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Transdiagnostic Dysfunctions in Brain Modules Across Patients with Schizophrenia, Bipolar Disorder, and Major Depressive Disorder: A Connectome-Based Study

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Psychiatric disorders, including schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD), share clinical and neurobiological features. Because previous investigations of functional dysconnectivity have mainly focused on single disorders, the transdiagnostic alterations in the functional connectome architecture of the brain remain poorly understood. We collected resting-state functional magnetic resonance imaging data from 512 participants, including 121 with SCZ, 100 with BD, 108 with MDD, and 183 healthy controls. Individual functional brain connectomes were constructed in a voxelwise manner, and the modular architectures were examined at different scales, including (1) global modularity, (2) module-specific segregation and intra- and intermodular connections, and (3) nodal participation coefficients. The correlation of these modular measures with clinical scores was also examined. We reliably identify common alterations in modular organization in patients compared to controls, including (1) lower global modularity; (2) lower modular segregation in the frontoparietal, subcortical, visual, and sensorimotor modules driven by more intermodular connections; and (3) higher participation coefficients in several network connectors (the dorsolateral prefrontal cortex and angular gyrus) and the thalamus. Furthermore, the alterations in the SCZ group are more widespread than those of the BD and MDD groups and involve more intermodular connections, lower modular segregation and higher connector integrity. These alterations in modular organization significantly correlate with clinical scores in patients. This study demonstrates common hyper-integrated modular architectures of functional brain networks among patients with SCZ, BD, and MDD. These findings reveal a transdiagnostic mechanism of network dysfunction across psychiatric disorders from a connectomic perspective.

Key words: graph theory/brain network/resting-state fMRI/modularity/connector

Introduction

Psychiatric disorders, such as schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD), account for 32.4% of years lived with disability and are responsible for enormous clinical and economic burdens globally.[1] Although each psychiatric disorder is associated with a distinct set of clinical symptoms, different disorders share genetic and environmental risk factors,[2,3] secondary symptoms (eg, anhedonia),[4] neuropsychological deficits,[5] and neurobiological alterations.[6–9] Thus, the traditional view that different psychiatric disorders are completely separate categories with distinct etiologies is being replaced with emerging conceptualizations based on the notion that a general psychopathological factor is shared among disorders.[10] In light of these emerging conceptualizations, it is important to understand transdiagnostic neurobiological alterations in patients with psychiatric disorders; for example, this information could be used to develop a novel model of pathology beyond traditional diagnostic boundaries and identify objective biomarkers for clinical diagnosis and treatment optimization across disorders.[11]

Recent advances combining resting-state functional magnetic resonance imaging (fMRI) techniques and connectomic analytical frameworks have enabled in vivo

studies that have helped clarify disruptions in the intrinsic functional brain networks of patients with psychiatric disorders.[10,12–17] Typically, the modular architecture of a healthy brain can be described as an optimized network organization that is composed of spatially separated functional modules with dense intramodular connections but sparse intermodular connections. This modular network organization plays a crucial role in maintaining the balance between functional specialization and integration, supporting individual cognitive and behavioral capacities.[16–19] Accumulating evidence suggests that this balance is disrupted in patients with psychiatric disorders due to dysconnectivity within and between functional modules involving both high-order and primary networks.[12,13,20–22] For instance, disrupted intra- and intermodular connections of the frontoparietal network (FPN) have been widely reported in a variety of patients with different psychiatric disorders, including SCZ,[23] BD,[24] and MDD.[22] These studies raise the possibility that the dysfunction of cognitive control that is relevant to FPN alterations represents a common substrate for patients with psychiatric disorders.[25] The default-mode network (DMN), which is implicated in emotional states and self-referential processing,[4] is another module that is frequently reported to be altered in patients with psychiatric disorders, particularly in patients with MDD,[26] where alteration of this module is thought to underlie self-focused rumination. Additionally, dysconnectivity of the primary visual and sensorimotor modules is observed in patients with numerous psychiatric disorders, with SCZ patients exhibiting a greater number of disrupted connections than patients with other disorders, such as BD and MDD.[27] Using a meta-analytical framework, we observed that many psychiatric and neurological disorders preferentially target the connectors of the functional networks (ie, the brain nodes that play critical roles in maintaining functional integrity between network modules).[9] These findings have led to the hypothesis that psychiatric disorders exhibit both transdiagnostic and diagnosis-specific disorganization patterns of the modular architecture in functional brain networks;[13,21] at present, however, this hypothesis lacks direct evidence, since the vast majority of previous studies have merely compared patients diagnosed with specific disorders against healthy controls.

Here, we collected resting-state fMRI data from 512 participants, including 121 patients with SCZ, 100 with BD, 108 with MDD, and 183 healthy controls (HCs), and systematically investigated the modular architecture of the high-resolution functional brain networks at the voxel level. We hypothesized that patients with different psychiatric disorders would exhibit transdiagnostic alterations in the modular organization, including (1) reduced global network modularity, (2) unbalanced module-specific segregation and integration with more intermodular connections, and (3) regional alterations related to network connectors. Finally, the relationship between the modular architecture and clinical symptoms was examined in the patient groups.

Methods

Participants

Five hundred fifty individuals (aged 13–45 years) were initially enrolled in this study, including 139 with SCZ, 108 with BD, 114 with MDD, and 189 HCs. All patients were recruited from the inpatient and outpatient services at Shenyang Mental Health Center and the Department of Psychiatry, First Affiliated Hospital of China Medical University, Shenyang, China. HCs were recruited from the local community through advertisements. Two professionally trained and experienced psychiatrists jointly performed the diagnoses and made the final decisions. Specifically, patients aged 18 years and older were diagnosed using the criteria from Structured Clinical Interview for Diagnostic (SCID) and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) Axis I Disorders, whereas patients under 18 years old were diagnosed using the criteria of the semistructured diagnostic interview for the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL). To ensure the accuracy of diagnosis, we conducted a follow-up interview for each patient approximately 1 year after the first diagnosis, and the final diagnosis was determined at that time. For each patient, information about illness duration, age at onset, and smoking history was collected, and clinical symptoms were assessed using a range of psychometrics, including the Brief Psychiatric Rating Scale (BPRS), the Hamilton Depression Rating Scale (HAMD), the Hamilton Anxiety Rating Scale (HAMA), and the Young Mania Rating Scale (YMRS). This study was approved by the Institutional Review Board of China Medical University, and written informed consent was provided by all participants. The dataset has previously been used to investigate the connectivity profile of functional brain networks in patients with psychiatric disorders.[7] See Supplementary Materials for detailed descriptions of the inclusion and exclusion criteria.

Image Acquisition

For each participant, resting-state fMRI data were acquired using a GE Signa HD 3.0-T scanner (General Electric, Milwaukee, USA). During the scan, participants were instructed to rest and relax with their eyes closed while remaining awake. Following scanning, each subject completed a questionnaire about his/her state during the scan. None of the subjects indicated on the questionnaire that they fell asleep during the scan. The scan lasted for 6 minutes and 40 seconds, resulting in 200 volumes. For details, see Supplementary Materials.

Data Preprocessing

All fMRI images were preprocessed using SPM12 (www.fil.ion.ucl.ac.uk/spm/) and DPARSF.[28] Preprocessing steps included the removal of the first 10 time points, slice-timing correction, head motion correction, spatial normalization to the Montreal Neurological Institute space using an echo-planar imaging template with a resampled size of 3-mm isotropic voxels, spatial smoothing with a 4-mm Gaussian kernel, linear detrending, regression of confounding covariates (Friston-24 motion parameters, white matter, cerebrospinal fluid, and global signals), and bandpass filtering (0.01–0.1 Hz). Data from 38 participants with head motion greater than 3 mm or 3° were excluded. Table 1 illustrates the clinical variables and demographics of the included samples.

Network Construction

The individual functional networks were constructed at the voxel level within a gray matter (GM) mask of 45,381 voxels (cerebral regions). By computing Pearson's correlation coefficients between all pairs of GM voxels, we obtained a 45,381 × 45,381 correlation matrix for each subject. These individual correlation matrices were further binarized with a density threshold of 1%, corresponding to 10,296,948 retained edges with the greatest positive correlation strength.

Modular Architecture

For each individual brain network, we investigated the modular architecture as described below. First, the overall modular properties of the whole-brain network were characterized by calculating the global modularity (Q), the number of modules and the number of connectors (nodes with a participation coefficient [PC] > 0.3[29]). Second, we parcellated the whole-brain functional networks into 8 modules using a predefined cortical parcellation to reduce disorder bias,[30] including the FPN, DMN, dorsolateral attention network (DAN), ventral attention network (VAN), limbic network (LIM), visual network (VIS), and sensorimotor network (SMN) as well as a subcortical module[31] (SUB, including the thalamus, putamen, hippocampus, caudate, amygdala, and pallidum). For each module i, we computed the modular segregation index (MSI_i)[32] as follows:

$$\mathrm{MSI_i} = \frac{(k_{within} - k_{between})}{k_{within}}$$

where k_{within} is the number of intramodular connections of module i, and $k_{between}$ is the total number of intermodular connections between module i and all other modules. A positive MSI value indicates greater functional segregation, while a negative value suggests greater functional

Table 1. Demographics and Clinical Characteristics of the Participants

	Healthy Control (n = 183)	Schizophrenia (n = 121)	Bipolar Disorder (n = 100)	Major Depressive Disorder (n = 108)	Statistical Test F or χ^2 (P)	Post hoc Comparison
Demographic characteristics						
Age at scanning, years	26.62 (8.00)	24.74 (9.03)	25.81 (8.31)	25.62 (8.43)	1.29 (.288)	
Gender (male/female)	73/110	54/67	48/52	35/73	6.07 (.108)	
Right-handed [a]	171 (96%)	100 (89%)	95 (97%)	93 (94%)	7.37 (.057)	
Smoking history (smoking/no smoking/no record)	29/128/26	12/76/33	21/62/17	22/67/19	-	-
Clinical characteristics						
Age at illness onset	-	22.82 (8.89)	21.72 (7.24)	23.57 (8.20)	1.15 (.318)	
Illness duration, months	-	21.87 (36.15)	41.48 (56.18)	20.58 (31.00)	7.23 (.001)	
First episode, yes [a]	-	86 (74%)	52 (57%)	85 (88%)	34.78 (<.001)	
Medication, yes [a]	-	71 (59%)	65 (65%)	43 (40%)	172.36 (<.001)	
HAMD-17	(n = 165) 1.17 (1.67)	(n = 86) 8.12 (6.96)	(n = 99) 11.77 (9.48)	(n = 107) 21.16 (8.77)	186.93 (<.001)	HC<SCZ<BD<MDD
HAMA	(n = 164) 0.77 (1.76)	(n = 69) 6.80 (7.26)	(n = 96) 8.52 (8.80)	(n = 93) 16.32 (9.49)	103.51 (<.001)	HC<SCZ=BD<MDD
YMRS	(n = 158) 0.15 (0.57)	(n = 60) 2.20 (4.50)	(n = 95) 8.07 (10.05)	(n = 89) 1.47 (2.87)	45.29 (<.001)	HC<SZ<BD, MDD<BD
BPRS	(n = 96) 18.30 (0.68)	(n = 116) 35.59 (14.32)	(n = 60) 25.83 (8.38)	(n = 46) 25.41 (6.08)	57.01 (<.001)	HC<MDD=BD<SCZ

Note: Data are presented as either n (%) or means (standard deviations).
BD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; HC, healthy control; MDD, major depressive disorder; SCZ, schizophrenia; YMRS, Young Mania Rating Scale.
[a]Information was missing for some participants.

integration. Then, we computed intermodular connections for every pair of modules and the intramodular connection number for each module to determine which modular connections were responsible for driving the module specialization. Finally, we calculated PC to identify regions with altered nodal properties associated with module integrity.[33] For regions showing significant group effects on PC, we performed a region-to-module connectivity analysis to determine the contributions of different module connections to group differences in PC. For further details, see Supplementary Materials.

Statistical Analysis

Group differences in demographic and clinical characteristics were determined using one-way ANOVA or the chi-squared test with post hoc analyses. For the modular metrics, nonparametric permutation tests were performed. Briefly, for each metric, we initially estimated the group effect by calculating the F_{real}-statistic, which reflects the ratio of between-group variance to within-group variance. Then, an empirical null distribution of the group effect was obtained by randomly reallocating all participants to 4 groups with the same sample sizes as the real categories and recomputing the group effect, $F_{surrogate}$, among the randomized groups (10,000 permutations). Thus, a *P*-value was calculated by estimating the proportion of the observed group effect F_{real} occupied in the null distribution. The post hoc analyses were implemented using the nonparametric permutation tests in a similar method for metrics with a significant group effect, as we estimated the *t*-statistic to determine between-group differences in the permutation (10,000 permutations). Age and gender were controlled in the permutation analyses. We also conducted additional analyses including smoking history as a covariate.

For the overall modular measures (global modularity, number of modules, and number of connectors) and module-specific metrics (MSI and intra- and intermodular connections), the false discovery rate (FDR) correction was performed for multiple comparisons (ie, for overall modular measures: across 3 measures; for MSI: across 8 intramodular and 28 intermodular connections), and the significance was set to a corrected $P < .05$. For PC, we first applied a height threshold of $P < .01$ for each voxel and then recorded the maximal cluster size that exceeded this threshold in each permutation test. A null distribution of cluster size was observed after 10,000 permutations. Then, the 95th percentile of the null distribution was used as the significance threshold for cluster correction, corresponding to $P < .05$. Importantly, the significance level for post hoc pairwise comparisons was set to an FDR-corrected $P < .05$ across all pairs of groups.

Finally, we performed Spearman's correlation analyses between each module-related measure and clinical variables. For each modular measure, the FDR correction was performed across clinical variables, and the significance was set to a corrected $P < .05$. Age and gender were controlled in the correlation analyses. To assess the robustness of the results, we also conducted additional correlation analyses including illness duration, medication status and first-episode status as the additional covariates along with age and gender. Notably, these correlations were performed across all patients for measures with transdiagnostic alterations and in each patient group for diagnosis-specific alterations (Supplementary Materials).

Confounding Considerations

To assess the reliability of our results, we examined the influence of demographic and clinical variables (ie, participants' age, medication status, first-episode status, psychotic symptoms, and smoking history) and analysis strategies (ie, head motion control, global signal regression, network density, module detection algorithm, and connector-defining threshold). For details, see Supplementary Materials.

Results

Demographic and Clinical Characteristics

No significant differences in age ($F_{(3,508)} = 1.258$, $P = .288$), gender ($\chi^2_{(3)} = 6.073$, $P = .108$), or handedness ($\chi^2_{(3)} = 7.370$, $P = .057$) were observed among the SCZ, BD, MDD, and HC groups, and age at onset also did not differ among the 3 patient groups (all $P > .057$). In contrast, significant differences were observed in illness duration ($F_{(3,291)} = 7.230$, $P = .001$), medication status ($\chi^2_{(3)} = 172.360$, $P < .001$), and first-episode status ($\chi^2_{(3)} = 34.780$, $P < .001$), as well as HAMD ($F_{(3,288)} = 186.930$, $P < .001$), HAMA ($F_{(3,254)} = 103.510$, $P < .001$), YMRS ($F_{(3,240)} = 45.290$, $P < .001$), and BPRS ($F_{(3,218)} = 57.010$, $P < .001$) scores, among the 3 patient groups (table 1).

Overall Modular Properties of Brain Networks in the SCZ, BD, and MDD Groups

Transdiagnostic Alterations. Significant group effects on global modularity ($F_{(3,508)} = 19.626$, $P = .0006$, FDR-corrected) and the number of connectors ($F_{(3,508)} = 5.052$, $P = .005$, FDR-corrected) were found among the 4 groups (figure 1 and Supplementary table S1). The post hoc analyses revealed significantly lower modularity (all $P < .001$, FDR-corrected) in all 3 patient groups than in the HC group. Additionally, we observed a trend toward a greater number of connectors in the brain networks of the 3 patient groups relative to the HC group (for SCZ and BD, both $P < .002$, FDR-corrected; for MDD, $P = .084$, FDR-corrected). The results derived using the Newman algorithm were identical to these findings (Supplementary table S1).

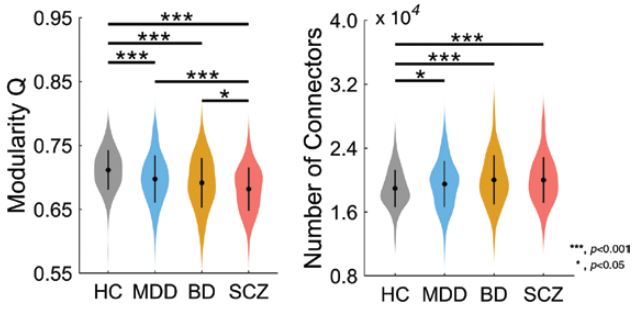

Fig. 1. Differences in measurements of global modular architectures among the 4 groups. Violin plots depict the distributions of measurements in each group, with the dots and lines representing means and standard deviations, respectively. All plots were generated controlling for age and gender. The significance level was set to $P < .05$ with FDR correction. ***$P < .001$ and *$P < .05$. A trend toward significance was observed in the number of connectors (PC > 0.3) between patients with MDD and HCs. BD, bipolar disorder; HC, healthy control; MDD, major depressive disorder; SCZ, schizophrenia.

Diagnosis-Specific Alterations. The SCZ group showed significantly lower modularity than the BD ($P = .026$, FDR-corrected) and MDD groups ($P = .002$, FDR-corrected).

Module Segregation of Brain Networks in the SCZ, BD, and MDD Groups

Transdiagnostic Alterations. Significant group effects on the MSI were observed in the FPN ($F_{(3,508)} = 9.464$, $P = .0002$, FDR-corrected), SUB ($F_{(3,508)} = 7.039$, $P = .0003$, FDR-corrected), VIS ($F_{(3,508)} = 6.785$, $P = .0006$, FDR-corrected), SMN ($F_{(3,508)} = 11.318$, $P = .0003$, FDR-corrected), and LIM ($F_{(3,508)} = 4.159$, $P = .008$, FDR-corrected) (figure 2B and Supplementary table S1). The post hoc analysis revealed a common decrease in MSI values in the FPN, SUB, VIS, and SMN in all 3 patient groups (all $P < .045$, FDR-corrected). Further analyses revealed that these alterations were mainly driven by increased numbers of intermodular connections, including FPN-VAN ($F_{(3,508)} = 4.282$, $P = .019$, FDR-corrected), FPN-SUB ($F_{(3,508)} = 5.877$, $P = .008$, FDR-corrected), SUB-DAN ($F_{(3,508)} = 8.832$, $P = .001$, FDR-corrected), SUB-VIS ($F_{(3,508)} = 4.637$, $P = .012$, FDR-corrected), VIS-DMN ($F_{(3,508)} = 3.549$, $P = .033$, FDR-corrected), VIS-LIM ($F_{(3,508)} = 5.646$, $P = .005$, FDR-corrected), and DAN-LIM ($F_{(3,508)} = 7.972$, $P = .002$, FDR-corrected) (figures 2C and 2D, Supplementary table S1).

Diagnosis-Specific Alterations. The SCZ group exhibited a significantly lower MSI in the FPN, SUB, LIM, and SMN than the MDD group (all $P < .040$, FDR-corrected) and in the LIM and SMN than the BD group (both $P < .025$, FDR-corrected) (figure 2B). Additionally, the SCZ group exhibited a greater number of FPN-DMN, DAN-SUB, DAN-LIM, and VAN-DMN intermodular connections and fewer intramodular connections in the SMN than the MDD group (all $P < .036$, FDR-corrected), and a greater number of intermodular connections between the VAN and DMN and fewer connections within the SMN than the BD group (both $P < .028$, FDR-corrected) (figure 2D). See Supplementary Materials for a comparison between each patient group and HCs.

Roles of Nodes in the Modular Brain Networks in the SCZ, BD, and MDD Groups

Transdiagnostic Alterations. The average PC maps in the brain networks for each group are illustrated in figure 3A. A significant group effect on PC was observed in the bilateral dorsal medial prefrontal cortex (dmPFC) ($F_{(3,508)} = 6.894$, $P = .022$, FDR-corrected), bilateral dorsal lateral prefrontal frontal cortex (dlPFC) ($F_{(3,508)} = 10.360$, $P = .009$, FDR-corrected), right angular gyrus (ANG) ($F_{(3,508)} = 10.455$, $P = .036$, FDR-corrected), and left thalamus (THA) ($F_{(3,508)} = 9.802$, $P = .011$, FDR-corrected) (10,000 permutations) (figure 3B and Supplementary table S1). The 3 patient groups exhibited common alterations in the right dlPFC, right ANG, and left THA (all $P < .016$, FDR-corrected), as indicated by significantly higher PC values for all 3 patient groups than for the HC group (figure 3C). Notably, the right dlPFC and right ANG were identified as the network connectors (with PC > 0.3) in each patient group (figure 3A). These alterations in network nodes were mainly attributed to the greater number of connections involving right dlPFC-SUB ($F_{(3,508)} = 5.471$, $P = .049$, FDR-corrected), left THA-SMN ($F_{(3,508)} = 4.655$, $P = .010$, FDR-corrected), and left THA-DAN ($F_{(3,508)} = 5.292$, $P = .009$, FDR-corrected) (figure 3D). Additionally, we observed a trend toward common alterations in PC in the left dlPFC (for SCZ and MDD, both $P < .018$, FDR-corrected; for BD, $P = .058$, FDR-corrected).

Diagnosis-Specific Alterations. Patients with SCZ exhibited significantly higher PC values in the left dlPFC and left THA than patients with MDD (all $P < .016$, FDR-corrected) (figure 3B) and significantly higher PC in the left dlPFC than patients with BD ($P = .003$, FDR-corrected). The BD group showed significantly higher PC values in the bilateral dmPFC than the MDD group ($P = .028$, FDR-corrected) (figure 3B). Additionally, the SCZ group exhibited a trend toward higher PC values in the right dlPFC ($P = .057$, FDR-corrected) and left thalamus than the BD group ($P = .056$, FDR-corrected). The MDD group showed a trend toward higher PC values in the right ANG than the BD group ($P = .075$, FDR-corrected). See Supplementary Materials for a detailed summary of the differences in PC values between each patient group and HCs and relevant region-to-module connectivity.

Relationship Between Brain Module Measures and Clinical Variables

For transdiagnostic alterations, we observed significant positive correlations between the MSI in the FPN and

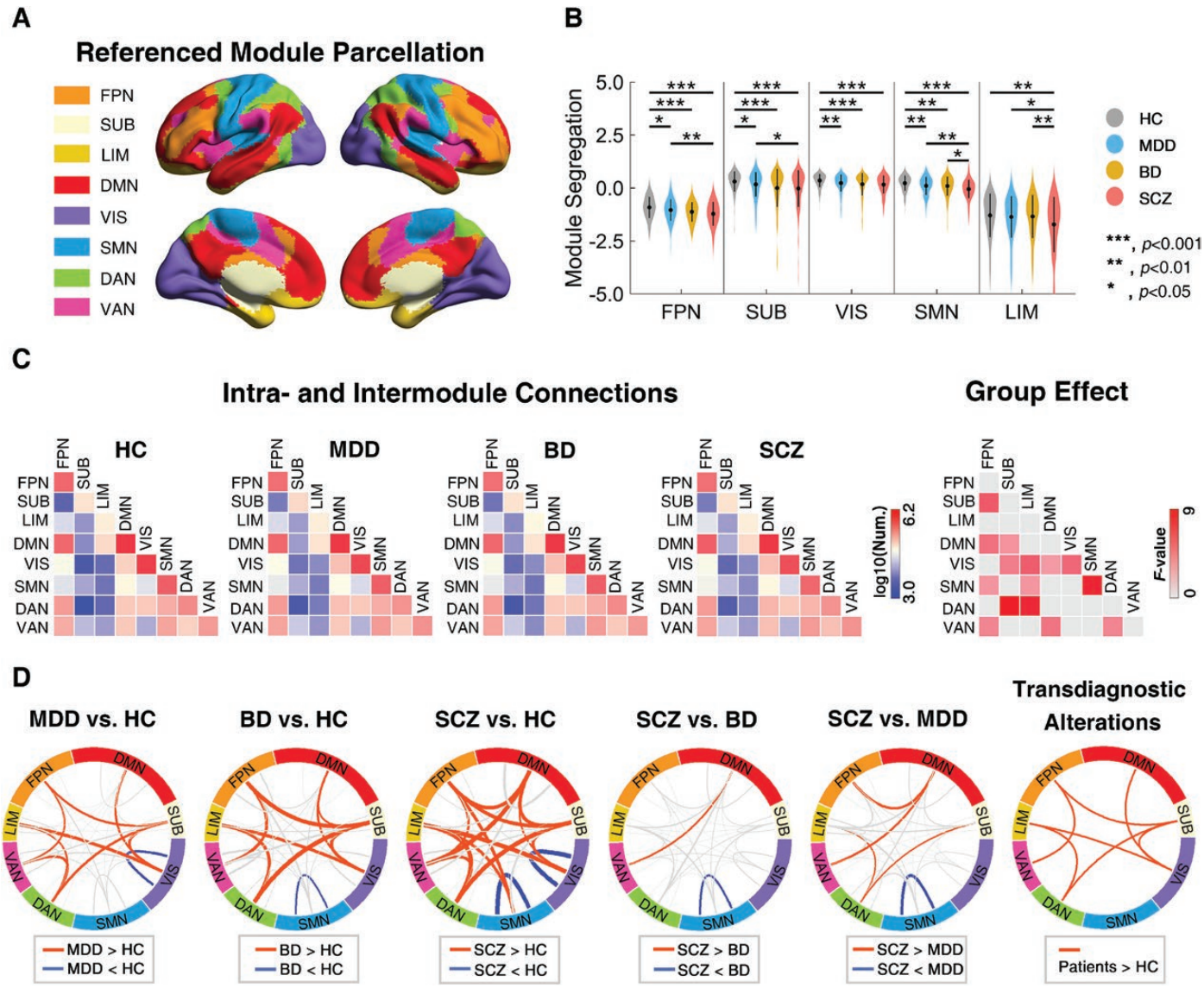

Fig. 2. Differences in module segregation index and intra- and intermodular connections among the 4 groups. (A) The referenced 8-module parcellation was generated by combining the 7-module parcellation reported by Yeo et al.[30] and the subcortical regions extracted from the Automated Anatomical Labeling atlas.[31] (B) Between-group differences in module segregation. The violin plots depict the distributions of module segregation values in each group, with the dots and lines representing the means and standard deviations, respectively. (C) The matrices on the left present intra- and intermodular connections for each of the 4 groups, and the color bar indicates the number of connections. The matrix on the right illustrates the group effects among the 4 groups. (D) Between-group differences in intra- and intermodular connections for each pair of groups. Red and blue lines indicate significantly more connections and fewer connections, respectively. All of the significance levels were set to $P < .05$ with the FDR correction. ***$P < .001$; **$P < .01$; and *$P < .05$. BD, bipolar disorder; DAN, dorsal attention network; DMN, default-mode network; FPN, frontoparietal network; HC, healthy control; LIM, limbic network; MDD, major depressive disorder; SCZ, schizophrenia; SMN, sensorimotor network; SUB, subcortical; VAN, ventral attention network; VIS, visual network.

the HAMD ($R_{(290)}$ = 0.134, P = .035, FDR-corrected) and HAMA ($R_{(256)}$ = 0.167, P = .020, FDR-corrected) scores, between the VIS-DMN connections and illness duration ($R_{(293)}$ = 0.151, P = .029, FDR-corrected), and between the PC values in the left dlPFC and BPRS scores ($R_{(220)}$ = 0.165, P = .008, FDR-corrected) (figure 4 and Supplementary table S7). Moreover, inclusion of illness duration, medication status, and episode status did not affect most of our main results (Supplementary Materials: Results). We also calculated the correlations between diagnosis-specific alterations and clinical variables in each patient group.

Confounding Effects

Under each confounding factor, the results were largely consistent with our main findings (Supplementary Materials: Confounding Considerations).

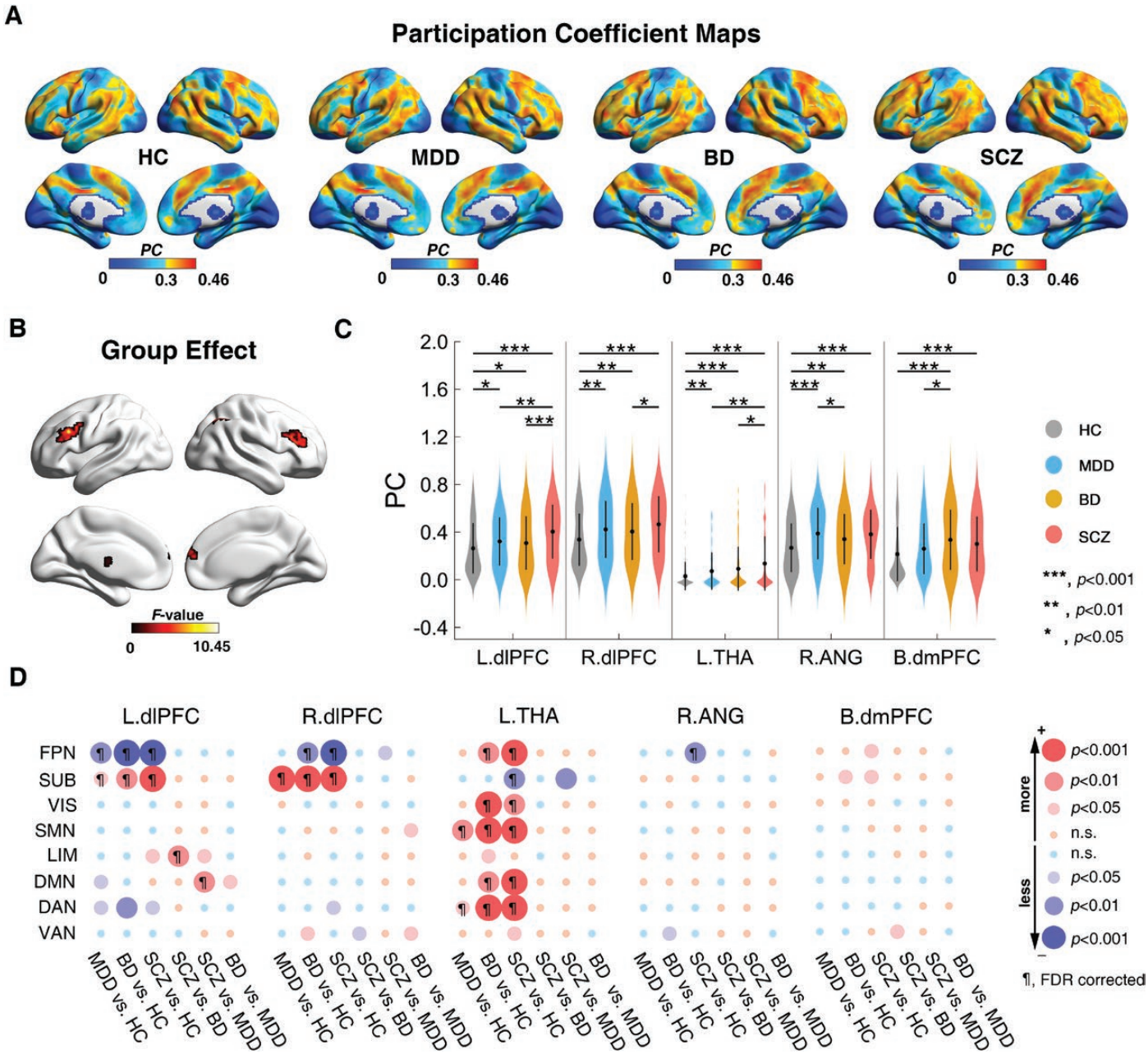

Fig. 3. PCs and connections across psychiatric disorders. (A) Mean PC map for each group. (B) Regions showing significant group effects on PC ($P < .05$, 10,000 permutations). (C) Pairwise comparisons in regions with significant group effects on PCs. Trends toward significance were observed in the L.dlPFC between patients with MDD and HCs in the R.dlPFC and L. THA between patients with SCZ and BD and in the R. ANG between patients with BD and MDD. (D) Between-group differences in region-to-module connections between each pair of groups. The size of the solid circle represents the significance level. Warmer and cooler colors represent more and fewer connections, respectively. The significance levels for the data shown in C and D were set to $P < .05$ with the FDR correction. ***$P < .001$; **$P < .01$; and *$P < .05$. ANG, angular gyrus; B, bilateral; BD, bipolar disorder; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; HC, healthy control; L, left; MDD, major depressive disorder; SCZ, schizophrenia; R, right; THA, thalamus. The surface visualization was generated using BrainNet Viewer (http://www.nitrc.org/projects/bnv).[93]

Discussion

Using a high-resolution connectomic analysis framework, we identified transdiagnostic and diagnosis-specific alterations in modular brain networks among patients with SCZ, BD, and MDD. Specifically, the primary transdiagnostic alterations include lower global modularity; lower modular specialization in the FPN, SUB, VIS, and SMN driven by a great number of intermodular connections; and hyper-integrated network nodes in the dlPFC, ANG, and THA. In contrast, diagnosis-specific findings were particularly evident in SCZ, as indicated by

broader alterations in modular architectures in SCZ than in BD or MDD. Together, these findings provide crucial insights into the transdiagnostic and diagnosis-specific pathophysiological mechanisms of psychiatric disorders from a modular perspective.

Greater Transdiagnostic Integration Among Higher-Order and Primary Modules

Modular architecture is an optimized network organization that combines specialization and integration to enable a balance between energy cost and communication efficiency.[17] Intriguingly, we found that altered modular architectures in psychiatric disorders were mostly due to excess intermodular connections involving both higher-order and primary modules, suggesting a de-differentiation of network organization. Previously, we demonstrated that the clustering coefficient of the brain networks was smaller in patients than in controls,[7] implying randomized brain networks as a common feature of psychiatric disorders. Such alterations were mainly driven by reduced short-range connectivity in primary cortices and increased medium-/long-range connectivity in frontoparietal regions. On the one hand, the findings of the current study were partially consistent with this former finding, as indicated by the significant positive correlations of modularity Q values with both the clustering coefficient and the shortest path length of the whole-brain network (Supplementary Materials). On the other hand, we considered the modular architecture of the brain network and found transdiagnostic alterations in patients compared to controls, including lower global modularity, lower modular segregations driven by more intermodular connections, and higher PCs in several network connectors. Both the modular analysis methods and the findings of the current study are new and original compared to the previous study. In addition, the effect of onset age on the alterations in both brain structure[34] and function[35] in psychiatric disorders should be noted. Specifically, a recent study found a significantly lower nodal efficiency in SCZ patients aged 12–14 years, but not in those aged 15–18 years, compared to HCs.[36] This result is opposite to the current finding of decreased global modularity and increased nodal participant coefficient in patients with SCZ. Notably, the SCZ patients in our study were 13–45 years old, and only 7 out of 121 patients were under 14 years old. Thus, the inconsistency between studies may reflect the differential effects of age on psychopathology: SCZ patients aged under and over 14 might show opposite network configurations in comparison to HCs. Additionally, we performed a separate set of analyses in adult participants only, and the results were highly similar to the main results (Supplementary Materials). Taken together, these findings suggest that the disruptions of global network topology include a consistent partial contribution from alterations of specific module-level integration and specialization, providing new insight into the contribution of specific modular alterations to global network dysfunctions.

The higher-order modules support a wide range of cognitive functions, as the FPN, DAN, and VAN are typically involved in processing external stimuli, whereas the DMN is closely related to the self and to stimulus-independent memory recall.[37] A number of studies have reported altered neuroanatomy, metabolism, and regional activation as well as dysconnectivity within and among these higher-order modules in psychiatric disorders.[10,14,38,39] According to our recent meta-analysis, hyper- and hypoconnectivity between the FPN, DMN and salience network (which overlaps with the VAN) are shared features of different psychiatric disorders, and these altered connections are associated with general cognitive performance in healthy subjects.[9] In contrast to this meta-analysis, we found altered connections including other modules such as DAN, LIM, SUB, and VIS (see figure 2D). Such incongruence may be attributed to many possible causes. First, we focused on 3 major psychiatric disorders, while a larger range of categories were involved in the meta-analysis, suggesting that the more inclusive list of disorders in the meta-analysis may drive the inconsistency. Second, the voxelwise method we used for calculating the functional connection targeted the whole brain, while the seed-based connections omitted synchronization with the nonseed regions. Third, the meta-analytic study was hypothesis driven and focused only on the DMN, FPN, and salience network, while our study was data driven and encompassed the connections among all functional modules of the brain. Thus, this study was responsive to alterations outside the modules that appeared in the meta-analysis. Notably, a triple-network psychopathological model highlights the interactions among these higher-order modules; specifically, the attention network plays a crucial role in re-orienting attention to unexpected events and in regulating the interactions between the FPN and DMN.[9,40] Additionally, 2 studies[9,41] revealed that a broad range of psychiatric disorders showed a common loss of GM volume in the anterior cingulate and bilateral anterior insula. These brain regions are the key regions of the VAN that engage in salience processing.[30] Although we did not find significant functional alterations in these specific regions in the current study, we revealed significantly altered connections between the VAN and FPN. The discrepencies in results at the regional level might be due to differences in imaging modalities, analysis strategies, and disorder categories. Further research combining multimodal imaging data could better illustrate the structural basis underlying functional alterations in psychiatric disorders.

Transdiagnostic modular alterations were also observed in the primary modules, as indicated by the greater number of intermodular connections of the VIS. Consistent with this finding, hyperconnectivity between

the visual association cortex and both the FPN and the DMN was recently found to be associated with the general psychiatric symptoms score (p factor) in healthy subjects and patients with psychiatric disorders.[42] Visual sensory information is a dominant modality in guiding the receipt and processing of stimuli from the external world in humans. The connections between visual and heteromodal association cortices (eg, the FPN the and DMN) are critical for selecting task-relevant information and accomplishing goal-oriented tasks.[43] Thus, alterations in intermodular connections of the VIS can result in inappropriate integration between bottom-up sensory input and top-down regulation in patients with psychiatric disorders. Furthermore, previous studies showed that the connections between visual and frontal cortices can also discriminate patients with depression[44] or schizophrenia[45] from HCs. These findings together suggest that VIS-related connections are a potential biomarker for the diagnosis and prediction of psychiatric disorders, although further evidence for such an implication is needed.

Transdiagnostic modular alterations might arise from the common underlying genetic basis of psychiatric disorders. Genome-wide association studies have identified genetic correlations among SCZ, BD, and MDD.[2,3,46] For example, CACNA1C, the gene encoding the L-type voltage-gated calcium channel subunits, is considered a common susceptibility gene for these disorders.[46] Moreover, recent transcriptome-connectome association studies have revealed a tight nexus between gene expression and the architectures of structural and functional brain networks.[47,48] For instance, overrepresentation of genes related to NMDA potentiation, PKA/immune response signaling, synaptogenesis, and axon guidance are significantly correlated with altered DMN connectivity in both SCZ and BD.[49] This evidence implies common genetic risks and molecular mechanisms for the transdiagnostic alterations in brain network architectures in patients with psychiatric disorders.

Higher Transdiagnostic Nodal Integration of Modular Brain Networks

Several network nodes, including bilateral dlPFC, left THA, and right ANG, exhibited higher modular integration in patients with psychiatric disorders. The dlPFC is a critical network connector with extensive connections to several network modules that regulates attention, planning, and working memory.[50,51] Numerous molecular, cellular, neuropsychological, and neuroimaging studies have convergently indicated that deficits in the dlPFC are a prominent feature of a variety of psychiatric disorders.[52–54] Specifically, we observed a greater number of transdiagnostic connections between the dlPFC and the SUB, consistent with the typical prefrontal-subcortical psychopathological pathway.[55] For instance, the dlPFC-hippocampus and dlPFC-striatum connections are 2 vulnerable circuits in psychiatric disorders and are related to the regulation of emotional-motivational states and reward-related stimuli, respectively.[56] All of these findings highlight the transdiagnostic role of dlPFC alteration. This role was particularly reflected in the dlPFC-subcortical pathophysiological pathway, which might

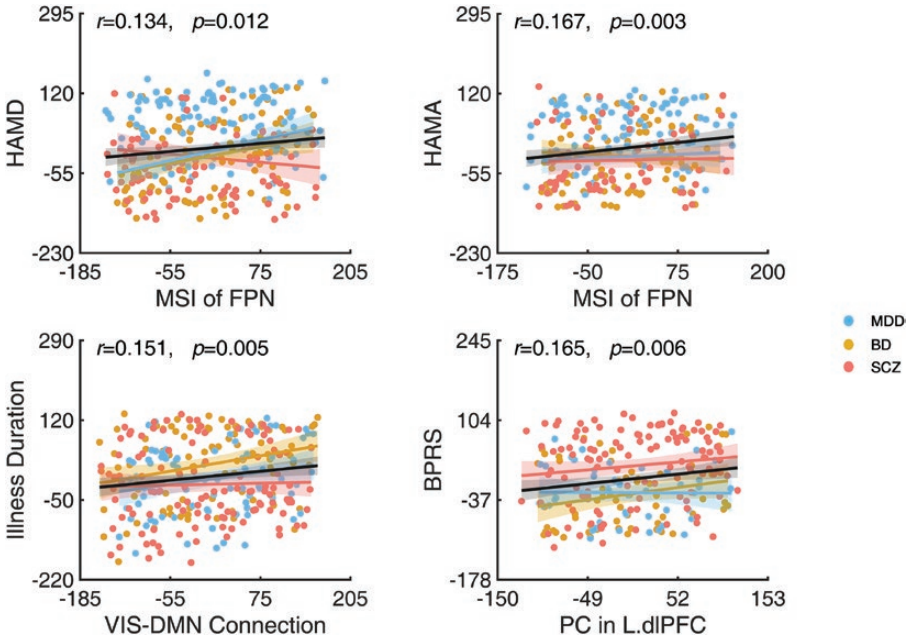

Fig. 4. Correlations between clinical variables and modular architectures in patient groups. Data were fitted by regressing age and gender before Spearman's correlation analysis was performed. B, bilateral; BPRS, Brief Psychiatric Rating Scale; dlPFC, dorsolateral prefrontal cortex; DMN, default-mode network; FPN, frontoparietal network; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression scale; L, left; MSI, module segregation index; PC, participation coefficient; R, right; VIS, visual network.

induce cognitive dysregulation of various affective and reward cues in psychiatric populations. Notably, dlPFC has been increasingly recognized as an effective treatment target for psychiatric disorders, as its activity and connections are regulated by brain stimulation,[57–59] antidepressant treatment,[60] and cognitive enhancement therapy.[61] However, the underlying mechanisms are poorly understood. Our research highlighted the critical roles of several key connector regions, such as the dlPFC, for the integration of multiple functional modules, providing a new perspective both for understanding the mechanisms of current therapies and for identifying potential treatment targets for psychiatric disorders.

The THA is important for bidirectional information transfer between cortical and subcortical areas.[62] We observed a great number of intermodular connections between the THA and both SMN and DAN in patient groups, consistent with previous region-to-region connectivity studies in MDD[63] and SCZ.[64] A recent study also revealed a common THA-SMN dysconnectivity pattern in patients with SCZ, BD, and MDD.[65] Deficits in the thalamic connections can induce impairments in relaying and modulating sensory and motor signals to the cerebral cortex.[66] Altered THA-SMN connection is linked to severe catatonia and dyskinesia in patients with SCZ[67] and depressive symptoms in patients with MDD.[63] Deep brain stimulation of the THA has proven to be effective in reducing core depressive symptoms in patients with MDD.[63] Furthermore, the THA of the SCZ and BD groups displayed a wider distribution of altered connections to almost all modules, which might provide an explanation for the SCZ-like symptoms at the time of acute exacerbation in patients with BD,[68] but rarely in patients with MDD.

The ANG is a heteromodal association region that is involved in high-order cognitive processing.[69] In SCZ, alterations in this region have been observed in different modalities; these alterations included reduced GM volume,[70] higher dopamine (D1) receptor density,[71] and reduced activation during a phonological task.[72] In BD and MDD, alterations in the functional connectivity or network centralities in the ANG have also been reported.[73,74] Our results provide further evidence of the common dysfunction of the ANG across SCZ, BD, and MDD, which implies a neural basis of cognitive disturbances in patients with psychiatric disorders.

Diagnosis-Specific Alterations in Modular Architectures

The SCZ group exhibited significantly lower MSI in the SMN and LIM, a greater number of VAN-DMN interconnections, and higher integration of the left dlPFC and THA than the BD and MDD groups. These widespread, SCZ-specific alterations in modular configuration support the observation that patients with SCZ present the most severe deficits in clinical performance.[23] These findings are consistent with a recent meta-analysis showing that SCZ exhibit diagnosis-specific hyper-/hypoconnectivity in the limbic, frontoparietal, default-mode, and thalamus regions.[75] In the current study, we revealed that SCZ showed lower intra-SMN connectivity than BD or MDD, which is consistent with the previous finding that SCZ presented the greatest decrease in the local functional connectivity of the sensorimotor cortices among the 3 disorders.[7,76] Motor abnormalities are historically recognized as the most apparent premorbid symptoms of SCZ, particularly for childhood-onset schizophrenia,[77–79] and deficits in motor coordination in childhood can serve as biomarkers to predict the onset of schizophrenia in adulthood.[80] Findings from neuroimaging studies also suggest that functional and structural alterations in SMN are generalized across different SCZ groups (eg,, different onset ages)[81,82] and even in populations with ultrahigh SCZ risk.[83] Although alterations in SMN have also been reported in BD and MDD, the research conclusion was not as consistent as in SCZ. For instance, MDD has been shown to reduce the surface area of the SMN only in adolescents and not in adults.[34] Thus, although all psychiatric disorders showed similar alterations in the SMN, the underlying mechanisms might be different from those of diagnosis-specific disease progression. Collectively, these findings suggest that the connection profiles of functional brain networks are more strongly, or at least differently, altered in patients with SCZ, which might allow clinicians to distinguish these disorders at a large-scale neurobiological level.

Relationship Between Brain Module Measures and Clinical Variables

Regarding the transdiagnostic alterations, we found positive correlations between the VIS-DMN connections and the duration of illness and between the PC of the left dlPFC and the BPRS score across all patients. The distant geodesic connections between the visual cortex and the DMN facilitate the expression of stimulus-independent aspects of cognition, a process that is necessary for mind wandering.[84] Thus, the enhanced connectivity between these parts might imply that the DMN exerts disproportionate influence over ongoing visual perception as the disease progresses, resulting in psychotic-like phenomena, such as hallucinations or misperceptions, which are likely to incorporate autobiographical information.[85] This implication is consistent with a previous finding that psychotic-like experiences are associated with a range of common psychiatric disorders.[86] The dlPFC has been subjected to intense scrutiny in a variety of psychiatric disorders.[87] Altered connections of the dlPFC with widespread brain regions may account for the disturbances in decision making, working memory and emotion regulation that are associated with a wide range of psychiatric disorders.[10] Moreover, we found that the MSI of the FPN

showed positive correlations with HAMD and HAMA scores, suggesting excessive intermodular connection and reduced intramodular connection accompanying depressive and anxious symptoms in patients with psychiatric disorders. These correlations might reflect compensatory reactions by neural systems required for executive control of emotional processing in response to brain changes associated with psychiatric disorders. However, these transdiagnostic correlations were not significant in all of the within-group analyses. This inconsistency may largely arise from the following 3 sources. First, a simple but clear univariate correlation analysis was used in the current study. However, the relationship between brain module measures and clinical behavior might not follow a strict one-to-one correspondence. Multivariate methods (eg, canonical correlation analysis) might further explore the complex relationships among these variables. Second, the number of samples in each group is much less than the sample size of the pooled data, which could reduce the statistical power of the correlation analysis. Third, our clinical variables were mostly limited in typical symptoms of the disorders; however, the alterations in functional brain networks might also be responsible for declines in a wider range of cognitive performance and emotion processing of the patients. Thus, future studies should attempt to collect additional cognitive and emotional data to illustrate these transdiagnostic alterations in psychiatric disorders.

For the diagnostic part, only the SCZ group showed a significantly negative correlation between the left dlPFC-LIM connection and illness duration, indicating its potential to capture the progress of SCZ. Functional abnormalities of the frontolimbic circuitry in SCZ have frequently been demonstrated, suggesting an apparent failure to engage cortical and limbic regions during downregulation of emotion processing.[88] Moreover, given that the anatomical basis underlying dlPFC-limbic functional circuitry is also disrupted even in the early stages of schizophrenia,[89] it is not difficult to understand the changes in functional connectivity with disease progression.

Limitations and Future Work

First, a large proportion of our patients had received medication, which is known to be able to cause alterations in brain function and structure.[90,91] Although we found that medication status did not appear to have a major effect on our main findings, we cannot rule out a more subtle effect of medication use. Second, a previous study has shown that smoking may preserve dynamic functional connectivity from the substantia nigra (SN) to the DMN and enhance dynamical connectivity from the DMN to the FPN in patients with SCZ.[92] In the current study, after we added smoking history as an additional covariate, most of the transdiagnostic alterations remained significant except for the increased number of connections between the FPN and SN, indicating the potential effect of smoking on intermodular connections across psychiatric disorders. Future works with detailed smoking information (eg, years of smoking and daily amount) might better characterize the relationship between network disruptions and smoking in psychiatric disorders. Third, although none of the subjects' postscan questionnaires indicated that they fell asleep in the scanner, we still cannot rule out that these subjective reports may have had errors. Further studies taking advantage of physiological signals (eg, EEG) recorded simultaneously with fMRI will be helpful in resolving this issue. Fourth, our study included only patients with 3 major psychiatric disorders. We encourage future studies with a greater number of diagnostic groups covering a broader spectrum of psychiatric disorders to expand our understanding of the transdiagnostic and diagnosis-specific pathophysiological mechanisms. Finally, the value of these transdiagnostic and diagnosis-specific alterations in modular brain networks for developing effective psychiatric treatment strategies remains to be further elucidated. Further longitudinal studies are required to assess the utility of these alterations for predicting the occurrence of disorders at the prodromal stage and monitoring therapeutic progress.

Conclusion

Our study provides comprehensive evidence of transdiagnostic alterations in modular architecture across psychiatric disorders, as indicated by excess intermodular integration involving both higher-order and primary modules and increased integration in connector regions. Moreover, patients with SCZ showed a diagnosis-specific increase in the range of alterations in modular architectures. Together, these findings provide crucial insights into the transdiagnostic and diagnosis-specific pathophysiological mechanisms of psychiatric disorders from a modular perspective.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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