162:475-484.

41. Perlstein WM, Carter CS, Noll DC, Cohen JD (2001): Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. *American Journal of Psychiatry*. 158:1105-1113.

42. Barch DM, Carter CS, MacDonald III AW, Braver TS, Cohen JD (2003): Context-processing deficits in schizophrenia: diagnostic specificity, 4-week course, and relationships to clinical symptoms. *Journal of abnormal psychology*. 112:132.

43. Anticevic A, Brumbaugh MS, Winkler AM, Lombardo LE, Barrett J, Corlett PR, et al. (2013): Global prefrontal and fronto-amygdala dysconnectivity in bipolar I disorder with psychosis history. *Biological psychiatry*. 73:565-573.

44. Anticevic A, Cole MW, Repovs G, Murray JD, Brumbaugh MS, Winkler AM, et al. (2013): Characterizing thalamo-cortical disturbances in schizophrenia and bipolar illness. *Cerebral cortex*. 24:3116-3130.

45. Pizzagalli DA (2011): Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology*. 36:183.

46. Holmes AJ, Pizzagalli DA (2008): Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. *Archives of general psychiatry*. 65:179-188.

47. Holmes AJ, Pizzagalli DA (2008): Response conflict and frontocingulate dysfunction in unmedicated participants with major depression. *Neuropsychologia*. 46:2904-2913.

48. Cole MW, Reynolds JR, Power JD, Repovs G, Anticevic A, Braver TS (2013): Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature neuroscience*. 16:1348.

49. Zanto TP, Gazzaley A (2013): Fronto-parietal network: flexible hub of cognitive control. *Trends in cognitive sciences*. 17:602-603.

50. Ptak R (2012): The frontoparietal attention network of the human brain: action, saliency, and a priority map of the environment. *The Neuroscientist*. 18:502-515.

51. Diamond A (2013): Executive functions. *Annual review of psychology*. 64:135-168.

52. van den Heuvel MP, Sporns O (2019): A cross-disorder connectome landscape of brain dysconnectivity. *Nature Reviews Neuroscience*.1.

53. Yang Y, Liu S, Jiang X, Yu H, Ding S, Lu Y, et al. (2019): Common and specific functional activity features in schizophrenia, major depressive disorder, and bipolar disorder. *Frontiers in psychiatry*. 10.

54. Chang M, Edmiston EK, Womer FY, Zhou Q, Wei S, Jiang X, et al. (2019): Spontaneous low-frequency fluctuations in the neural system for emotional perception in major psychiatric disorders: amplitude similarities and differences across frequency bands. *Journal of psychiatry & neuroscience: JPN*. 44:132.

55. Pearlson GD (2015): Etiologic, Phenomenologic, and Endophenotypic Overlap of Schizophrenia and Bipolar Disorder. *Annual Review of Clinical Psychology*. 11:251-281.

56. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001): A default mode of brain function. *Proceedings of the National Academy of Sciences*. 98:676-682.

57. Buckner RL, Andrews‐Hanna JR, Schacter DL (2008): The brain's default network. *Annals of the New York Academy of Sciences*. 1124:1-38.

58. Anticevic A, Cole MW, Murray JD, Corlett PR, Wang X-J, Krystal JH (2012): The role of default network deactivation in cognition and disease. *Trends in cognitive sciences*. 16:584-592.

59. Corbetta M, Shulman GL (2002): Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews neuroscience*. 3:201.

60. Vossel S, Geng JJ, Fink GR (2014): Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. *The Neuroscientist*. 20:150-159.

61. Lefort‐Besnard J, Bassett DS, Smallwood J, Margulies DS, Derntl B, Gruber O, et al. (2018): Different shades of default mode disturbance in schizophrenia: Subnodal covariance estimation in structure and function. *Human brain mapping*. 39:644-661.

62. Yan CG, Wang XD, Zuo XN, Zang YF (2016): DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. *Neuroinformatics*. 14:339-351.

63. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD (2012): Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cereb Cortex*. 22:158-165.

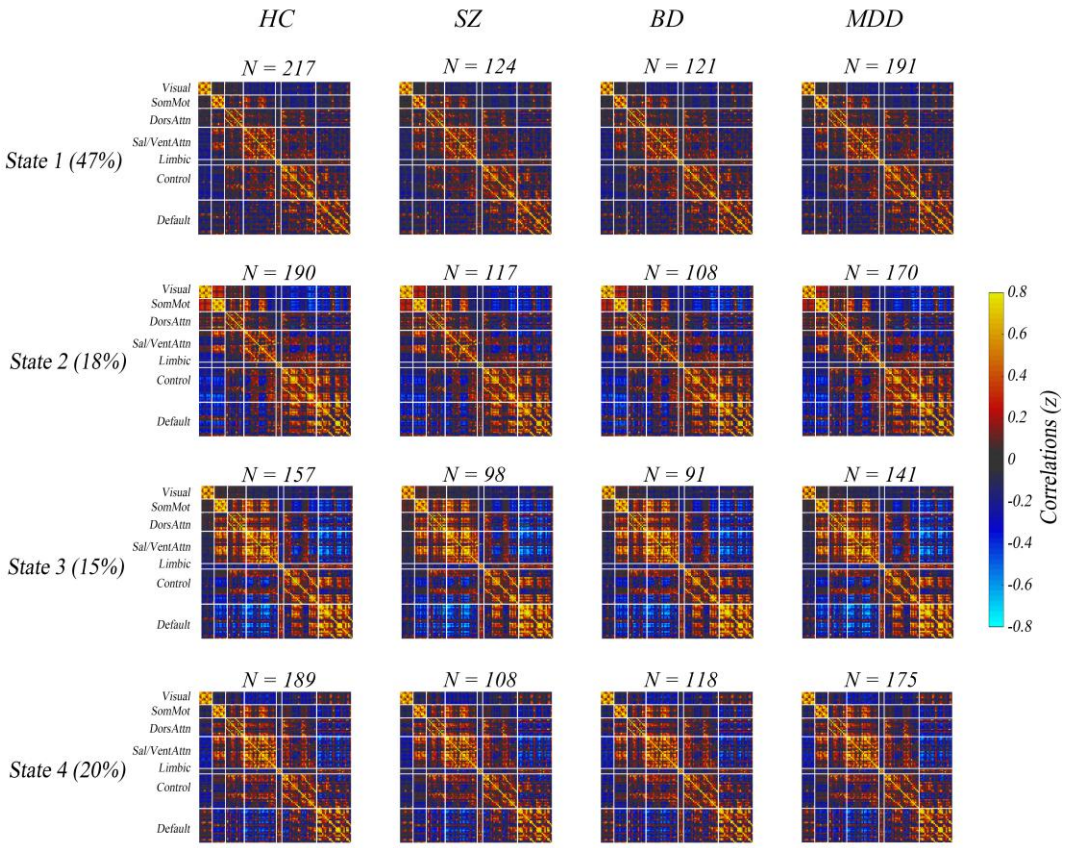

Fig. 1. The cluster medians by state for healthy controls (the first column), schizophrenia (the second column), bipolar disorder (the third column) and major depressive disorder (the forth column) along with the count of subjects that had at least one window in each state. The percentage in parentheses denotes the percentage of occurrences of each state. The color bar represents z value of dynamic functional connectivity.

HC, healthy controls; SZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; SomMot, somatomoto; DorsAttn, dorsal attention; Sal/VentAttn, salience/ventral attention; Control, frontoparietal control; Default, default mode.

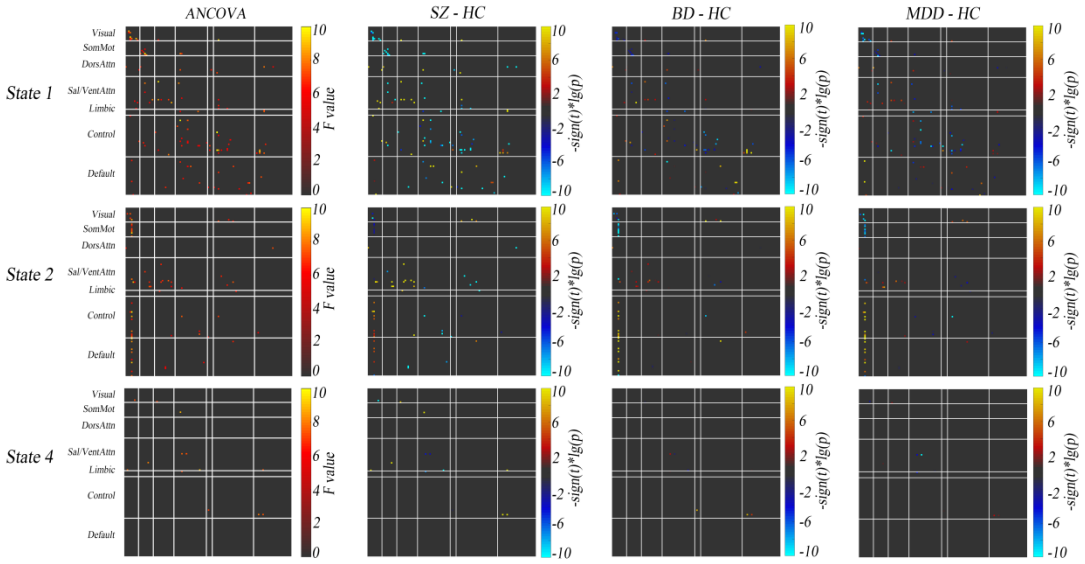

Fig. 2. Results obtained by ANCOVA (the first column) and post-hoc two-sample t-tests (from the second to the forth column) for dynamic connectivity in the four groups.

HC, healthy controls; SZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; SomMot, somatomoto; DorsAttn, dorsal attention; Sal/VentAttn, salience/ventral attention; Control, frontoparietal control; Default, default mode.

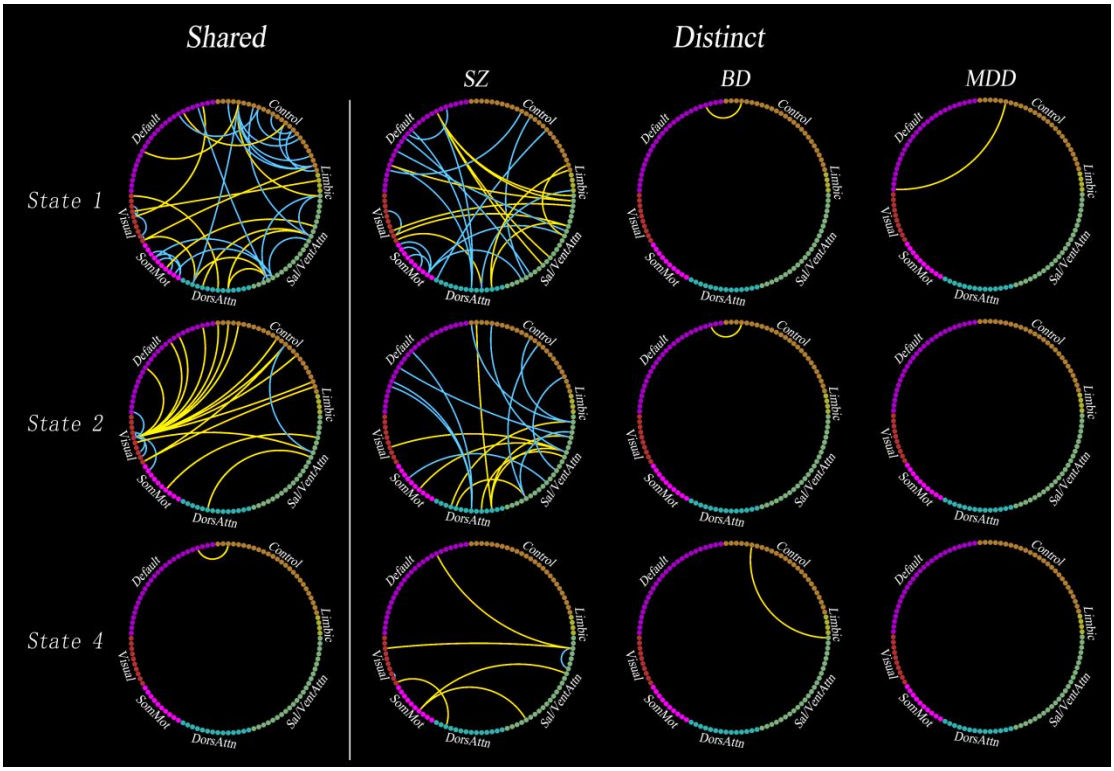

Fig. 3. Shared (the first column) and distinct (from the second to the forth column) dysconnectivity across schizophrenia, bipolar disorder, and major depressive disorder. Each dot in the circle represents a network node, and the nodes in the same network have the same color. The yellow line indicates increased dysconnectivity. The blue line indicates decreased dysconnectivity.

SZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; SomMot, somatomoto; DorsAttn, dorsal attention; Sal/VentAttn, salience/ventral attention; Control, frontoparietal control; Default, default mode.