

Supplementary Materials for

Transdiagnostic time-varying dysconnectivity across major psychiatric disorders

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Methods

Inclusion and exclusion criteria

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 participants 18 years and older, whereas the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) was used for participants younger than 18 years. All patients with SZ, BD, or MDD were required to meet the DSM-IV diagnostic criteria for their respective disorders and to have no other Axis I disorders. The HCs did not have a current or lifetime history of any 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. Potential participants were excluded if they had (1) a lifetime history of substance/alcohol abuse or dependence, (2) 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, or (5) any abnormality identified by T1- or T2-weighted imaging. Symptoms and cognitive measures were assessed using the Brief Psychiatric Rating Scale (BPRS), the Hamilton Depression Rating Scale (HAMD), the Hamilton Anxiety Rating Scale (HAMA), the Young Mania Rating Scale (YMRS), and the Wisconsin Card Sorting Test (WCST).

Examination of the medication effect on the dynamic functional connectivity

We examined the effect of patient medication on dynamic connectivity in each state by comparing connectivity between medicated patients and un-medicated patients using two-sample t-test, with group, age, sex and the mean FD as covariates. We used the false-discovery rate (FDR) to correct for multiple comparisons ($q < 0.05$).

Static connectivity analysis

The average BOLD time series of 114 nodes within the 17-network functional atlas of Yeo et al. were extracted for each individual by averaging the whole time series throughout all voxels in each node. Static FC between each pair of nodes was calculated using Pearson's correlation analysis, producing $(114 \times 113) / 2 = 6,441$ unique FCs for each subject. Fisher r-to-z transformation was performed for all FCs to improve the normality of the correlation coefficients.

Group effects were examined using one-way analysis of covariance (ANCOVA), with age, sex and the mean FD as covariates. Two-sample t-tests were performed on significant group effects identified by ANCOVA, which were compared in a pair-wise fashion with the HC group as the common comparison group. We used the false-discovery rate (FDR) to perform multiple-comparison correction for both the ANCOVA and post hoc analyses ($q < 0.05$).

Permutation test for the number of dysconnectivity patterns

To formally test whether significant edges tended to fall within specific networks than would be expected by chance, we performed a permutation test for the number of dysconnectivity patterns in each brain network. We generated 5,000 random networks with the same number of nodes, the same number of edges and the same degree distribution as the real binary network (transdiagnostic dysconnectivity). The P value of the permutation test for each sub-network was defined as: $P = N_{\text{rand}} / N$, where N_{rand} represents the number of dysconnectivity patterns in random networks that exceeded the real number of dysconnectivity. The code is as follows:

Results

Medication effect on the dynamic functional connectivity

We found that the patient medication had no significant effect on dynamic functional connectivity in each state in this study (Figure S1).

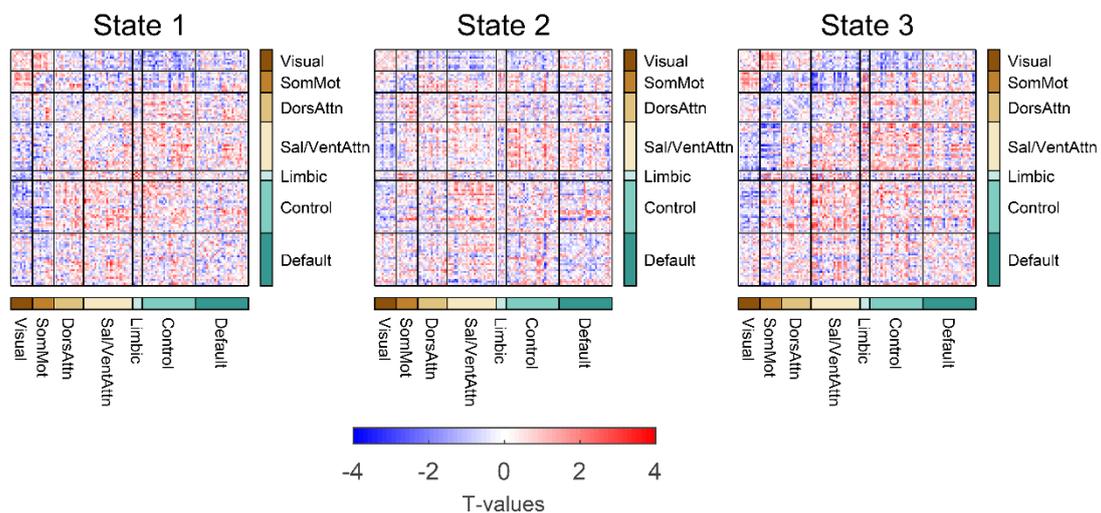


Figure S1. Medication effect on the dynamic functional connectivity. No connectivity survived the FDR correction ($q < 0.05$). SomMot = somatomotor; DorsAttn = dorsal attention; Sal/VentAttn = salience/ventral attention; Control = frontoparietal control; Default = default mode.

Effect size for two-sample t-test among four groups

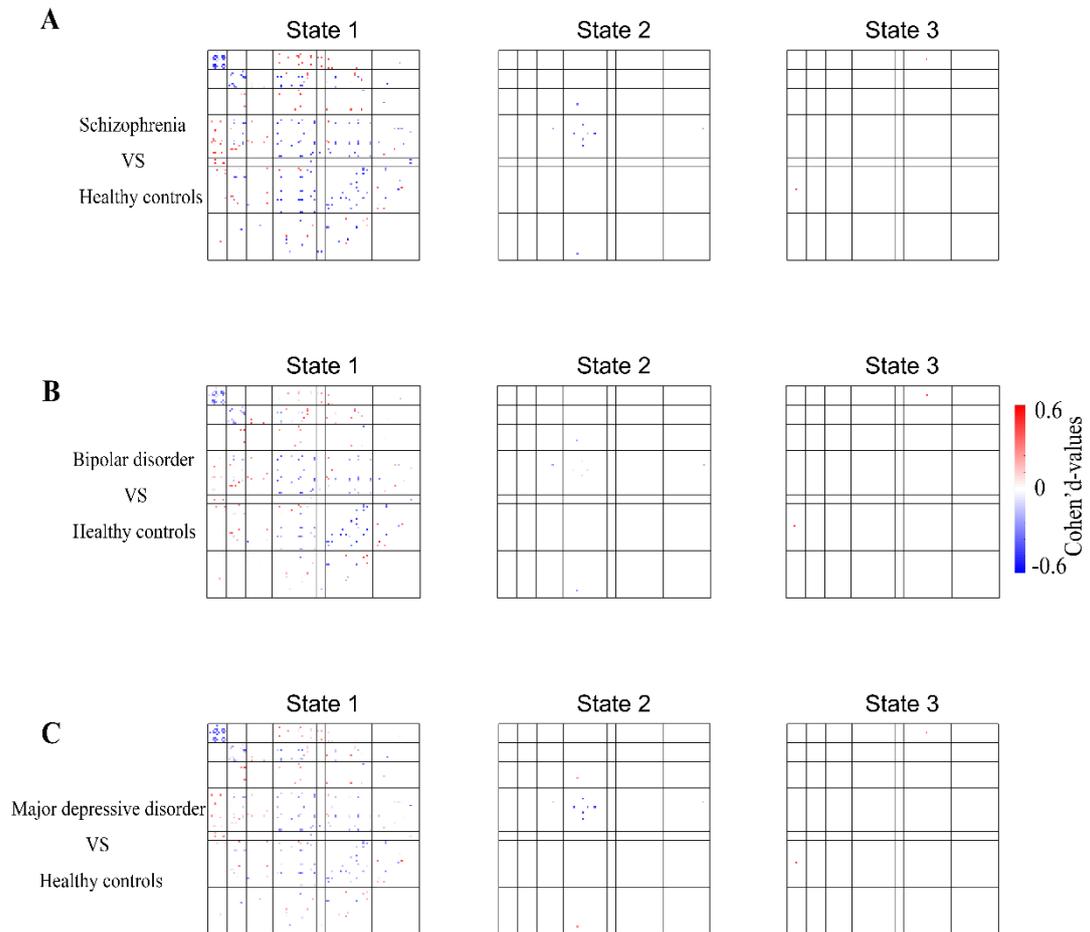


Figure S2. Effect size for two-sample t-test between patients and healthy controls.

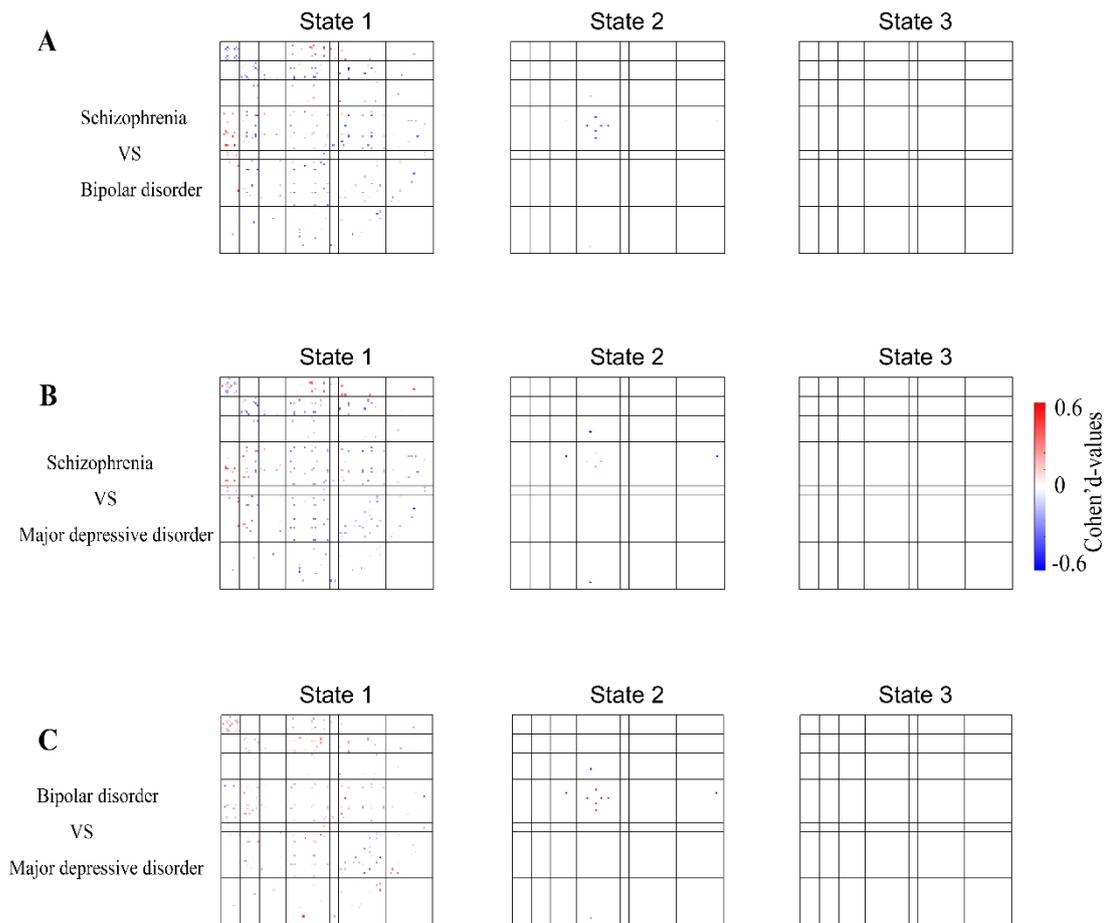


Figure S3. Effect size for two-sample t-test among patients.

Results of 20 TR window size for 610 participants

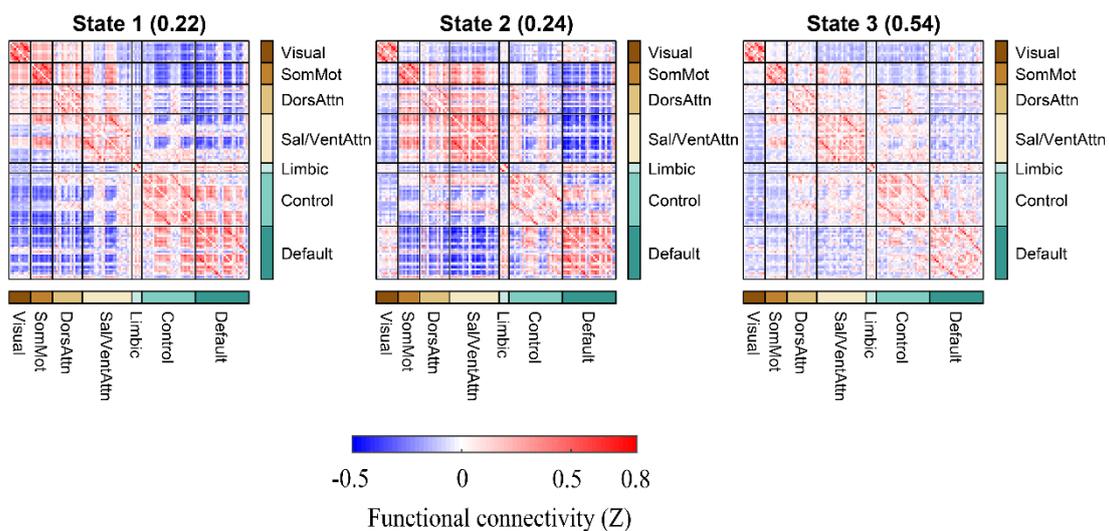


Figure S4. The cluster medians for each state. The percentage of total occurrences

is listed above each cluster median. The color bar represents the z value of dynamic functional connectivity. SomMot = somatomotor; DorsAttn = dorsal attention; Sal/VentAttn = salience/ventral attention; Control = frontoparietal control; Default = default mode.

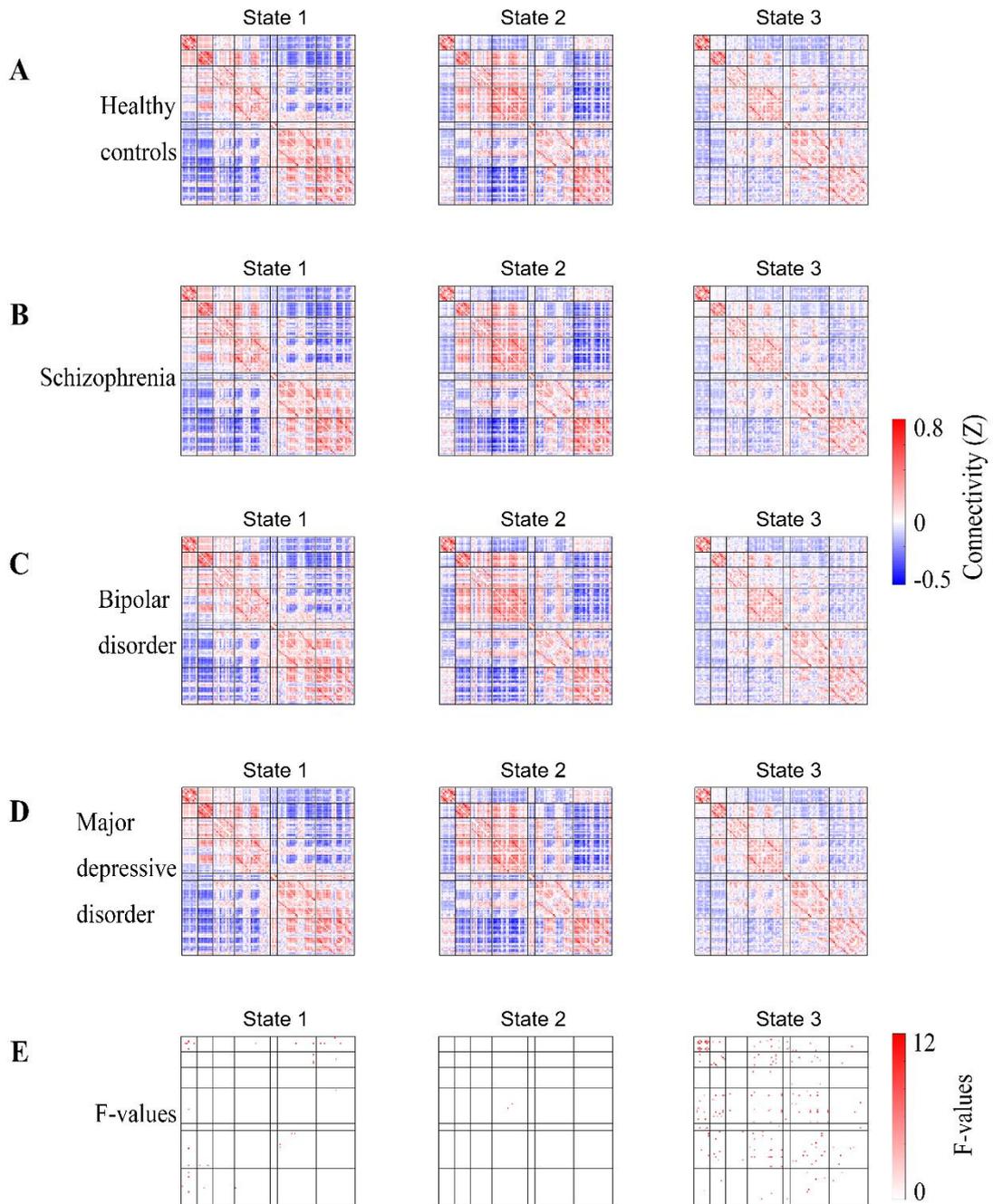


Figure S5. Group mean dynamic functional connectivity and significant 4-group differences. (A-D) Group mean dynamic functional connectivity for each group. (E)

Four-group differences among schizophrenia, bipolar disorder, and major depressive disorder patients and healthy controls (ANCOVA, FDR-corrected $q < 0.05$).

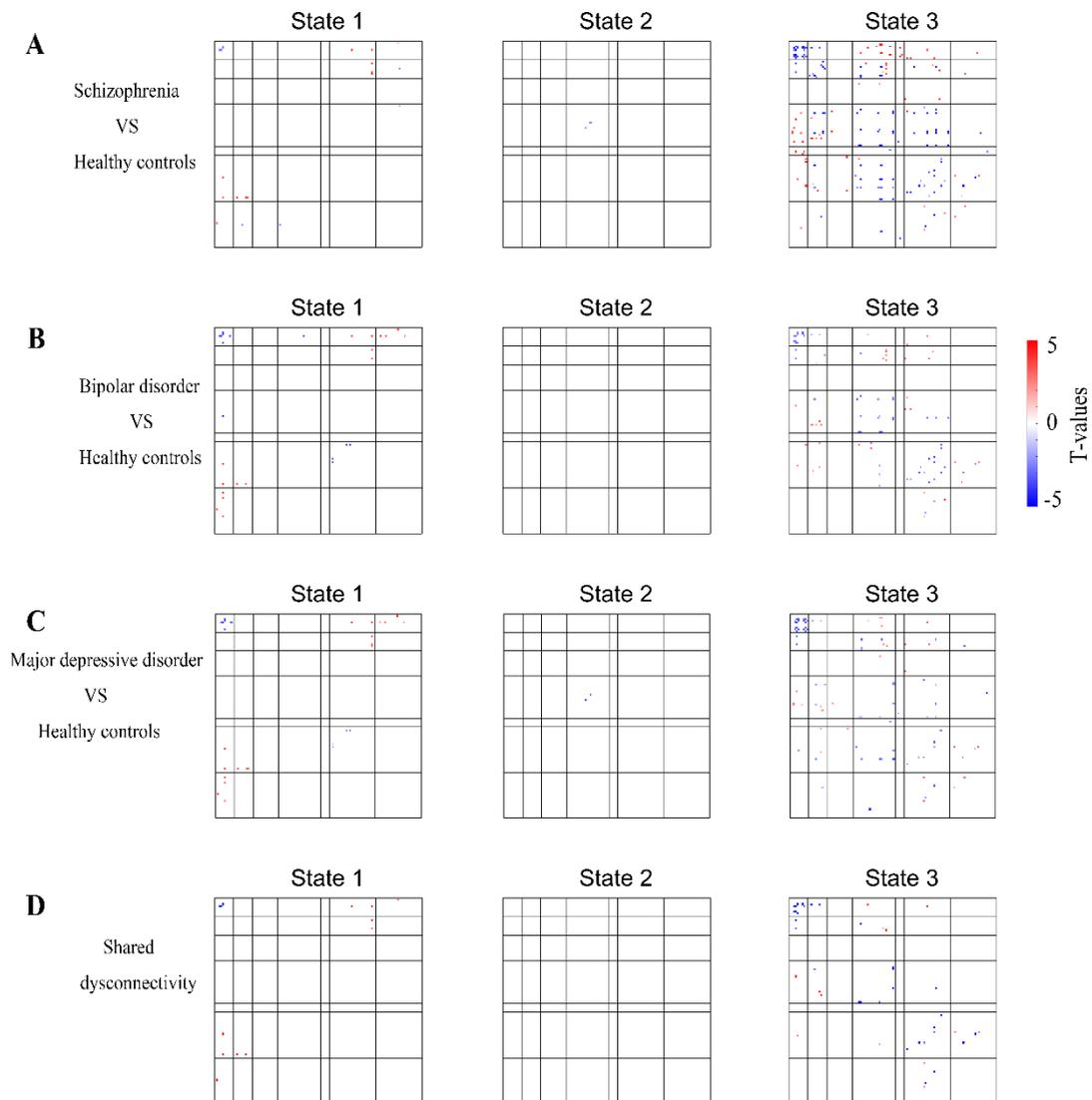


Figure S6. Significant differences in dynamic functional connectivity between patients and healthy controls. (A-C) Group differences between patients and healthy controls (two-sample t-test, FDR-corrected $q < 0.05$). (D) Transdiagnostic dysconnectivity across the 3 disorders. The red dots indicate increased connectivity, and the blue dots indicate decreased connectivity.

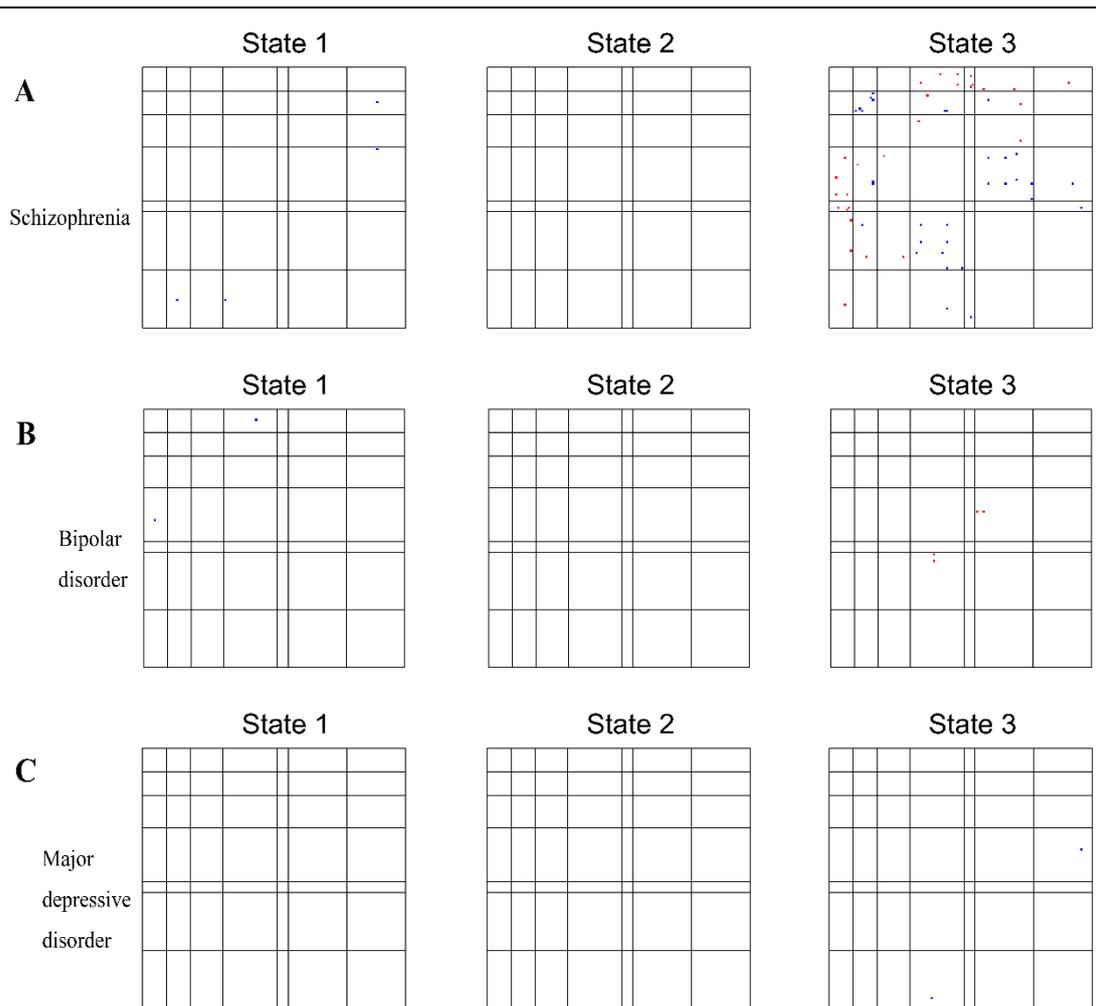


Figure S7. Unique dysconnectivity for each disorder. The red dots indicate increased connectivity, and the blue dots indicate decreased connectivity. Patients with schizophrenia had obviously more unique dysconnectivity than patients with bipolar and major depressive disorders, and these unique dysconnectivity only showed in state 1.

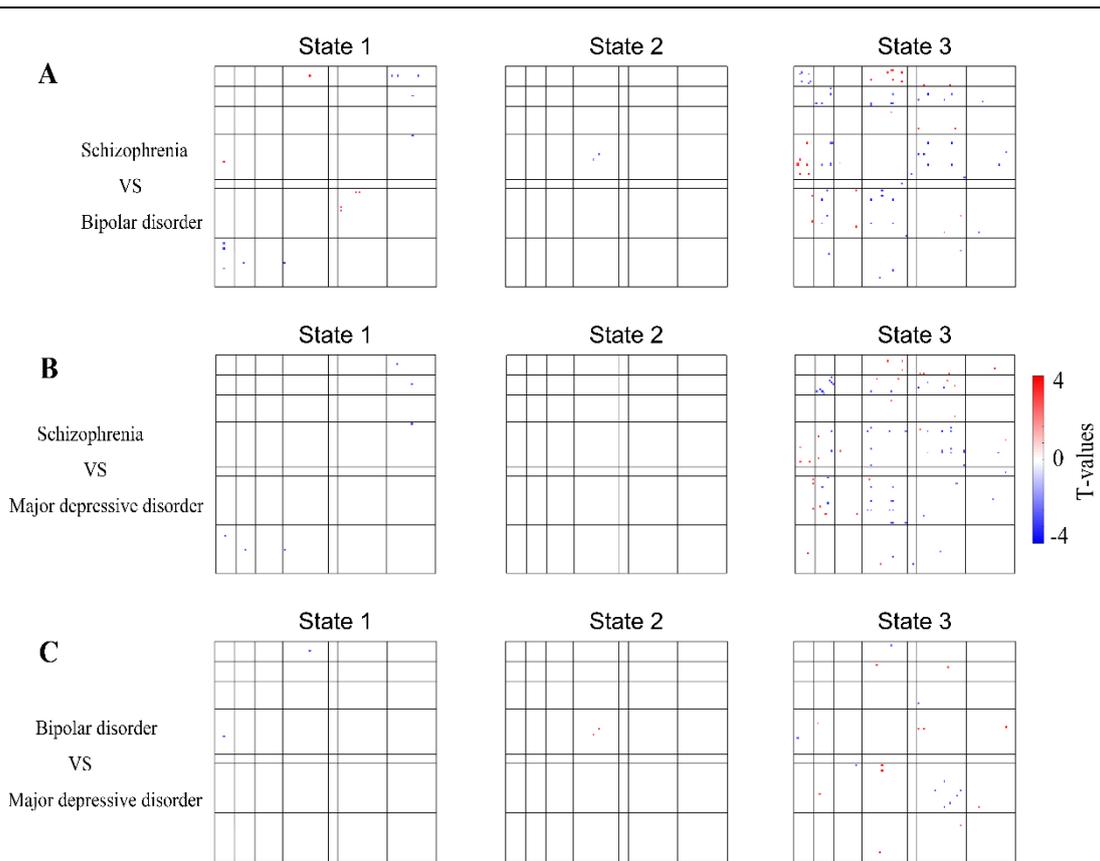


Figure S8. Significant differences in dynamic functional connectivity among patients' groups. The comparison among the patient groups showed that the schizophrenia was the most serious in extent among the three disease in most networks. Two-sample t-test, FDR-corrected $q < 0.05$.

Results of 17 TR window size for all subjects with good head motion (737 subjects)

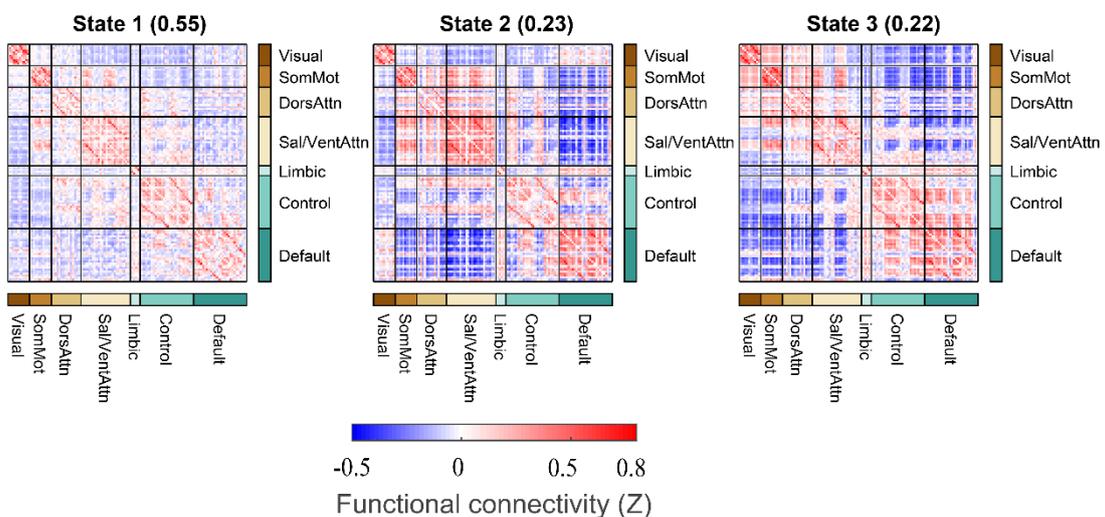


Figure S9. The cluster medians for each state. The percentage of total occurrences

is listed above each cluster median. The color bar represents the z value of dynamic functional connectivity. SomMot = somatomotor; DorsAttn = dorsal attention; Sal/VentAttn = salience/ventral attention; Control = frontoparietal control; Default = default mode.

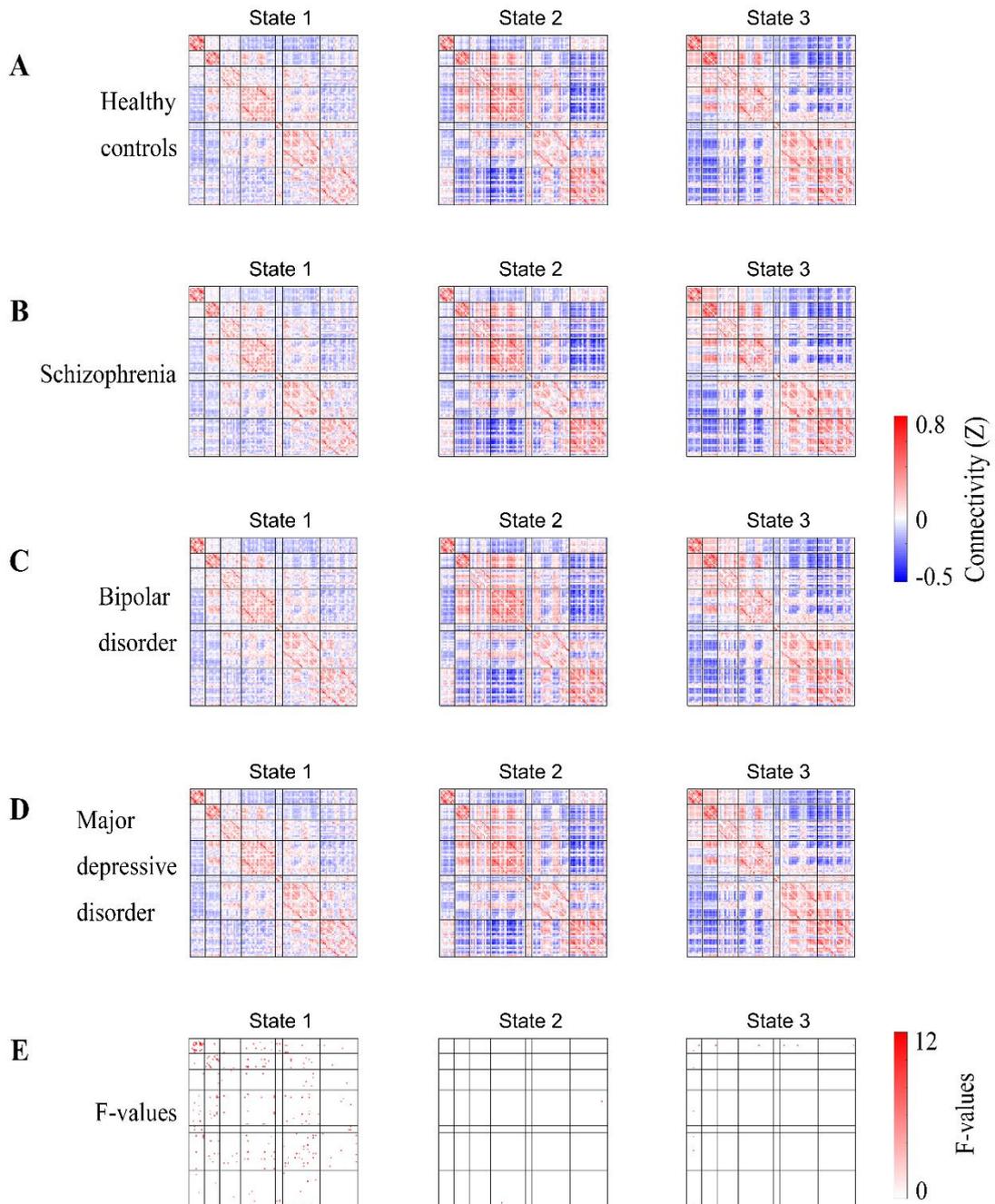


Figure S10. Group mean dynamic functional connectivity and significant 4-group differences. (A-D) Group mean dynamic functional connectivity for each

group. (E) Four-group differences among schizophrenia, bipolar disorder, and major depressive disorder patients and healthy controls (ANCOVA, FDR-corrected $q < 0.05$).

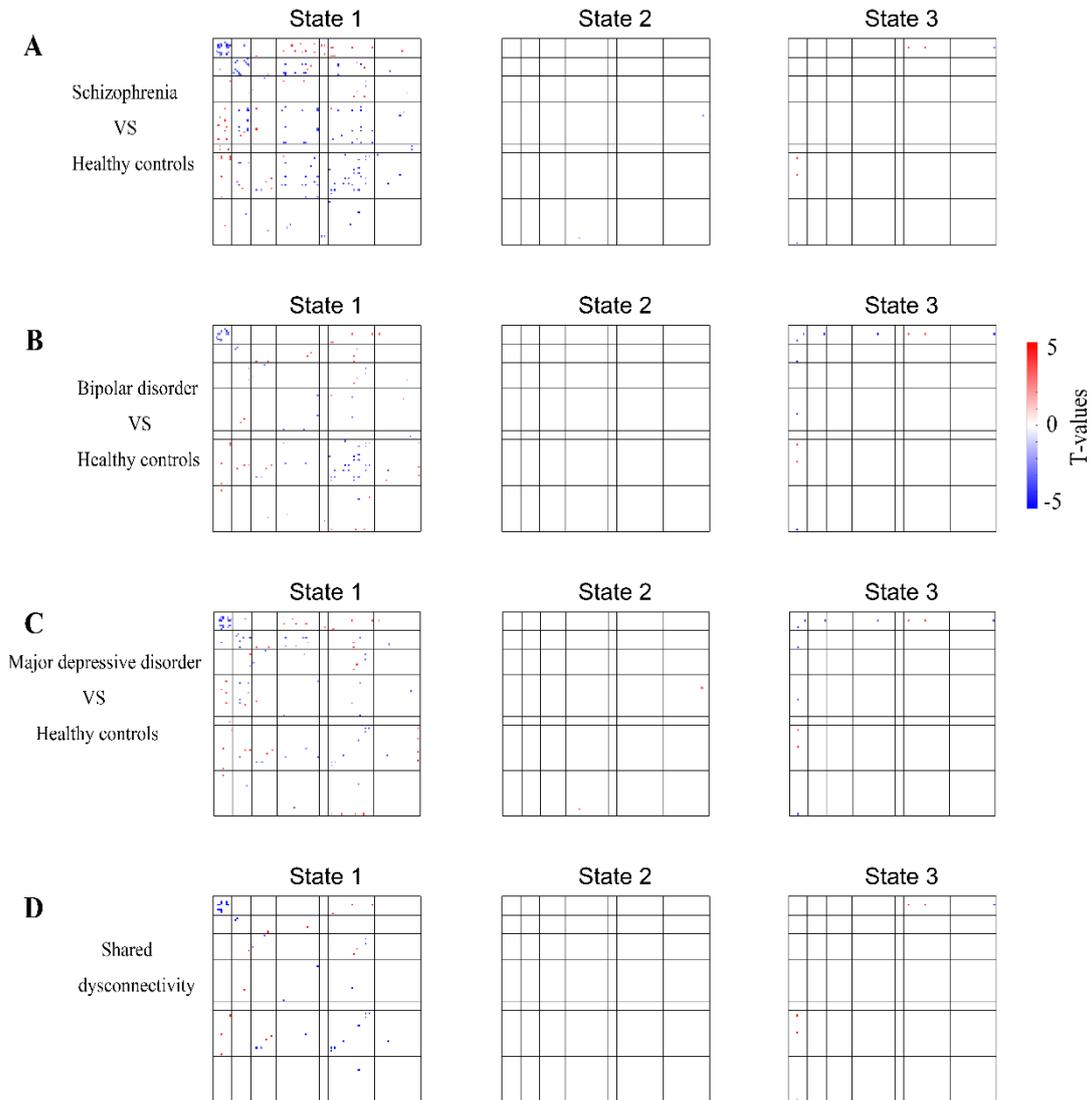


Figure S11. Significant differences in dynamic functional connectivity between patients and healthy controls. (A-C) Group differences between patients and healthy controls (two-sample t-test, FDR-corrected $q < 0.05$). (D) Transdiagnostic dysconnectivity across the 3 disorders. The red dots indicate increased connectivity, and the blue dots indicate decreased connectivity.

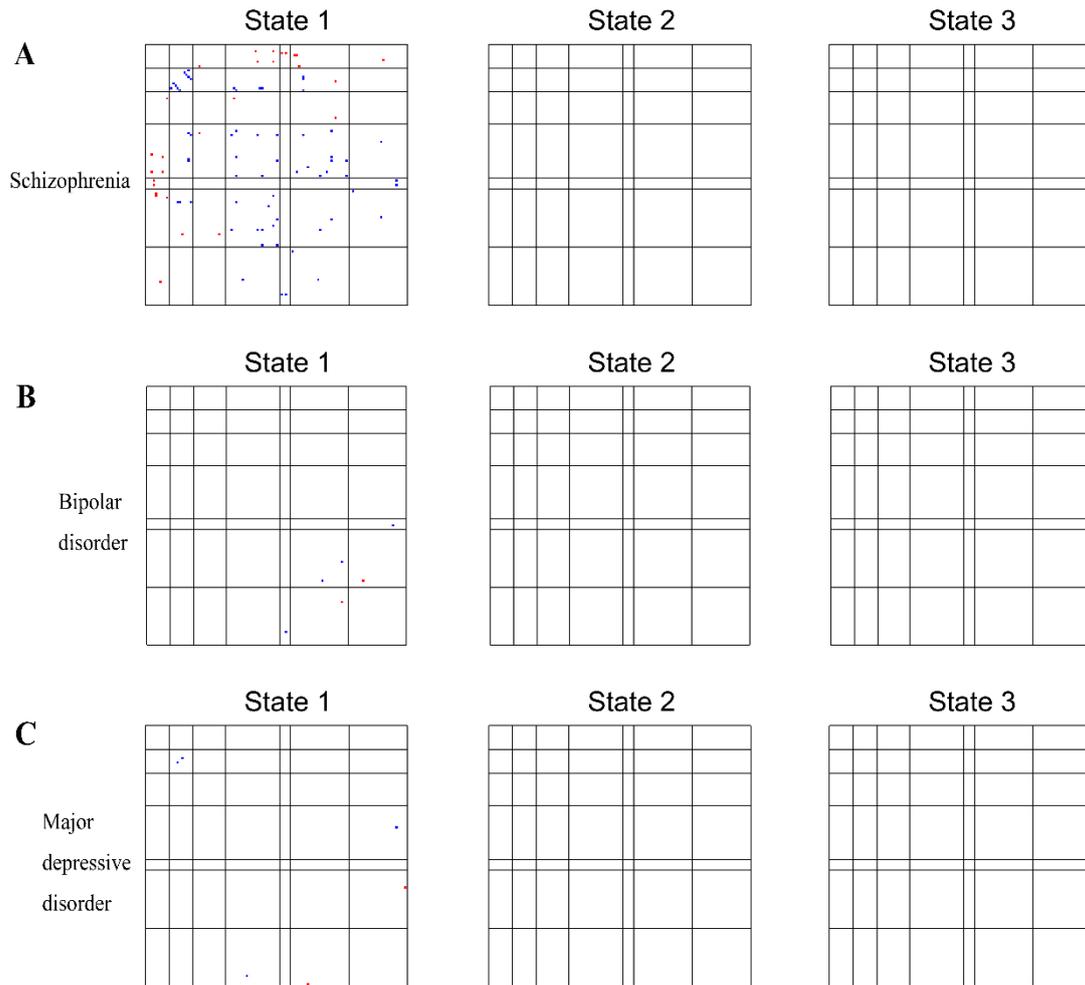


Figure S12. Unique dysconnectivity for each disorder. The red dots indicate increased connectivity, and the blue dots indicate decreased connectivity. Patients with schizophrenia had obviously more unique dysconnectivity than patients with bipolar and major depressive disorders, and these unique dysconnectivity only showed in state 1.

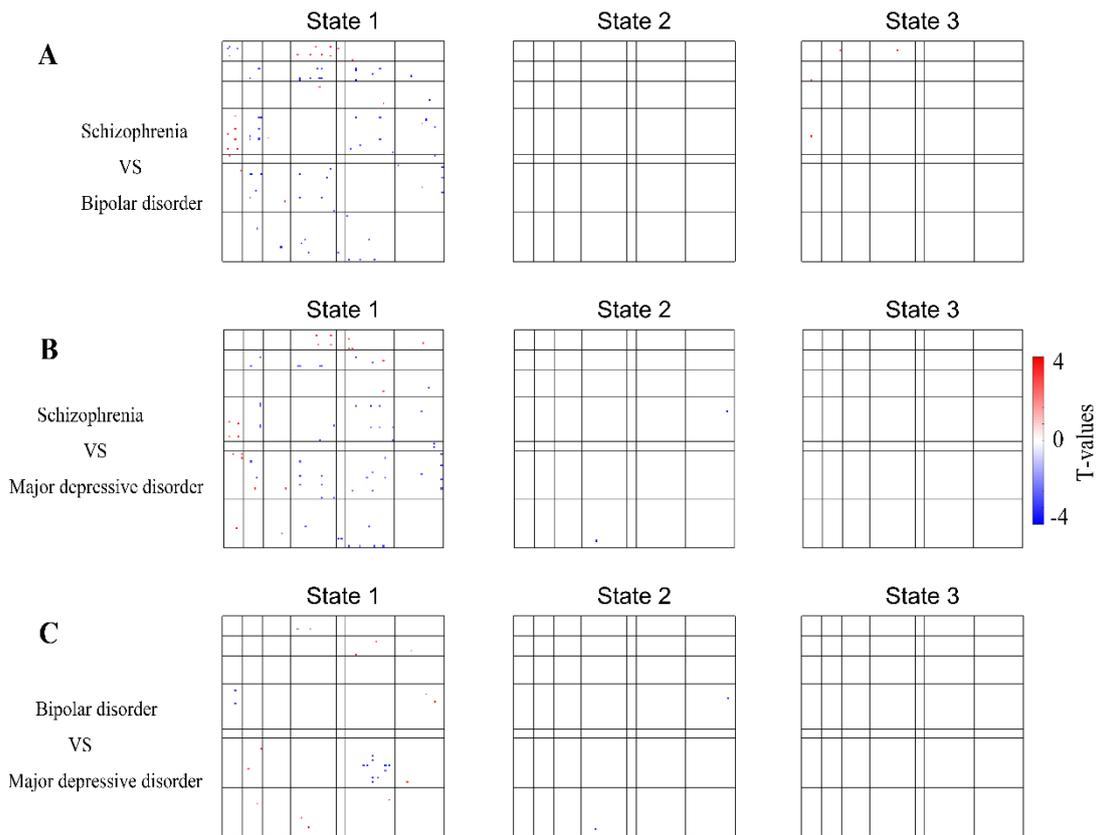


Figure S13. Significant differences in dynamic functional connectivity among patients' groups. The comparison among the patient groups showed that the schizophrenia was the most serious in extent among the three disease in most networks. Two-sample t-test, FDR-corrected $q < 0.05$.

Static connectivity

The transdiagnostic dysconnectivity of the static method was consistent with that of the dynamic methods in our main manuscript (Figure S1.F, Figure 1). For example, decreased connectivity was observed within the visual, somatomotor and frontoparietal networks. The increased connectivity between the visual and limbic networks and between the frontoparietal and default mode networks was also in line with the main findings for dynamic connectivity. However, some transdiagnostic dysconnectivity patterns were not found by the dynamic analysis, especially the increased connectivity within the default mode network. The average static functional connectivity and all significant differences in static functional connectivity are shown

in Figure S1.

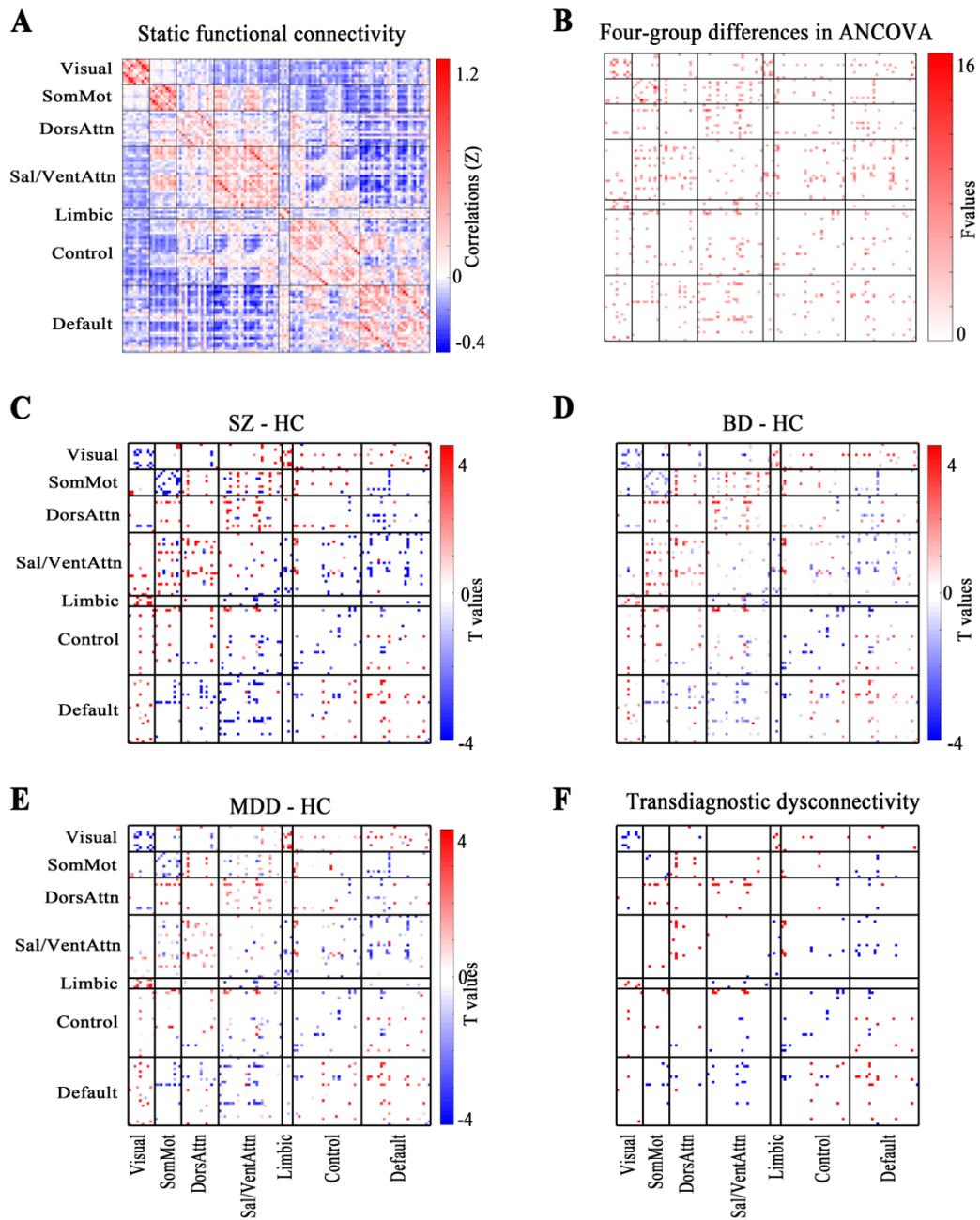


Figure S14: Static functional connectivity and significant differences in static functional connectivity. (A) The average static functional connectivity at the group level. (B) Four-group differences among schizophrenia, bipolar disorder, and major depressive disorder patients and healthy controls (ANCOVA, FDR-corrected $q < 0.05$). (C-E) Group differences between patients and healthy controls (two-sample t-test, FDR-corrected $q < 0.05$). (F) Transdiagnostic dysconnectivity across these 3 disorders.

The red dots indicate increased connectivity, and the blue dots indicate decreased connectivity. HC = healthy control; SZ = schizophrenia; BD = bipolar disorder; MDD = major depressive disorder; SomMot = somatomotor; DorsAttn = dorsal attention; Sal/VentAttn = salience/ventral attention; Control = frontoparietal control; Default = default mode.

Networks with statistically more dysconnectivity

As shown in Figure S15, the number of transdiagnostic dysconnectivity patterns within the visual and salience/ventral attention networks, between the visual and limbic networks, between the somatomotor and dorsal attention networks, and between the frontoparietal and default mode networks revealed statistically more dysconnectivity.

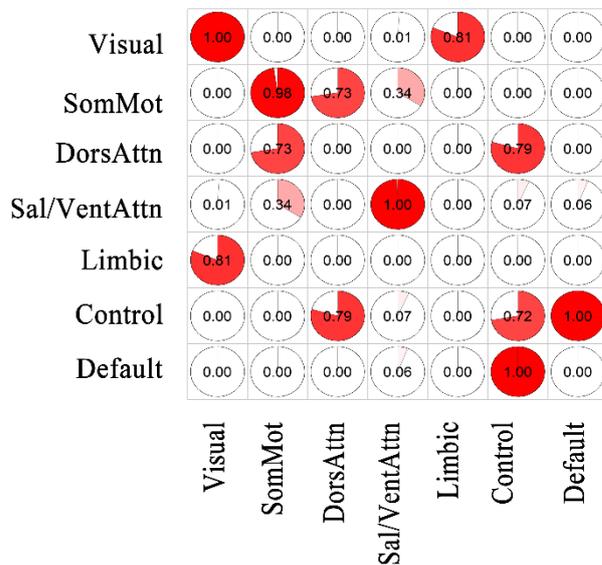


Figure S15: Permutation test for the number of dysconnectivity patterns in each brain network. The numbers in the small grid represent the 1 - P values. SomMot = somatomotor; DorsAttn = dorsal attention; Sal/VentAttn = salience/ventral attention; Control = frontoparietal control; Default = default mode.