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Transdiagnostic and Illness-Specific Functional Dysconnectivity Across Schizophrenia, Bipolar Disorder, and Major Depressive Disorder

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ABSTRACT

BACKGROUND: Mental disorders are typically defined as distinct diagnostic entities, but similar patterns of clinical and cognitive impairments are frequently found across diagnostic groups. We investigated whether these transdiagnostic deficits result from common neural substrates across disorders or various illness-specific mechanisms, or a combination of both.

METHODS: Functional magnetic resonance imaging data were collected from clinically stable patients with major depressive disorder (n = 53), bipolar disorder (n = 78), or schizophrenia (n = 100) and matched healthy control subjects (n = 109) using a single scanner. Group comparisons were conducted to identify transdiagnostic and illness-specific features, and possible confounding effects of medication were considered. A multivariate approach with cross-validation was used to associate dysconnectivity features with shared cognitive deficits.

RESULTS: Transdiagnostic dysconnectivities were identified within somatomotor (Cohen's d = 0.50–0.58) and salience (Cohen's d = 0.52–0.58) networks and between subcortical-limbic (Cohen's d = 0.55–0.69) and subcortical-dorsal attention (Cohen's d = 0.56–0.61) networks. The executive control network was found to be illness-specifically disconnected from the prefrontal-limbic-pallidal circuit in major depressive disorder (Cohen's d = 0.57–0.58), prefronto-striato-parietal circuit in bipolar disorder (Cohen's d = 0.48–0.53), and default mode network in schizophrenia (Cohen's d = 0.47–0.56). Working memory deficits were associated with a linear combination of 11 transdiagnostic and 5 illness-specific dysconnectivities (r = .322, $p = 9.7 \times 10^{-4}$, n = 340). The associations of the identified dysconnectivities with medication dosage were nonsignificant.

CONCLUSIONS: Disconnectivity in the somatomotor network was a common transdiagnostic profile, while there were illness-specific patterns in different parts of the prefrontal cortex for different disorders. These findings suggest that prominent psychiatric disorders share common impairments, possibly linked to perception and motor output, as well as unique dysconnectivity profiles that hypothetically mediate the more distinctive features of the disorder-specific psychopathology.

Keywords: Bipolar disorder, Depression, Dysconnectivity, Functional magnetic resonance imaging, Schizophrenia, Transdiagnostic

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The Kraepelinian dichotomy dividing psychotic disorder and mood disorder into schizophrenia (SCZ) and bipolar/unipolar mood disorder has been a traditional feature of psychiatric nosological classification. However, accumulating evidence suggests continuous gradients or dimensions of both neurodevelopmental and cognitive behavioral pathology for these mental disorders (1). For example, it has been suggested that SCZ shows more severe cognitive impairment than bipolar disorder (BIP), while major depressive disorder (MDD) is least severe (2). The deficits in verbal memory, executive functioning, and processing speed are particular concerns, as they often persist despite psychotropic treatments, and even show deteriorating trajectories after remission of clinical symptoms (3,4). As the illness progresses, the difference of impaired cognition between disorders becomes less strong in the chronic stage (2). Therefore, Research Domain Criteria have been suggested as a means of reconceptualizing mental disorders using both transdiagnostic and illness-specific features (5). Several studies have reported shared or distinct deficits across different psychiatric diagnoses from the perspective of regional structure (6), local/global connectivity (7,8), or network architectures (9). However, there has been little direct evidence of possible transdiagnostic and illness-specific alterations in functional neurocircuitry among the major

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psychiatric disorders. Thus, there is an urgent need of such a transdiagnostic neuroimaging study.

Despite the scarcity of neuroimaging data collected using a single scanner for these 3 groups of patients, meta-analyses have identified common changes in both the salience network (anterior-cingulo-insular network) (10) and the executive control network (ECN) (frontoparietal-cingulo-insular network) (11). Targeting these well-established brain networks, a recent multicenter neuroimaging study (12) reported that the ECN connectivity was disrupted in a graded manner from primary affective disorders (e.g., unipolar depression, BIP without psychosis) to primary psychotic disorders (e.g., BIP with psychosis and SCZ or schizoaffective disorder), while disruptions in default mode network (DMN) (i.e., the ventral and dorsal medial prefrontal, posterior cingulate, retrosplenial, and inferior parietal cortices) connectivity were present in patients with but not in patients without psychotic illness. These changes in the functional brain networks, especially the global network efficiencies of both the salience and subcortical networks, have also been associated with impaired general cognitive ability across different diagnostic groups (13).

However, choosing networks of interest a priori in these transdiagnostic studies may not have revealed distributed whole-brain abnormalities in network integration (14). This may be particularly important in psychiatric disorders, as hypo- or hyperconnectivity disruptions have been reported both within and between these brain networks (15–17). Recent studies have reported both disintegration (i.e., decreased functional connectivity [FC] within a network) and desegregation (i.e., increased FC between 2 networks) of brain functional networks (e.g., DMN, ECN, sensorimotor network, subcortical network) across affective and psychotic disorders (7,9,18). Compared with healthy control (HC) subjects, such functional brain networks have been observed to be disrupted to different extents, as the global topologies of these networks shift toward incrementally randomized configurations in patients with MDD, BIP, and SCZ (9). These differences among diagnostic groups might be understood by the characteristic psychopathological dysfunctions in each disorder [e.g., cognitive deficit in SCZ (19), emotional regulation in BIP (20), and loss of motivation in MDD (21)]. Various dimensions of psychopathology (e.g., mood, psychosis, fear, and externalizing behavior) were associated with both common and specific patterns of brain FC in a population-based cohort (22).

Therefore, we first hypothesized that reduced FC within the salience network described above might be a major transdiagnostic neural correlate (10,13). We additionally hypothesized that illness specificity might arise from disrupted connections between the ECN and other neural networks. More specifically, we proposed that 1) for SCZ, dysconnectivity between the ECN and DMN may be prominent, possibly linked to its characteristic cognitive deficits (23,24); 2) for BIP, dysconnectivity of the ECN with the limbic system may be more dominant in view of problems of emotional regulation (20); and 3) for MDD, dysconnectivity of the ECN with the subcortical network may be most significant, and related to loss of motivation (21). We could not have a full characterization of cognitive deficits in the patients, but we examined the association between the functional dysconnectivity identified and the working memory assessed by the backward digit span (BDS) to test whether the transdiagonastic dysconnectivity identified was also associated with the shared working memory deficit across the 3 diagnostic groups.

To test these hypotheses, we investigated large samples of patients with SCZ, BIP, and MDD recruited at the same site and undergoing neuroimaging in the same scanner, which precluded many sources of confounding effects present in previous multicenter studies. We also recruited patients in a stable condition, rather than those experiencing changes in symptoms, in order to increase the probability of identifying transdiagnostic trait markers instead of state markers (25). We also examined any associations between functional dysconnectivity and working memory, as assessed by a simple measure of BDS.

METHODS AND MATERIALS

Participants

This study initially recruited a total of 291 patients (patients with MDD = 65, patients with BIP = 103, patients with SCZ = 123) from the Taipei Veteran General Hospital, Taiwan, and 135 HC subjects from northern Taiwan through advertisements placed in the community and in universities. For all recruited participants, the Mini-Mental State Examination was used to screen for dementia, and the forward digit span (FDS) and BDS tests were assessed at graded levels of difficulty for working memory (26). Details regarding the inclusion criteria, exclusion criteria, and clinical status for participants are provided in the Supplemental Methods and Materials. All patients were diagnosed according to the DSM-IV criteria and validated using Mini-International Neuropsychiatric Interview (27). The evaluation of a clinically stable condition was based on the progress of treatment and the interviews conducted by one of the board-certified psychiatrists (M-NL, ACY, or S-JT), especially no change of hospitalization status over the last 4 to 6 weeks. The details of medication use are described in Supplemental Table S1.

The severity of depression and anxiety was rated using Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale, respectively, in all patients. Mania was evaluated by the Young Mania Rating Scale in patients with MDD and patients with BIP. The Positive and Negative Syndrome Scale was used to evaluate psychotic symptoms in patients with SCZ. (More details are provided in the Supplement.) All ratings were evaluated by a trained research assistant supervised by a board-certified psychiatrist (ACY) within the same week of the magnetic resonance imaging (MRI) scanning. According to the clinical records of the DSM-IV-TR, 26.5% of patients with MDD and 41.7% of patients with BIP had psychotic features, but their psychotic symptoms were diminished or remitted at the time of the MRI scan. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital. Written informed consent was obtained from all participants before commencement of the study.

Image Acquisition

MRI scanning was performed at National Yang-Ming University in Taiwan using a 3.0T Siemens MAGNETOM Tim Trio MRI Scanner (Siemens Healthcare, Erlangen, Germany) with a 12-channel head coil. High-resolution structural T1 images were

acquired with 3-dimensional magnetization prepared rapid gradient-echo sequence. Resting-state functional MRI (fMRI) was acquired using a gradient echo-planar imaging (EPI) sequence (repetition time = 2500 ms, echo time = 27 ms, field of view = 220 mm, flip angle = 77°, matrix size = 64 × 64 × 43, voxel size = 3.44 × 3.44 × 3.40 mm^3). The resting-state fMRI scan consisted of 200 contiguous EPI volume, which was acquired along the anterior commissure–posterior commissure plane. Total scan time for T1 imaging and resting-state fMRI was 17 minutes for each participant. See the Supplemental Methods and Materials for detailed imaging protocols.

fMRI Preprocessing

MR images were preprocessed using AFNI (http://afni.nimh.nih.gov/afni/) and FSL V.5.0.4 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). The overall preprocessing pipeline included the drop of first 10 volumes from whole series; slice-timing correction; brain extraction; spatial smoothing with a 6-mm full width at half maximum Gaussian kernel; intensity normalization; band-pass filter (0.01–0.08 Hz); and removing variance owing to white matter [WM], cerebrospinal fluid [CSF], and cardiorespiratory nuisance signals. To ensure adequate correction of artifactual signal changes and to ensure that the results were not biased owing to any excessive head motion, we followed the motion criteria in our previous work (28). See the Supplemental Methods and Materials for detailed preprocessing steps and motion criteria.

Statistical Analysis

Analysis of covariance was performed to examine the differences of general cognitions, such as FDS, BDS, and Mini-Mental State Examination between groups, by covarying the confounding effect of age, sex, and educational level.

Identifying Transdiagnostic and Illness-Specific Functional Dysconnectivity

We used Yeo *et al.*'s (29) cortical parcellation map of 114 cortical regions defined by voxelwise patterns of resting-state FC (Supplemental Table S2, Supplemental Figure S1). These cortical regions constitute 7 networks, including the ECN, DMN, dorsal attention network (DAN), limbic network, salience/ventral attention network (SVN) (comprising both the salience and cingulo-opercular networks), somatomotor network (SMN), and visual network (VSN). Fourteen subcortical regions (bilateral thalamus, putamen, pallidum, hippocampus, caudate, amygdala, and nucleus accumbens) defined by the FreeSurfer subcortical segmentation of the MNI 152 template were used. In total, we had 128 brain regions and 8128 FCs between each pair of the brain regions. After Fisher's z transformation, we conducted an analysis of variance for each FC considering 5 covariates, including age, sex, handedness, educational level, and the mean framewise displacement.

We compared each patient group with the HC group to identify common functional dysconnectivity across the 3 diagnostic groups. After false discovery rate correction ($q < .05$), a transdiagnostic dysconnectivity in patients was defined by 1) a significant difference between each patient group and the HC group or 2) a nonsignificant difference between patient groups (i.e., HC > MDD = BIP = SCZ or HC < MDD = BIP = SCZ). Illness-specific dysconnectivity was identified if the significant difference of an FC was shown between 1 patient group and the other 3 groups (e.g., MDD-specific FC: MDD > HC = BIP = SCZ or MDD < HC = BIP = SCZ). To establish the 95% confidence interval (CI) of the effect sizes of the dysconnectivity identified, we further conducted 5000 bootstrap resampling. To examine the effects of psychotropic medications, we determined correlations between dose equivalents and the identified dysconnectivities.

Association Analysis Between Functional Dysconnectivity and the Shared Cognitive Deficit. We applied the LASSO regression analysis to examine the FC correlates of the BDS and FDS. Here, we used the GLMNET package in MATLAB 2017b (The MathWorks, Inc., Natick, MA) (30) to generate regression models that include all functional dysconnectivities identified above (68 FCs) as predictors and digit span performance as the response variable. Details regarding the use of LASSO and cross-validation are described in the Supplement. In LASSO analysis, all the input variables (FC, BDS, FDS) were residuals after regressing out the confounding effects of age, sex, educational level, and the mean framewise displacement. Within each patient group, we further controlled for the corresponding symptom severity (i.e., Positive and Negative Syndrome Scale for patients with SCZ, Hamilton Depression Rating Scale for patients with MDD, and Young Mania Rating Scale for patients with BIP) to see whether the predicted values could still be associated with the actual BDS score.

RESULTS

Demographics

Eighty-six subjects were excluded from further analyses owing to excessive motion during the fMRI scans (Supplemental Table S6). Therefore, the current study used the data from 231 patients (53 with MDD, 78 with BIP, 100 with SCZ) and 109 matched HC subjects. All patients were pharmacologically treated (Supplemental Table S1) and in a clinically stable condition amounting to mild severity of illness-specific symptom scores (Table 1).

Transdiagnostic Functional Dysconnectivity

We identified 35 (11 within-network and 24 between-network) transdiagnostic functional dysconnectivities shared across 3 diagnostic groups, compared with HC subjects (Table 2; Figure 1; Supplemental Table S3 lists the bootstrapped 95% CI for each of the identified dysconnectivities). These instances of dysconnectivity were mainly associated with the sensorimotor system, including the SMN and VSN (63%; 22 FCs with Cohen's d ranging from −0.653 to −0.505). A total of 31% of dysconnectivity (11 FCs) was associated with attentional systems, including both the SVN and DAN. The Cohen's d of these diminished connections to the attention system ranged between −0.618 and −0.526, with only one example of increased connectivity between the right thalamus and the left temporal-occipital cortex in the DAN (Lt_DANa_TempOcc-Rt_Thal: Cohen's d = 0.573). We identified no functional

Table 1. Subject Demographics and Clinical Characteristics

	MDD Group (n = 53)	BIP Group (n = 78)	SCZ Group (n = 100)	HC Group (n = 109)	p Value (Group)
Demographic Characteristics					
Age, years	46.8 ± 11.7	45.3 ± 11.9	43.2 ± 11.3	44.2 ± 11.9	.298
Male/female	21/32	21/57	40/60	43/66	.460
Education, years	12.9 ± 3.4[a]	13.1 ± 3.5[a]	12.9 ± 3.6[a]	15.1 ± 3.3	.000
Handedness (left/right/neither)	1/52/0	2/76/0	5/94/1	4/106/0	.730
General Cognitive Function					
Forward digit span	12.9 ± 2.6[a]	13.4 ± 2.5	12.9 ± 2.4[a]	14.4 ± 1.9	.005
Backward digit span	7.1 ± 3.4[a]	7.2 ± 2.9[a]	6.6 ± 2.9[a]	9.1 ± 3.0	.000
MMSE	27.6 ± 2.4	27.4 ± 2.6[a]	27.4 ± 2.3[a]	28.6 ± 1.4	.009
Clinical Characteristics					
Duration of illness, years	9.3 ± 7.9[b,c]	15.7 ± 11.1	15.8 ± 1.8	–	.000
CPZ	151.4 ± 149.9[c]	170.6 ± 192.3[c]	475.2 ± 433.5	–	.000
BZD (0/1)	23/30	41/37	46/54	–	.536
HAM-A	8.2 ± 5.1[b,c]	4.5 ± 4.1	4.3 ± 3.0	–	.000
HAM-D	10.9 ± 6.3[b,c]	5.8 ± 5.3	5.4 ± 4.0	–	.000
YMRS	–	3.0 ± 4.3	–	–	
PANSS-Positive	–	–	9.6 ± 2.9	–	
PANSS-Negative	–	–	9.6 ± 2.8	–	
PANSS-General	–	–	21.1 ± 5.2	–	
PANSS-Total	–	–	40.3 ± 9.3	–	
Head Motion Parameters					
Maximum translation, mm	0.632 ± 0.375	0.709 ± 0.468[a]	0.668 ± 0.517[a]	0.527 ± 0.297	.019
Maximum rotation, °	0.704 ± 0.609	0.635 ± 0.479	0.749 ± 0.624[a]	0.571 ± 0.395	.091
Mean FD, mm	0.108 ± 0.037	0.114 ± 0.042	0.113 ± 0.039	0.120 ± 0.039	.283

Values are mean ± SD or n.

BIP, bipolar disorder; BZD, benzodiazepine; CPZ, chlorpromazine equivalent dose; FD, framewise displacement; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; HC, healthy control; MDD, major depressive disorder; MMSE, Mini-Mental State Examination; PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia; YMRS, Young Mania Rating Scale.

[a]Post hoc analysis: significant difference compared with HC group ($p < .05$).

[b]Post hoc analysis: significant different compared with BIP group ($p < .05$).

[c]Post hoc analysis: significant different to compared with SCZ group ($p < .05$).

dysconnectivity associated with either the DMN or ECN as a transdiagnostic feature.

Illness-Specific Functional Dysconnectivity

In total, we identified 7 MDD-specific, 7 BIP-specific, and 19 SCZ-specific examples of dysconnectivity (Table 2 and Supplemental Table S3; Figure 2). Most of these illness-specific instances of dysconnectivity (75%; n = 28 of 33) were between-network links. Compared with HC subjects, most of the dysconnectivity reflected decreased activity (97%; n = 32 of 33), and only one instance showed increased connectivity in SCZ only, between the right lateral prefrontal cortex in the SVN and the left striate cortex in the VSN (Cohen's d = 0.479 in patients with SCZ; Cohen's d = 0.059 in patients with BIP; Cohen's d = −0.041 in patients with MDD).

We found that DMN-connected illness-specific disconnectivities were mostly prominent (47%; n = 9 of 19 links) in SCZ patients between the DMN and SMN/DAN/ECN, with Cohen's d ranging from −0.455 to −0.566. Patients with MDD had only 2 illness-specific forms of dysconnectivity between the DMN and SVN, with Cohen's ds of −0.545 (Lt_DMNc_PHC-Lt_SVNb_IPL) and −0.564 (Lt_DMNb_PFCd-Rt_SVNb_PFCl). In patients with BIP, only one DMN-subcortical network disconnectivity (between the left posterior inferior parietal cortex and the left hippocampus; Cohen's d = −0.605) and 1 within-DMN disconnectivity (between the left posterior inferior parietal cortex and the left parahippocampal complex; Cohen's d = −0.500) were observed.

Illness-specific dysconnectivities between the right dorsal prefrontal cortex in the ECN and the brain regions in the DMN were shown only in the patients with SCZ. The disconnected DMN regions included the bilateral inferior parietal lobule (IPL) (right IPL: Cohen's d = −0.566; left IPL: Cohen's d = −0.56) and right anterior temporal cortex (Cohen's d = −0.467). Patients with BIP had a similar frontoparietal disconnectivity between the left lateral ventral prefrontal cortex (in the ECN) and the right medial parietal cortex (in the SVN; Cohen's d = −0.525). However, the patients with MDD had 2 examples of illness-specific disconnectivity attached to the ECN regions, including the right medial posterior prefrontal cortex (with the left pallidum; Cohen's d = −0.580) and the left lateral prefrontal cortex (with the right postcentral gyrus; Cohen's d = −0.553).

Table 2. Transdiagnostic and Illness-Specific FCs in the Patient Groups

		Cohen's *d* (MDD/BIP/SCZ – HC)		
Region-Region	Effect Size (Meta)	MDD – HC	BIP – HC	SCZ – HC
Transdiagnostic FCs				
Lt_DANa_TempOcc-Rt-Thal	0.573	0.583	0.489	0.646
Lt_DANb_PostC-Rt_LMN_OFC	−0.583	−0.547	−0.492	−0.708
Lt_DANb_PostC-Rt-Hipp	−0.618	−0.618	−0.566	−0.666
Rt_DANb_FEF-Rt_DANb_PrCv	−0.608	−0.645	−0.545	−0.631
Rt_DANb_PrCv-Rt_SVNa_ParMed	−0.515	−0.614	−0.488	−0.447
Lt_LMN_TempPole-Rt_SMNb_Ins	−0.549	−0.554	−0.616	−0.478
Lt_LMN_TempPole-Lt-Accm	−0.694	−0.649	−0.705	−0.714
Rt_LMN_OFC-Lt_SVNa_FrMed	−0.544	−0.604	−0.533	−0.507
Rt_LMN_OFC-Lt_SMNb_Ins	−0.550	−0.549	−0.499	−0.599
Rt_LMN_TempPole-Lt-Accm	−0.563	−0.556	−0.557	−0.575
Lt_SVNa_ParOper-Rt_SMNb_Ins	−0.526	−0.600	−0.509	−0.477
Lt_SVNa_PrCv-Rt_SVNa_ParMed	−0.546	−0.590	−0.517	−0.543
Rt_SVNa_PrCv-Rt_SVNa_ParMed	−0.572	−0.589	−0.587	−0.548
Lt_SVNa_ParOper-Rt_SVNa_ParMed	−0.574	−0.631	−0.498	−0.594
Rt_SVNa_ParOper-Rt_SVNa_ParMed	−0.591	−0.732	−0.545	−0.501
Lt_SMNa-Lt_SMNb_Aud	−0.507	−0.542	−0.511	−0.478
Lt_SMNa-Rt-Amyg	−0.545	−0.544	−0.602	−0.490
Lt_SMNa-Lt_SMNb_S2	−0.563	−0.598	−0.562	−0.540
Lt_SMNa-Lt-Amyg	−0.607	−0.605	−0.583	−0.630
Lt_SMNb_Aud-Rt_SMNb_S2	−0.517	−0.581	−0.517	−0.463
Lt_SMNb_S2-Rt_VSNp_ExStrSup	−0.536	−0.585	−0.522	−0.508
Lt_SMNb_Aud-Rt-Puta	−0.564	−0.555	−0.526	−0.612
Lt_SMNb_Aud-Rt_SMNa	−0.575	−0.605	−0.59	−0.538
Lt_SMNb_S2-Rt_SMNa	−0.586	−0.608	−0.597	−0.557
Lt_SMNb_Cent-Lt-Hipp	−0.592	−0.642	−0.596	−0.55
Lt_SMNb_Aud-Lt_VSNp_ExStrSup	−0.595	−0.555	−0.526	−0.701
Lt_SMNb_S2-Lt_VSNp_ExStrSup	−0.612	−0.785	−0.482	−0.572
Lt_SMNb_Aud- Lt_VSNp_ExStrInf	−0.634	−0.625	−0.542	−0.731
Lt_SMNb_S2-Lt_VSNp_ExStrInf	−0.653	−0.681	−0.587	−0.691
Rt_SMNb_Cent-Lt-Hipp	−0.505	−0.578	−0.49	−0.459
Rt_SMNb_S2-Lt_VSNp_ExStrInf	−0.562	−0.644	−0.477	−0.566
Rt_SMNb_S2-Rt-Puta	−0.566	−0.551	−0.68	−0.466
Rt_SMNb_S2-Lt-Hipp	−0.628	−0.604	−0.514	−0.765
Rt_TempPar-Lt-Hipp	−0.621	−0.566	−0.560	−0.734
Rt_VSNp_ExStrInf-Lt-Amyg	−0.628	−0.568	−0.666	−0.642
MDD-Specific FCs				
Lt_ECNb_PFCl-Rt_DANb_PostC	–	−0.553	−0.016	−0.172
Rt_ECNb_PFCmp-Lt-Pall	–	−0.580	−0.001	0.078
Lt_DMNc_PHC-Lt_SVNb_IPL	–	−0.545	−0.088	−0.162
Lt_DMNb_PFCd-Rt_SVNb_PFCl	–	−0.564	−0.038	−0.061
Rt_SVNa_FrMed-Lt_VSNp_ExStrInf	–	−0.546	−0.142	−0.224
Lt_LMN_TempPole-Lt-Pall	–	−0.565	0.032	−0.048
Lt-Hipp-Rt-Pall	–	−0.563	−0.052	−0.139
BIP-Specific FCs				
Lt_ECNa_PFClv-Rt_SVNa_ParMed	–	−0.107	−0.525	−0.194
Lt_DMNa_IPL-Lt_DMNc_PHC	–	0.040	−0.509	−0.077
Lt_DMNa_IPL-Lt-Hipp	–	0.048	−0.605	−0.149
Lt_DANb_PostC-Rt-Puta	–	−0.254	−0.657	−0.107
Lt_SVNa_FrMed-Rt_SVNb_IPL	–	−0.035	−0.527	−0.171
Rt_SVNb_PFCmp-Lt-Caud	–	0.265	−0.480	−0.087
Rt_SVNb_PFCmp-Rt-Caud	–	0.083	−0.490	−0.199

Table 2. Continued

Region-Region	Effect Size (Meta)	Cohen's *d* (MDD/BIP/SCZ – HC)		
		MDD – HC	BIP – HC	SCZ – HC
SCZ-Specific FCs				
Rt_ECNa_PFCd-Rt_DMNb_AntTemp	–	−0.128	−0.110	−0.467
Rt_ECNa_PFCd-Lt_DMNb_IPL	–	−0.131	−0.012	−0.560
Rt_ECNa_PFCd-Rt_DMNa_IPL	–	−0.069	−0.160	−0.566
Lt_DMNa_PCC-Lt_SMNb_Aud	–	−0.163	−0.026	−0.464
Lt_DMNb_IPL-Rt_SMNb_Aud	–	−0.057	−0.131	−0.462
Lt_DMNb_Temp-Rt_DANa_SPL	–	−0.253	−0.111	−0.557
Rt_DMNb_AntTemp-Rt_SVNb_Cinga	–	−0.071	−0.161	−0.455
Rt_DMNb_PFCv-Lt_DANb_FEF	–	−0.027	0.013	−0.503
Rt_DMNc_PHC-Lt_SVNa_ParOper	–	−0.108	−0.211	−0.525
Lt_DANb_TempOcc-Lt-Hipp	–	−0.125	−0.193	−0.467
Rt_DANa_ParOcc-Rt_LMN_TempPole	–	−0.071	−0.207	−0.487
Lt_LMN_TempPole-Lt_TempPar	–	−0.029	−0.290	−0.544
Lt_LMN_OFC-Rt_SMNb_Aud	–	−0.138	−0.213	−0.616
Rt_LMN_TempPole-Rt_TempPar	–	0.006	−0.220	−0.500
Rt_LMN_TempPole-Lt_SVNb_IPL	–	−0.066	−0.109	−0.531
Rt_LMN_TempPole-Lt_TempPar	–	−0.052	−0.293	−0.618
Rt_SVNb_PFCl-Lt_VSNp_Striate	–	−0.041	0.059	0.479
Rt_SVNb_PFCd-Rt_SVNb_PFClv	–	−0.020	−0.044	−0.444
Lt_SMNb_Ins-Lt_SMNb_Aud	–	−0.254	−0.176	−0.687

This table shows the transdiagnostic FCs discovered across patients with MDD, patients with BIP, and patients with SCZ, and illness-specific FCs of each patient group. The identified FCs are listed in alphabetic order, corresponding to the connected network. Cohen's *d* of each identified FC is shown for the strength of group difference between the patient group and the HC group. Detailed abbreviations for other brain regions are listed in Supplemental Table S2. The effects of medication, duration, and clinical symptoms on the FC are shown in Supplemental Tables S4 and S5.

Accm, accumbens; Amyg, amygdala; Aud, auditory; BIP, bipolar disorder; Caud, caudate; Cinga, anterior cingulate; d, dorsal; DAN, dorsal attention network; DMN, default mode network; ECN, executive control network; ExStrInf, inferior peripheral extrastriate; ExStrSup, superior peripheral extrastriate; FC, functional connectivity; FEF, frontal eye field; FrMed, medial frontal; Hipp, hippocampus; Ins, insula; IPL, inferior parietal lobule; l, lateral; LMN, limbic network; Lt, left; m, medial; MDD, major depressive disorder; mp, medial posterior; Occ, occipital; OFC, orbitofrontal cortex; Pall, pallidum; Par, parietal; ParMed, medial parietal; ParOper, parietal operculum; pCun, precuneus; PFC, prefrontal cortex; PHC, parahippocampal complex; PostC, postcentral gyrus; PrCv, precentral ventral; Puta, putamen; Rt, right; S2, secondary somatosensory; SCZ, schizophrenia; SMN, somatomotor network; SVN, salience/ventral attention network; Temp, temporal; TempOcc, temporal-occipital; TempPole, temporal pole; Thal, thalamus; v, ventral; VSN, visual network.

We also found disconnectivity of the left hippocampus with distinct brain regions in patients from different diagnostic groups, including the right pallidum in patients with MDD (Cohen's $d = -0.563$), the left posterior inferior parietal cortex within the DMN in patients with BIP (Cohen's $d = -0.605$), and the left temporal-occipital junction within the DAN in patients with SCZ (Cohen's $d = -0.467$).

Control Over Possible Head Motion or Medical Treatment Effects

After quality control, head movements were small in all participants, and no differences in mean framewise displacement were identified among groups (Table 1). To control for possible confounding effects, all group differences were reported using age, sex, educational level, and mean framewise displacement as covariates. Although sample sizes differed among the 3 patient groups, the effect sizes of these identified transdiagnostic FCs were comparable for them (Table 2). Most of the identified transdiagnostic FCs were not associated with medication doses (chlorpromazine or antidepressant dosage), except for a negative correlation between chlorpromazine and FC of the right temporal-parietal junction within the left hippocampus ($r = -.217$, $p = .0012$, $n = 218$) (Supplemental Table S4). The correlations between illness-specific FC and the effect of medication, illness duration, and clinical symptoms are shown in Supplemental Table S5.

Association of Working Memory Deficits With Multiple Interactions Among Networks

We found the working memory deficit assessed by the BDS score but not the impaired general attention/short-term memory function evaluated by the FDS score to be shared among all 3 patient groups ($F_{3,336} = 7.702$, $p = .0001$) to comparable levels ($p = .427$) when compared with the HC group (Table 1). Instead of any one dysconnectivity having a dominant association with working memory (Supplemental Tables S4 and S5), we found that the BDS score was associated with a combination of 16 functional dysconnectivities, including 11 transdiagnostic, 0 MDD-specific, 1 BIP-specific, and 4 SCZ-specific dysconnections identified above (testing sample: $r = .322$; 95% CI, 0.137 to 0.414 by random partition; $p = .003$ by permutation; $n = 102$) (Supplemental Table S8).

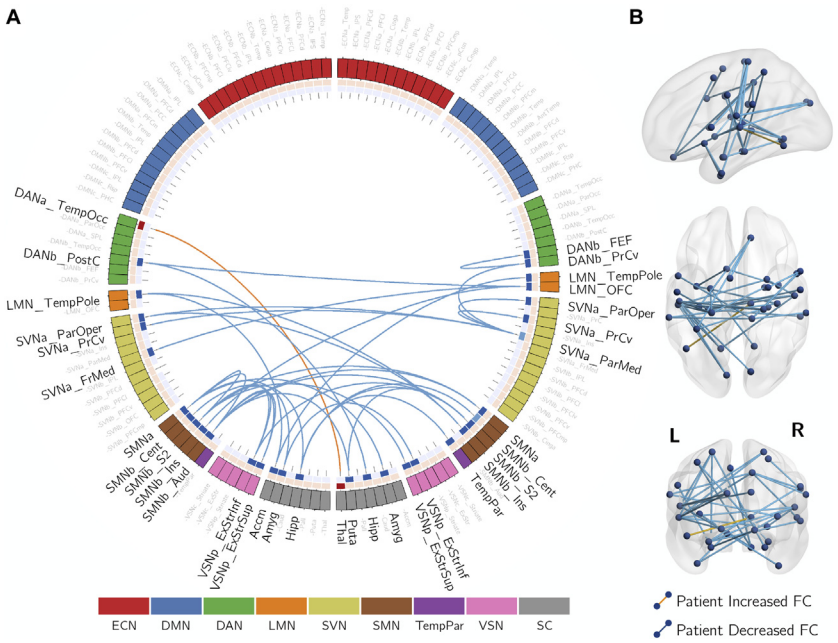

Figure 1. The transdiagnostic functional dysconnectivity pattern among patients with major depressive disorder, bipolar disorder, and schizophrenia. **(A)** Transdiagnostic functional connectivity (FC) shared among the 3 psychiatric illnesses. The brain regions are arranged by the brain functional networks to which they belong. The left hemisphere (L) is represented by the left ring, and right hemisphere (R) by the right ring. Each color lump on the ring represents 1 brain region. The line linking 2 brain regions represents 1 significant FC identified (the hypoconnectivity in patients compared with healthy control subjects is marked in blue and the hyperconnectivity is in orange). **(B)** Three-dimensional mappings of the identified transdiagnostic FC onto the brain. Aud, auditory; Cent, precentral; DAN, dorsal attention network; DMN, default mode network; ECN, executive control network; ExStrSup, superior peripheral extrastriate; ExtrInf, inferior peripheral extrastriate; FrMed, medial frontal; LMN, limbic network; ParOper, parietal operculum; PostC, postcentral gyrus; PrCv, precentral ventral; S2, secondary somatosensory; SC, subcortical network; SMN; somatomotor network; SVN, salience/ventral attention network; TempOcc, temporal-occipital; TempPar, temporal-parietal network; TempPole, temporal pole; VSN, visual network.

Transdiagnostic links accounted for 67% of the total weights in the LASSO model, and the performances if this model were comparable among both all 3 patient groups and the HC group (Figure 3). Within each patient group, the model predictions remained unchanged after controlling for the corresponding symptom severity, suggesting that the model was specific for the cognitive deficit. In contrast, the same procedure could not build a similar model for the FDS score, i.e., the association between the predictions and the assessments could not survive the procedure of random partitions (95% CI, −0.0418 to 0.3562). This observation also suggested that our finding was a less likely consequence of overfitting.

DISCUSSION

The current study has dissociated transdiagnostic from illness-specific profiles of brain FC in clinically stable patients across 3 major psychiatric disorders. We were able to remove possible confounding effects of scanning on different MRI machines through the use here of a single scanner to assess large, well-diagnosed groups of patients with MDD, BIP, and SCZ.

Loss of FC as a Feature Shared Among Psychiatric Disorders

Recent transdiagnostic meta-analyses of both gray matter volume and brain activation have reported deficits in the ECN (10,11,31). Given that human behavior may be generated by the dynamic integration of multiple brain systems (32), these simple imaging indicators (e.g., volume or activation) at the regional level may be insufficient for investigating the neural circuits underlying psychiatric disorders. The current study conducted a direct investigation of brain functional architecture and revealed disconnectivity (hypoconnectivity) patterns across psychiatric disorders, which have been widely observed in previous, though separate, fMRI studies (33–35). Decreased connectivity may reflect disintegration of brain functions underlying dysregulation of synaptic plasticity, which leads to less efficient communication in the brain (36).

Illness-Specific Findings Highlight Distinct Dysconnectivities of ECN in the 3 Disorders

Each of these major psychiatric disorders certainly has its own unique characteristics. However, most previous studies have identified neural correlates of a given psychiatric disorder by comparing patients with HC subjects. Little effort has been made to identify illness-specific neural correlates of a single psychiatric disorder by comparisons with not only HC subjects, but also patients with other psychiatric conditions. We have achieved this in the current study and have not only confirmed the involvement of SVN and DMN in these disorders (10,11,31), but also provided new insights on the illness-specific nature of the ECN, which has been previously considered as a transdiagnostic feature by the meta-analysis at a brain regional level (11). By investigating the functional connectivities of the ECN, we found that different ECN areas were disconnected from distinct brain systems, specifically in different psychiatric disorders.

We found that specific disconnectivities in MDD were attached to the lateral prefrontal cortex (with the somatosensory cortex) and the medial posterior prefrontal cortex (with the pallidum). Together, with the disconnectivities of the pallidum and both the hippocampus and the temporal pole, these findings are in line with the disrupted interactions between the ECN and affective circuitry (including the cingulate cortex, amygdala, hippocampus and basal ganglia, etc.) identified by a meta-analysis of MDD (37). Furthermore, our MDD-specific findings highlight the pallidum (43% of MDD-specific disconnectivities), of which 2 discrete circuits of parvalbumin-positive neurons projecting to the lateral habenula and the

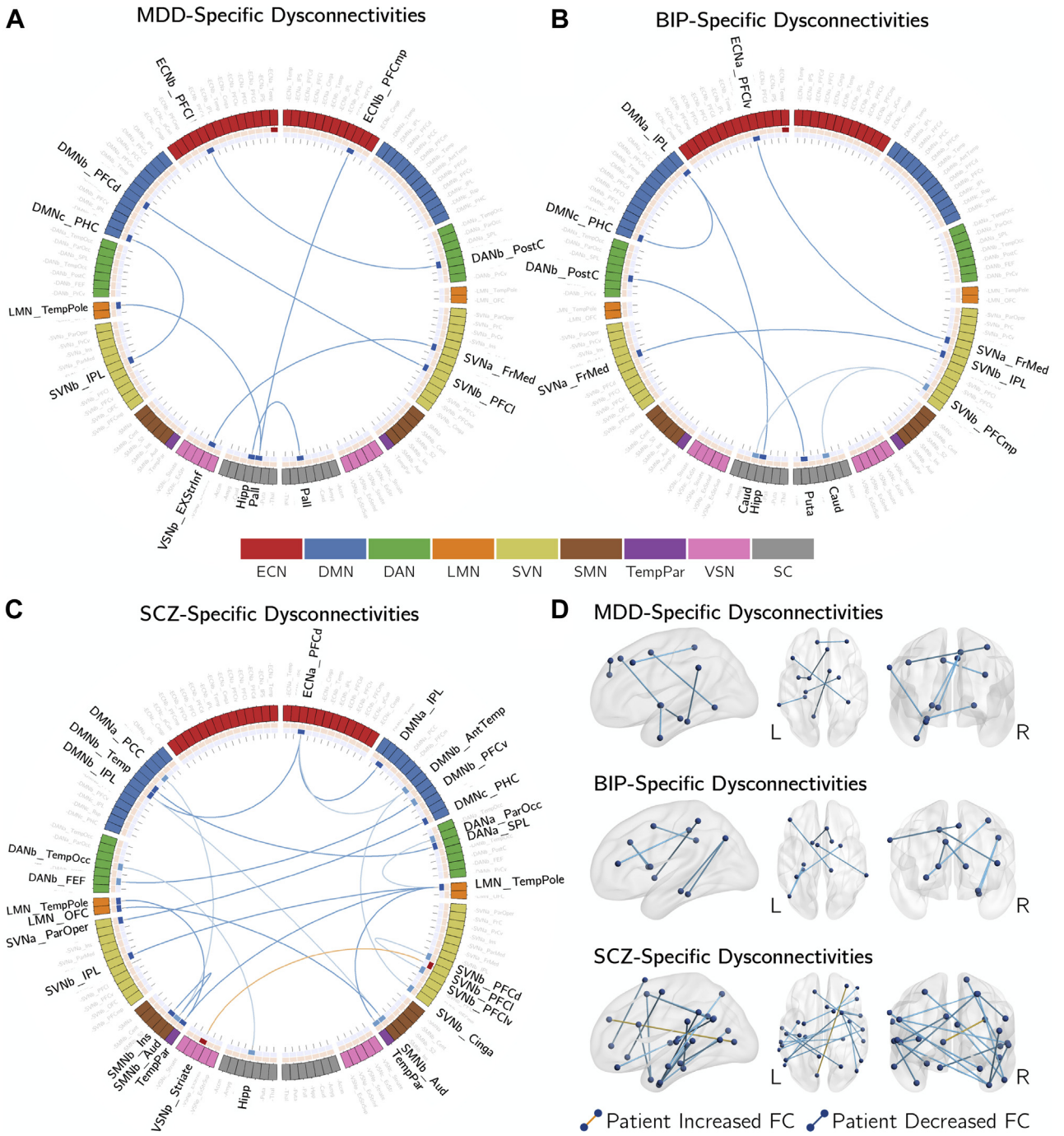

Figure 2. Illness-specific functional dysconnectivity pattern in each diagnostic group. The illness-specific functional connectivity (FC) identified for each diagnostic group: **(A)** major depressive disorder (MDD), **(B)** bipolar disorder (BIP), and **(C)** schizophrenia (SCZ). **(D)** The anatomical location of the identified FC in the brain using BrainNet viewer (58). The criteria for determining specific deficit of one diagnostic group is defined by the functional link showing a significant difference with the rest of 3 groups, along with no significant differences between them (e.g., MDD < BIP = SCZ = healthy control group). AntTemp, anterior temporal; Aud, auditory; Caud, caudate; Cinga, anterior cingulate; DAN, dorsal attention network; DMN, default mode network; ECN, executive control network; EXStrInf, inferior peripheral extrastriate; FEF, frontal eye field; FrMed, medial frontal cortex; Hipp, hippocampus; Ins, insular; IPL, inferior parietal cortex; L, left hemisphere; LMN, limbic network; OFC, orbitofrontal cortex; Pall, pallidus; ParOcc, parietal occipital; ParOper, parietal operculum; PCC, posterior cingulate; PFCd, dorsal prefrontal cortex; PFCl, lateral prefrontal cortex; PFClv, ventral lateral prefrontal cortex; PFCmp, medial posterior prefrontal cortex; PHC, parahippocampal; PostC, postcentral gyrus; Puta, putamen; R, right hemisphere; SC, subcortical network; SMN; somatomotor network; SPL, superior parietal; Striate, central striate; SVN, salience/ventral attention network; Temp, temporal; TempPar, temporal-parietal network; TempPole, temporal pole; VSN, visual network.

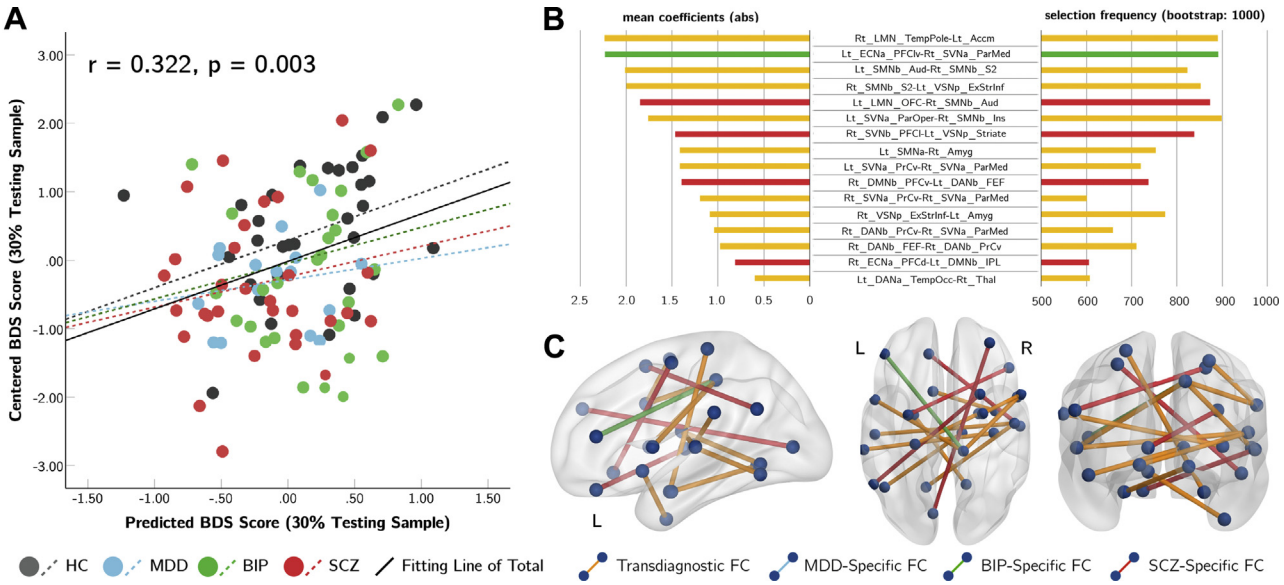

Figure 3. The backward digit span (BDS) performance is correlated with the transdiagnostic and specific dysconnectivities using LASSO regression. The LASSO regression analysis was used to find association between dysconnectivities and BDS score by selecting a subset of the most relevant feature among transdiagnostic and illness-specific functional connectivities (FCs). The LASSO model was trained by 70% of the sample using double cross-validation, with 30% of the sample held out for testing model performance. **(A)** The scatter plot and optimized fits for the BDS scores against the predicted BDS scores in the held-out sample using the trained LASSO model; no significant interaction between the prediction and the group effect was found. **(B)** The variable importance that represented by the absolute (abs) coefficients and selection frequency in the bootstrapping test were ranked and plotted; the orange bar represents the transdiagnostic FC, and the indigo, green, and red bars represent the major depressive disorder (MDD)–specific, bipolar disorder (BIP)–specific, and schizophrenia (SCZ)-specific FCs, respectively. **(C)** The spatial location for each selected FC. Detailed abbreviations for the FCs are described in Supplemental Table S2. L, left hemisphere; HC, healthy control subjects; R, right hemisphere.

ventral tegmental area in mice contribute to social withdrawal and behavioral despair, respectively (38).

BIP-specific ECN disconnectivity was between the ventrolateral prefrontal cortex and the medial parietal cortex. Together with the illness-specific disconnectivities of the bilateral caudate from the posterior medial prefrontal cortex, these findings constitute part of what has been described as "external emotional control circuitry" (i.e., including the ventrolateral prefrontal cortex, ventromedial striatum, pallidum, thalamus) in a consensus model of BIP (29). Furthermore, our BIP-specific findings highlight the putamen-caudate (43%), which has similarly been identified by a large body of multimodal neuroimaging studies of BIP and is at the center of the dopamine hypothesis of this disorder (i.e., a failure of dopamine receptor and transporter homoeostasis) (39).

In SCZ, we found that the ECN, especially the dorsal prefrontal cortex, was disconnected from the DMN, including the posterior inferior parietal cortex and the anterior temporal cortex, which was also reported in a 2018 meta-analysis (40). In fact, we found that the DMN disconnectivities were the most prominent in SCZ (i.e., 47% of the SCZ-specific findings) and were mainly disconnected from the dorsal and ventral attention networks, in line with results reported in a 2019 study pooling data from multiple centers (12). Together, these networks overlap with the cognitive control system (41) and might be especially associated with the working memory deficits in SCZ (42,43). In SCZ, we also identified the only example of increased illness-specific connectivity between the lateral prefrontal cortex in the SVN and the striate cortex in the VSN, which may possibly reflect neural substrates of "aberrant salience" (44).

Transdiagnostic Findings Highlight the Dysconnectivities of SMN

Compared with the dysconnectivities associated with both the SVN areas (10,11) and the thalamus (45–49) that have been reported in the literature as transdiagnostic features in various psychiatric disorders, our findings provide new evidence for the transdiagnostic hypoconnectivity of the SMN. In fact, delays in motor development have long been associated with a higher risk for developing psychosis (50). Previously, in psychiatric patients with significant clinical symptoms, decreased FCs within the motor cortex and its interactions with the subcortical areas have been reported (7,51), and a sensorimotor dimension has been newly added into the Research Domain Criteria framework as a domain for recognizing the importance of motor dysfunctions involved in various psychiatric disorders (52). A very recent study has similarly found reduced within- and between-SMN network connectivity in patients with attention-deficit/hyperactivity disorder, BIP, SCZ, and schizoaffective disorder, again highlighting this transdiagnostic signature (51). The current study further identified that the disconnectivities within the SMN were persistent in patients even after their clinical symptoms were well treated, which suggests that these SMN disconnectivities might be a trait marker for the psychiatric disorders. Moreover, our work dissociated the aberrant SMN connectivity from illness-specific pattern, which emphasized the critical role of the somatosensory-motor system as a transdiagnostic signature in chronic patients. Therefore, these findings highlight the motor-related symptoms and their neural correlates as an

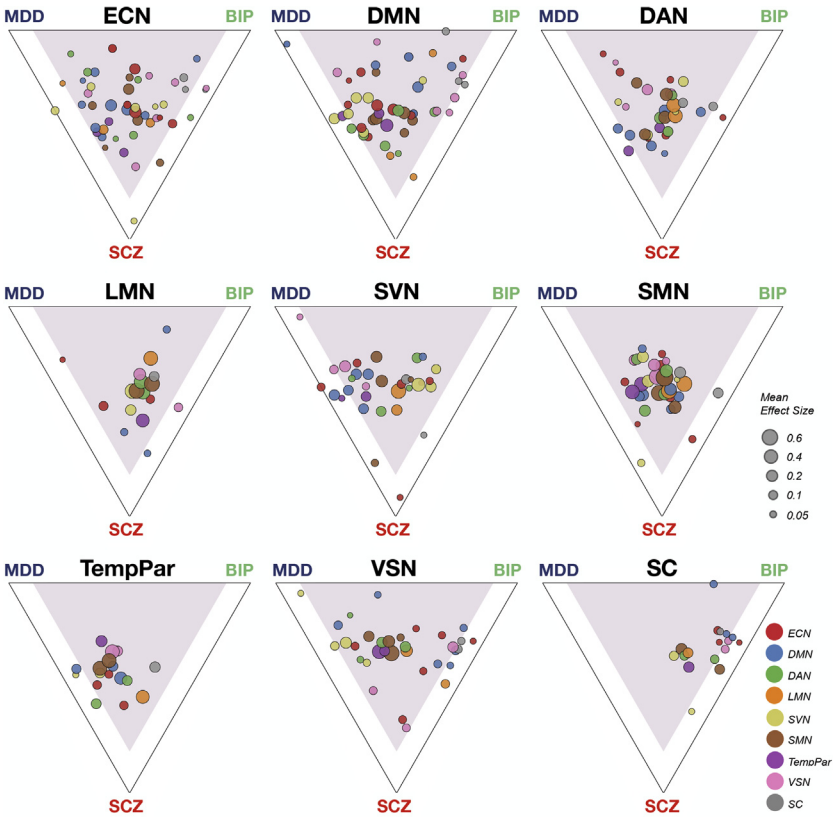

Figure 4. Ternary plot of the effect sizes in 9 large networks. Each dot in the triangle stands for the mean effect sizes of functional connectivities within or between the 9 large networks, including the executive control network (ECN), default mode network (DMN), dorsal attention network (DAN), limbic network (LMN), salience/ventral attention network (SVN), somatomotor network (SMN), temporal-parietal network (TempPar), visual network (VSN), and subcortical network (SC). The position of the dots in the major depressive disorder (MDD)–bipolar disorder (BIP)–schizophrenia (SCZ) triangle is determined by 3 effect sizes (MDD-healthy control group, BIP-healthy control group, and SCZ-healthy control group); for example, the dot is closer to the corner of MDD if the absolute value of the MDD effect size is greater than those for BIP and SCZ. The size of the dot is determined by the averaged MDD, BIP, and SCZ effect size. The color of the dot represents whether the corresponding network is within-network or between-network; for example, the red dots in the ECN triangle represent the mean within-ECN functional connectivity, whereas the green dots represent the mean functional connectivity between the ECN and DAN. Among these ternary plots, we observed that the functional dysconnectivities among diagnoses widely distributed in the ECN, DMN, and VSN without a clear pattern, while the SMN dysconnectivities are located in the center of most triangles, and the SC dysconnectivities are more likely to be observed in BIP. The interactive version of this is available at https://wayalan.github.io/TernaryPlot/ (59).

important component of a general psychopathological factor for psychiatric disorders (53). This may possibly be associated with disruptions in dopaminergic function, as a recent pharmacological neuroimaging study of decreasing dopamine synthesis in healthy participants recently identified resting-state FC in the motor network as having the most significant changes (54).

Neural Network Associations With Working Memory

In this study, we also found a nonsignificant trend (SCZ > BIP > MDD) in the white matter deficit compared with HC subjects, which was consistent with the previous reports that SCZ may have the most severe white matter impairment compared with BIP and MDD (13). In a multivariate model of working memory based on whole-brain FC, the frontoparietal network and the sensorimotor network together contributed more than 50% to the accuracy of the prediction of the working memory performance (55). However, without the illness-specific dysconnectivity identified by the direct comparison between patient groups, it is not clear whether the transdiagnostic dysconnectivity or the illness-specific dysconnectivity contributed more to the white matter deficit. The neural correlates of working memory capacity have been linked with FC within the salience network (between the superior temporal, anterior cingulate, and frontoinsular cortices) (56). Our findings demonstrated that dysconnectivity of salience network was a transdiagnostic neuroimaging feature, and that this transdiagnostic feature was associated with a WM deficit, as measured by the proxy measure of BDS, in all 3 diagnostic groups. However, this index of WM may be insufficiently sensitive for analyzing the working memory impairment, and a more comprehensive cognitive battery should perhaps be applied in any future study to better define possible differences among the diagnostic groups.

Limitations

We acknowledge that lifetime medication exposure may moderate the connectivity, but we lacked the cumulative exposure data to verify this effect. Moreover, although the patterns of dysconnectivity may suggest novel interactions between different psychological mechanisms underlying specific symptomatology in these disorders, such interactions cannot be established simply by reference to previous functional neuroimaging data alone, and require concurrent cognitive measures (57). Targeting the disrupted brain systems reported here in our study, more specified task paradigms or cognitive tests will be the subject of future studies.

Conclusions

The common transdiagnostic profile identified highlights dysconnectivity in a SMN, while the identified illness-specific patterns revealed distinct dysconnectivity of different parts of the prefrontal cortex in different disorders. These findings offer the prospect that prominent psychiatric disorders may share common impairments, possibly linked to general executive functioning, including motor output, as well as unique impairments

that perhaps mediate the more distinctive parts of the psychopathology. Overall, our neuroimaging findings are less in favor of the linear spectrum of psychiatric disorders according to the Kraepelinian dichotomy, with SCZ at the psychotic end of the spectrum, MDD at the other end for mood disorder, and BIP intermediate (1). Instead, our findings present a more complex, ternary relationship among these 3 disorders (Figure 4).

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