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Aberrant Large-Scale Network Interactions Across Psychiatric Disorders Revealed by Large-Sample Multi-Site Resting-State Functional Magnetic Resonance Imaging Datasets

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***Background and Hypothesis*: Dynamics of the distributed sets of functionally synchronized brain regions, known as large-scale networks, are essential for the emotional state and cognitive processes. However, few studies were performed to elucidate the aberrant dynamics across the large-scale networks across multiple psychiatric disorders. In this paper, we aimed to investigate dynamic aspects of the aberrancy of the causal connections among the large-scale networks of the multiple psychiatric disorders. *Study Design*: We applied dynamic causal modeling (DCM) to the large-sample multi-site dataset with 739 participants from 4 imaging sites including 4 different groups, healthy controls, schizophrenia (SCZ), major depressive disorder (MDD), and bipolar disorder (BD), to compare the causal relationships among the large-scale networks, including visual network, somatomotor network (SMN), dorsal attention network (DAN), salience network (SAN), limbic network (LIN), frontoparietal network, and default mode network. *Study Results*: DCM showed that the decreased self-inhibitory connection of LIN was the common aberrant connection pattern across psychiatry disorders. Furthermore, increased causal connections from LIN to multiple networks, aberrant self-inhibitory connections of DAN and SMN, and increased self-inhibitory connection of SAN were disorder-specific patterns for SCZ, MDD, and BD, respectively. *Conclusions*: DCM revealed that LIN was the core abnormal network common to psychiatric disorders. Furthermore, DCM showed disorder-specific abnormal patterns of causal connections across the 7 networks. Our findings suggested that aberrant dynamics among the large-scale networks could be a key biomarker for these transdiagnostic psychiatric disorders.**

Key words: dynamic causal modeling/schizophrenia/major depressive disorder/bipolar disorder

Introduction

Large-scale functional networks can be defined as distributed sets of brain regions synchronically activated at rest or during task performance.[1–3] They are thought to reflect distinct cognitive processes or mental states, including visual network (VIN), somatomotor network (SMN), dorsal attention network (DAN), salience network (SAN), limbic network (LIN), frontoparietal network (FPN), and default mode network (DMN).[1,2,4–8] An increasing number of studies have recently been conducted to investigate such abnormal large-scale functional network structures in psychiatric disorders using resting-state functional magnetic resonance imaging (rs-fMRI).[9–17] In particular, aberrant interactions between triple networks, including the DMN (related to the inner cognitive process), FPN (related to external goal-directed regulation), and SAN (related to salience processing) are thought to have important roles in multiple psychiatric disorders.[13,18,19] Aberrant SAN interactions with the DMN and FPN make differentiating self-representation and environmental salience processing challenging in patients with schizophrenia (SCZ).[10,15] Increased functional connectivity (FC) between the SAN and DMN and decreased connectivity between the DMN and FPN have been observed in patients with major depressive disorder (MDD)[20] and bipolar disorder (BD),[21] reflecting an abnormal balance between self-monitoring processing and external cognitive flexibility in affective disorders.[13]

However, most studies reporting the aberrancy of these networks in psychiatric disorders focused on the comparisons between patients with a single psychiatric disorder and healthy controls (HCs). Although only a limited number of studies directly compared multiple psychiatric disorders,[22–27] their results were inconsistent. For example, while Li et al. found that FPN-DMN hyperconnectivity and VIN-DMN hypoconnectivity were commonly involved across SCZ, BD, and attention-deficit hyperactivity disorder using data consisting of a total of 212 individuals,[27] another study found VIN-FPN and SAN-LIN hyperconnectivity, and SAN-DMN and DMN-SMN hypoconnectivity across SCZ, MDD, and BD upon applying the dynamic FC analysis in a total of 610 individuals.[22] Thus, further direct comparisons across multiple psychiatric disorders are indispensable for establishing consistent evidence for the commonality and disorder-specific features of neural modules across psychiatric disorders.

Furthermore, previous studies only investigated aberrant FC between networks whose temporal properties were static rather than dynamic. Since whole-brain synchronized neural dynamics are essential for the control of functionally remote brain networks[28–32] and are related to the changes in the emotional state and cognitive processes,[33,34] revealing the aberrant dynamics of the different brain systems across multiple psychiatric disorders is important.

Dynamic causal modeling (DCM) has been used to investigate the causal relationships among brain networks.[35,36] While conventional DCM analyses have been applied to task-based fMRI studies, new DCM methods have been used to estimate the causal relationships among the regions of interest (ROIs) for rs-fMRI,[37–44] which cannot be captured by an FC analysis. The DCM can also capture the self-inhibitory connection strength of each ROI. Several previous studies have investigated the abnormal causal relationships across large-scale networks in psychiatric disorders by using the DCM method for rs-fMRI. Xi et al. demonstrated that patients with SCZ had reduced SAN-centered cross-network connections, compared to HCs.[45] Li et al. demonstrated that patients with MDD had reduced causal connections within the DMN and bidirectional DMN-SAN connections, compared to HCs.[46] However, to the best of our knowledge, no study has conducted DCM analyses for direct network comparisons across multiple psychiatric disorders.

In the current study, we investigated the alteration of the dynamic aspects in large-scale networks between psychiatric disorders, including 4 different groups, HC, SCZ, BD, and MDD, using large-sample multi-site datasets. First, we applied DCM to a large-sample dataset of 739 participants from 4 imaging sites to estimate the causal relationships among the networks. We adopted the parametric empirical Bayes (PEB) framework, which makes it possible to consider both the mean and uncertainty (variance) of parameter estimation to infer group differences using a Bayesian hierarchical model across the parameters.[47,48] Thus, we investigated both the commonality and distinction of aberrancy between HC, SCZ, MDD, and BD in 7 large-scale functional networks.

We hypothesized that aberrant dynamics between the 7 large-scale networks would exist across SCZ, MDD, and BD, and that these aberrancies would be associated with symptom severity. Based on previous studies reporting aberrancies of the triple networks,[10,13,15,20,21] we hypothesized: (1) decreased SAN-to-FPN causal connections would be common in SCZ, MDD, and BD, (2) SAN-to-DMN causal connections would be increased in SCZ and decreased in MDD and BD, and (3) BD would have more decreased SAN-to-DMN and bidirectional DMN-FPN connections than would MDD.

Methods

Dataset and Participants

A total of 739 rs-fMRI images were used from the database of the Japanese Strategic Research Program for the Promotion of Brain Science DecNef Consortium (https://bicr.atr.jp/decnefpro/),[49,50] and additional brain images were

obtained from the Department of Psychiatry, University of Tokyo, following the contribution of the database. Participants with 3 different disorders and HCs were recruited to the study from 3 sites, which included 4 different protocols: The University of Tokyo (UTO) protocol, which was held at the University of Tokyo; Kyoto University Tim Trio (KUT) and Kyoto University Trio (KTT) protocols, which were performed at the Kyoto University; and the Center of Innovation at Hiroshima University (COI) protocol, which was performed at the Hiroshima University. A total of 390 HCs from 4 protocols, 143 patients with SCZ from 3 protocols, 163 patients with MDD from 3 protocols, and 43 patients with BD from one protocol were recruited. The demographic characteristics of all the participants and MRI parameters of all the sites are summarized in table 1, supplementary table S1, and supplementary material. All participants provided written informed consent, and the study was approved by the Ethics Committees of the University of Tokyo and the Faculty of Medicine, the University of Tokyo, the Committee on Medical Ethics of Kyoto University, and the Ethics Committee of Hiroshima University. Each participant underwent rs-fMRI and high-resolution anatomical MRI. As we eliminated the participants whose head movement was greater than 2 mm, 9 HCs, 4 participants with SCZ, and 8 participants with MDD were excluded from our analyses. Furthermore, one HC and 3 participants with SCZ were excluded owing to the misregistration of the fMRI data into the standard space during preprocessing. Thus, 714 participants were included in our analysis.

The Positive and Negative Syndrome Scale (PANSS) was used to evaluate symptom severity[51] for 128 participants with SCZ (8 participants were missing). The Beck Depression Inventory revised version (BDI-II)[52] was used to assess subjective depressive symptoms in patients with MDD at the KUT and COI. As for patients with MDD at UTO, the BDI-II was used to assess the subjective depressive symptoms of 50 participants with MDD, and the Center for Epidemiologic Studies Depression Scale[53] was used to assess the depressive symptoms of 22 participants with MDD (one and 4 patients were missing in the BDI-II and Center for Epidemiologic Studies Depression Scale, respectively). Center for Epidemiologic Studies Depression Scale scores were transformed into BDI-II scores, based on a previous study.[54] The BDI-II was also used to assess the depressive symptoms of 15 participants with MDD using the KUT protocol. The Young Mania Rating Scale (YMRS)[55] was used to assess manic symptom severity for the 43 participants with BD.

At the 3 sites (UTO, KUT, and KTT protocols), the medication equivalent doses were estimated as follows: Antipsychotics using chlorpromazine (CPZ) equivalent dose for the patients with SCZ, MDD, and BD; and antidepressants using imipramine (IMP) equivalent dose for the patients with MDD and BD. Since we only obtained information on whether the patients took benzodiazepines, we used benzodiazepine as a binarized variable. Since we did not have any data for medication information from the COI, we excluded the participants in COI from the analyses considering the effect of medication and clinical severity.

Preprocessing of rs-fMRI

fMRI data were preprocessed using the FMRIB software library (FSL version 6.0.3; http://www.fmrib.ox.ac.uk/fsl/). Skull stripping of the structural images was performed using Brain Extraction Tool.[56] We discarded the first 4 functional volumes for the datasets from UTO, KUT, and COI, and the first 5 volumes for the dataset from KTT, which corresponded to 10 seconds of scanning. Next, we applied head motion correction by realigning the time series to the first volume using MCFLIRT,[57] field-map-based distortion correction, slice timing correction, and spatial smoothing with a full-width half-maximum of 5 mm with SUSAN.[58] Registration was performed using FLIRT[57] and FNIRT.[59] Each functional image was registered to the participant's high-resolution brain-extracted structural image and the standard Montreal Neurological Institute 2 mm brain. Patients with head motion greater than 2 mm were excluded. We also examined the group differences in the translation and rotation of head movements.[60] The details are described in supplementary material. We compared these parameters (analysis of variance,

Table 1. Demographic Characteristics of the Participants

	HC			SCZ			MDD			BD		
	N	M/F	Age (y)	N	M/F	Age (y)	N	M/F	Age (y)	N	M/F	Age (y)
UTO	71	27/44	39.8 ± 9.3	52	29/23	29.7 ± 9.8	77	41/36	39.0 ± 12.1	43	25/18	33.8 ± 11.5
KTT	75	48/27	28.9 ± 9.1	46	25/21	38.2 ± 9.6	0	—	—	0	—	—
KUT	159	93/66	36.5 ± 13.6	45	21/24	41.4 ± 10.8	16	10/6	42.6 ± 12.5	0	—	—
COI	85	29/56	44.6 ± 9.4	0	—	—	70	31/39	45.0 ± 12.5	0	—	—

Note: HC, healthy controls; SCZ, schizophrenia; MDD, major depressive disorder; BD, bipolar disorder; M, male; F, female; UTO, The University of Tokyo; KTT, Kyoto University Trio; KUT, Kyoto University Tim Trio; COI, Center of Innovation at Hiroshima University.

$P < .05$; supplementary table 3) and added them as nuisance regressors in the group comparisons of the DCM.

Region Specification for the DCM Analysis

We classified the whole cortical brain regions into 7 functionally different brain networks[2] (https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation_Yeo2011): VIN, SMN, DAN, SAN, LIN, FPN, and DMN (figure 1).

Dynamic Causal Modeling

We employed spectral DCM implemented in SPM12 (version R7497, http://www.fil.ion.ucl.ac.uk/spm/software/) for preprocessed rs-fMRI data. DCM employs a neuronally plausible model for the observed blood-oxygen-level-dependent signals and allows the estimation of causal relationships between the different nodes of the network. Details of DCM are in supplementary information. The blood-oxygen-level-dependent time series of the ROIs were extracted, and non-neural signals of the white matter and cerebrospinal fluid and 6 head motion parameters were regressed out. We used a fully connected model with bidirectional connections between any pair of ROIs for each participant. We estimated 49 free parameters because the fully connected model contained 7 ROIs.

PEB for Group DCM

We used a standard PEB analysis process to conduct a group analysis and Bayes model averaging.[47,48] PEB took participant-specific connectivity parameters estimated from the spectral DCM to the group level, where they were modeled using a general linear model under the Bayesian hierarchical framework. Thus, the estimated connection strengths and their uncertainties were considered from the subject to the group level in the group analysis. The details of these analyses are in supplementary material.

We first compared the causal connections across the 4 groups under the PEB framework (SCZ vs. HC, MDD vs. HC, BD vs. HC, MDD vs. SCZ, BD vs. SCZ, and BD vs. MDD). We added age, sex, site, and translation and rotation parameters as nuisance covariates to the models. Thereafter, the effects of clinical severity and medication on the causal connections were tested for each psychiatric disorder group, including age, sex, and site as nuisance covariates in the models. We did not have any data on the medication effects for the patients with COI; therefore, we conducted the analyses using participants at 3 sites: UTO, KTT, and KUT (without COI). We focused on the connection parameters with abnormal connection values in psychiatric disorders. The effects of the PANSS, CPZ, and IMP on SCZ were assessed. The effects of BDI-II scores, CPZ dose, and IMP dose on MDD were assessed. The effects of the YMRS, CPZ, and IMP were assessed for BD. We adopted the definition of "strong evidence" by thresholding the effects at 95% posterior probability (PP).[61] The details of these analyses are in supplementary material.

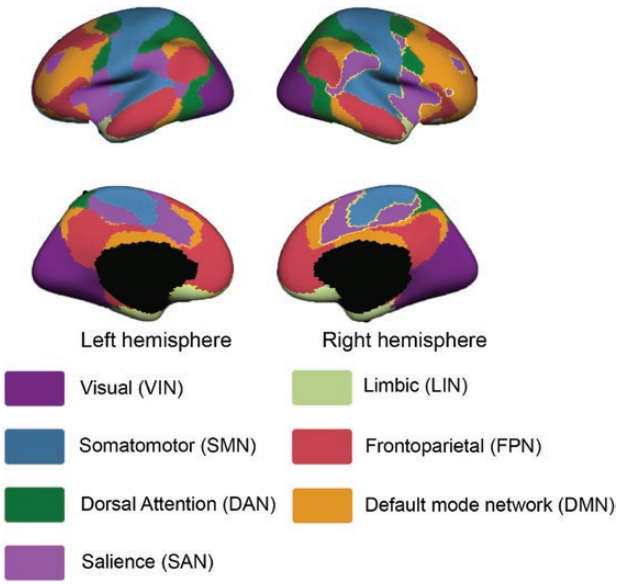

Fig. 1. Seven large-scale functional networks defined by Yeo's atlas. The whole cortical brain regions were parcellated into 7 functionally different brain networks, VIN, SMN, DAN, SAN, LIN, FPN, and DMN.

Results

Group Comparison of the Causal Connections Across HCs, and Patients With SCZ, MDD, and BD

Average DCM parameters for each group are shown in figure 2. SCZ had increased causal connections from LIN to multiple networks (ie, VIN, SMN, DAN, SAN, and FPN), increased self-inhibitory connection of SMN, and decreased self-connection of LIN and DMN, compared to HCs ($PP > .95$; figure 3). MDD showed the increased self-inhibitory connection of SMN, decreased FPN-to-VIN connection, and decreased self-connection of DAN and LIN, compared to HCs ($PP > .95$). BD showed increased self-connection of SAN and decreased self-connection of LIN, compared to HCs ($PP > .95$).

The comparison between the disease groups showed MDD had increased SMN-to-VIN connection, increased self-connection of DMN, decreased connection from LIN to multiple networks (ie, VIN, SMN, DAN, SAN, and FPN), and from FPN to SMN, and decreased self-connection of DAN and LIN, compared to SCZ ($PP > .95$). BD showed increased SMN-to-VIN connections, increased self-connection of SAN, decreased LIN-to-SMN connections, and decreased self-connection of LIN, compared to SCZ ($PP > 0.95$). BD showed increased self-connection of SAN and decreased self-connection of LIN, compared to MDD ($PP > .95$).

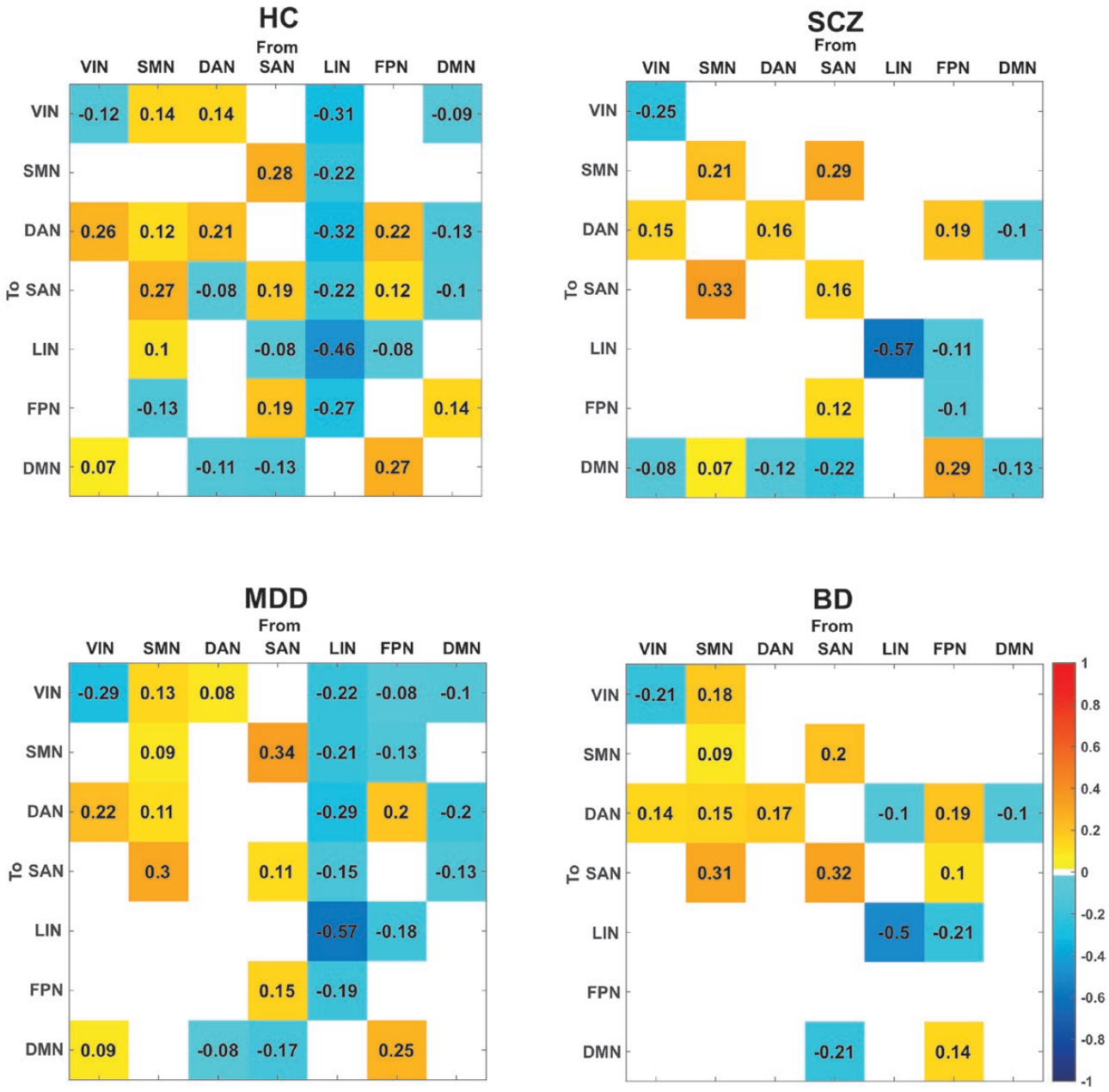

Fig. 2. Average causal connection for each group. Average causal connection parameters for all the connections among the 7 networks for HC, SCZ, MDD, and BD are shown. Connection values whose posterior probabilities are larger than 95% are depicted in color. Abbreviations: HC, healthy controls; SCZ, schizophrenia; MDD, major depressive disorder; BD, bipolar disorder; VIN, visual network; SMN, somatomotor network; DAN, dorsal attention network; SAN, salience network; LIN, limbic network; FPN, frontoparietal network; DMN, default mode network.

Associations Between the DCM Connection Parameters, Clinical Severity, and Medication Effects

Self-connection of DMN was positively associated and self-connection of LIN was negatively associated with the PANSS positive symptom scores in SCZ (figure 4). SMN-to-LIN connection was negatively associated with the PANSS negative symptom scores in SCZ. Furthermore, SMN-to-VIN connection was positively associated and VIN-to-DMN connection and self-connection of DMN were negatively associated with the PANSS general psychopathology scores in SCZ. In the MDD group, self-connection of DAN was positively associated with the BDI-II scores. In the BD group, self-connection of SAN was positively associated with the YMRS scores.

We found a negative association between CPZ and the self-inhibitory connection of LIN in SCZ (supplementary figure 1). We also found a negative relationship between

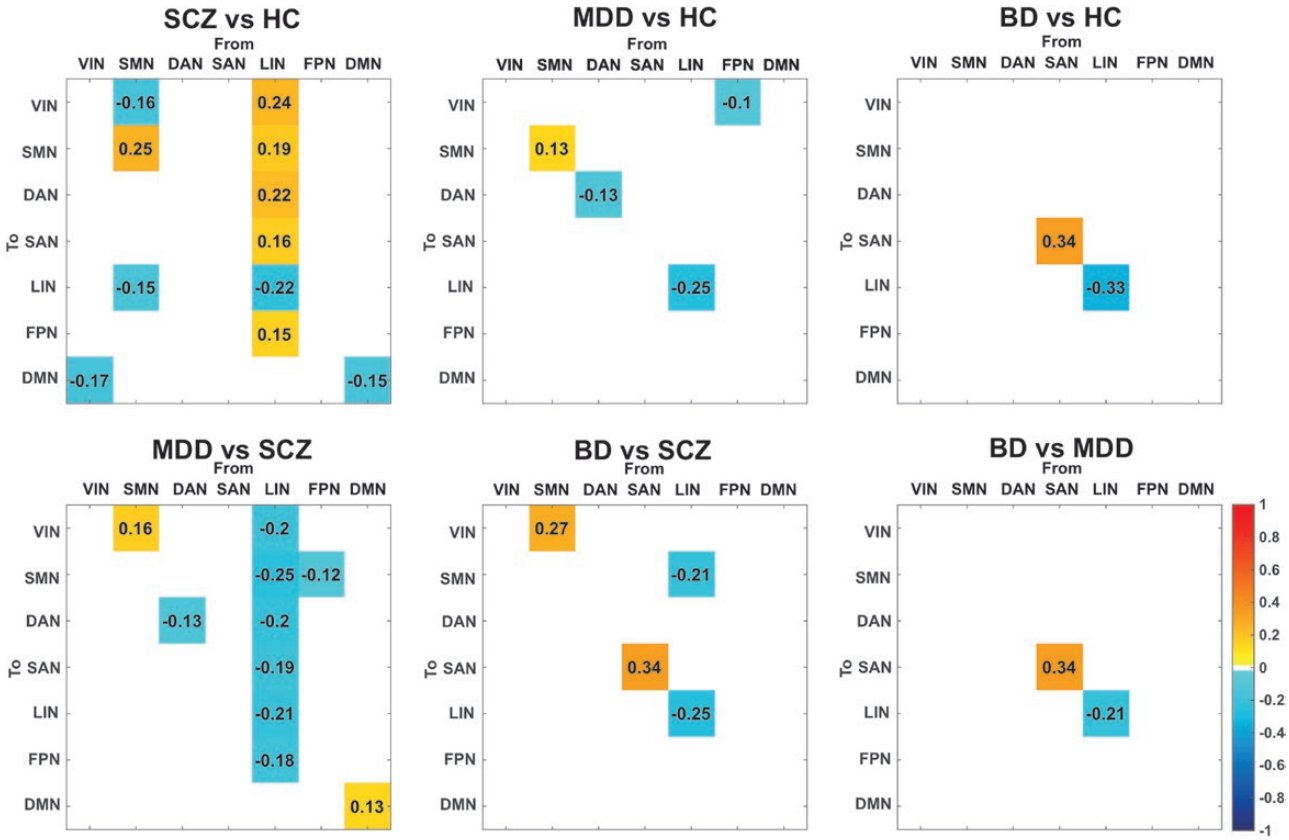

Fig. 3. Group comparison of the causal connection parameters across HC, SCZ, MDD, and BD. The connection parameters whose posterior probability is more than .95 (strong evidence) are shown. Edges colored in yellow to red/blue mean that the causal connection is larger/smaller in SCZ than in HC, in MDD than in HC, in BD than in HC, in MDD than in SCZ, in BD than in SCZ, and in BD than in MDD, respectively (from left to right in the top panel and in the bottom panel) (for color figure refer online version).

IMP equivalent and VIN self-connection in patients with MDD and BD.

Discussion

We investigated causal relationships among the 7 large-scale functional networks across SCZ, MDD, and BD by using large-sample multi-site datasets. DCM showed that decreased self-inhibitory connection of LIN was a common aberrant pattern across psychiatric disorders. Each disorder group had a specific pattern: (1) increased LIN-to-multiple-network connections in SCZ, (2) aberrant self-inhibitory connections of DAN and SMN and decreased FPN-to-VIN connections in MDD, and (3) increased self-inhibitory connection of SAN in BD. These aberrant connections were also associated with the clinical symptoms.

The strength of this study was that it investigated the aberrancy of the dynamic aspects of the 7 large-scale networks across the multiple psychiatric disorders with DCM by using large-sample multi-site datasets. To the best of our knowledge, our team is the first to demonstrate that the decreased self-inhibitory connection of LIN was a common aberrant network feature across the multiple psychiatric disorders, which could not be demonstrated by other previous studies investigating aberrant network-connection patterns among the transdiagnostic psychiatric disorders.[17,22,27,62] This finding suggested that DCM would provide new insights into the pathophysiological mechanism of various psychiatric disorders, which could not be captured by other studies applying conventional FC analyses.[17,22,27,62]

The common and disorder-specific features found in previous studies and in the present study were inconsistent. Baker et al. showed that graded disruptions in FPN were associated with the presence of affective and psychotic illnesses,[62] whereas another study showed aberrant SAN-FPN and DMN-FPN connectivity was a common feature across the transdiagnostic psychiatric disorders.[17] Several factors could explain the inconsistencies between the findings of the previous studies and our study. First, sample sizes were different across the studies. Future studies with much larger sample sizes are needed. Second, several studies investigated different psychiatric disorders.[17,27] For example, Brandl et al.[63] found no common features among the large-scale networks across MDD, anxiety disorder, and chronic pain, whereas we found that self-connection of LIN was the common

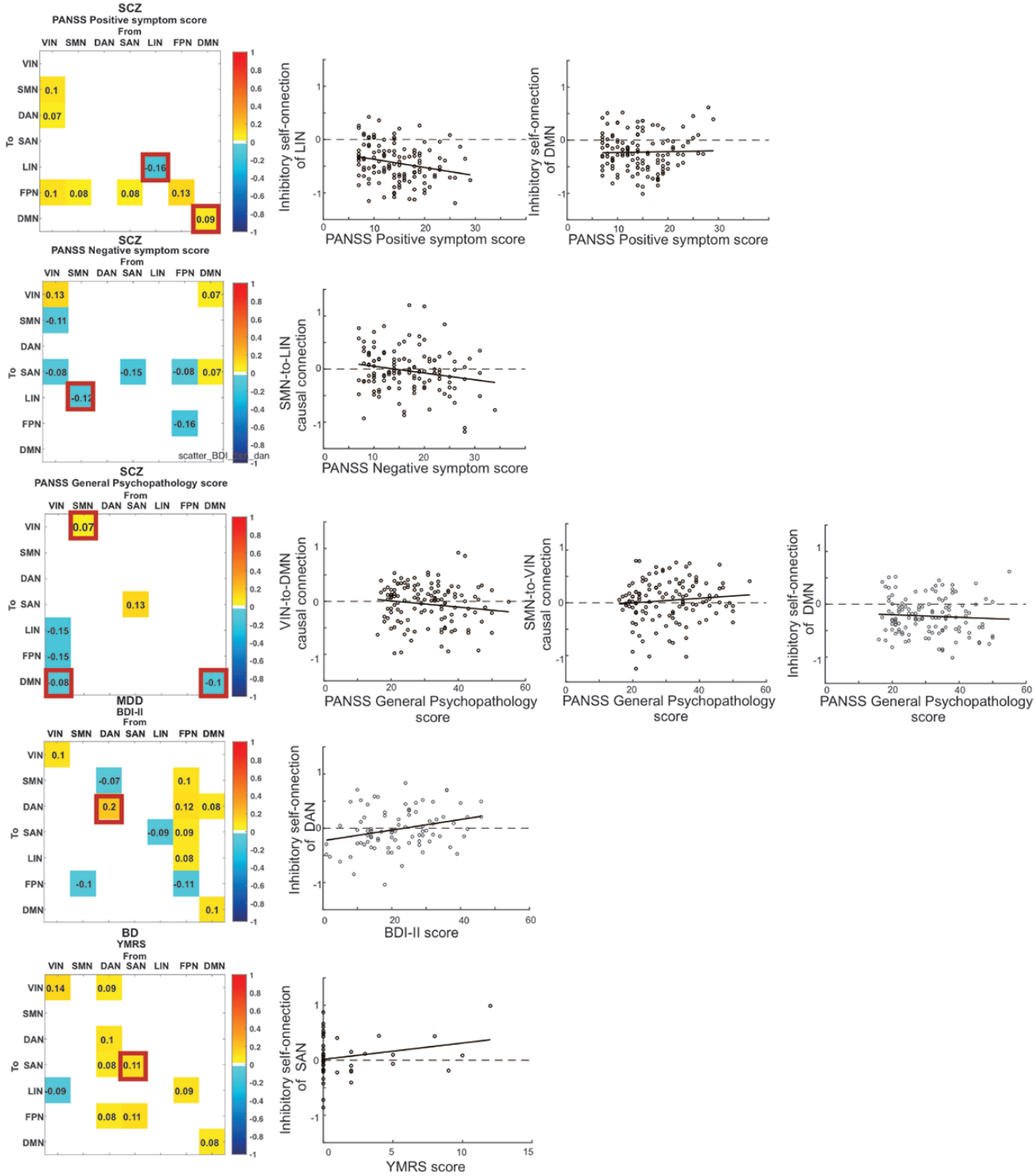

Fig. 4. Associations between the causal connection parameters and symptom severity. The connections which have strong evidence (P*P* > .95) are depicted in color. Those connections that have associations with the clinical ratings and abnormal connections in psychiatric disorders are enclosed by red squares (for color figure refer online version). Scatter plots between those connections and clinical ratings are also shown. Abbreviations: the Positive and Negative Syndrome Scale; BDI-II, the Beck Depression Inventory revised version; YMRS, the Young Mania Rating Scale; P*P*, posterior probability.

feature across SCZ, MDD, and BD. This inconsistency may be because the dimension of the continuum spectrum across MDD, anxiety disorder, and chronic pain differed from that across MDD, SCZ, and BD. Considering the dimension of the continuum spectrum is important for exploring aberrant network connections across various psychiatric disorders. Third, previous studies have focused on triple-network relationships (DMN, FPN,

and SAL), without considering the effects of other functional networks.[13,20,45]

DCM demonstrated that the decreased self-inhibitory connection of LIN was the common aberrant connection pattern across psychiatric disorders. The LIN, defined in Yeo's atlas,[2] includes the orbitofrontal and temporal cortices. The orbitofrontal cortex is associated with the affective evaluation of rewards and punishments,[64] expectations, motivation, and decision-making behavior.[65,66] The temporal cortex is involved in processing sensory input,[67] memory,[68] and language recognition.[69] Thus, functional impairment of LIN results in multiple psychopathological mechanisms across multiple psychiatric disorders. In actuality, abnormal network structures in LIN and aberrant FC associated with the LIN were consistently found in SCZ[70–74] and associated with the severity of psychosis or hallucination.[75,76] Our results also showed that the self-connection of LIN had a negative correlation with the PANSS positive symptom scores in patients with SCZ. Abnormal structural and functional frontotemporal connectivity, including LIN, has been reported in MDD[77–79] and is correlated with symptom severity.[79] Abnormal network structure and low-frequency amplitude fluctuations in the LIN have been shown in BD[80–82] in association with mood dysregulation.[81] Furthermore, the self-inhibitory connection of LIN was decreased in MDD and BD, than in SCZ. This finding indicated that the impairment of the self-inhibitory connection of LIN was directly linked to mood dysregulation,[83] which leads to the affective disorder.[81,83] DCM showed that LIN took more excitatory influences on VIN, SMN, DAN, SAN, and FPN in SCZ, thereby inducing aberrant FC among these distributed networks. This finding could partly explain the functional hypoconnectivity among LIN, SAN, FPN, and DMN as SCZ-specific patterns, as revealed by previous meta-analysis findings.[84] Furthermore, SCZ had an increased causal connection from LIN to other networks, compared to MDD, while SCZ had an increased causal connection from LIN to only SMN compared to BD. This finding suggested that BD is closer to SCZ than to MDD on the continuum spectrum of psychiatric disorders and that SCZ is at one end of the spectrum.[85]

MDD had reduced self-connection of DAN and FPN-to-VIN connection and increased self-connection of SMN, compared to HC. Previous studies found impaired visual and prefrontal preprocessing during the control of visual information selection and maintenance in MDD.[86] Furthermore, compared to HCs, patients with MDD have decreased nodal degrees in DAN and SMN, which are involved in cognitive executive processes, emotional processing, and sensory/motor functions in MDD.[87] This finding could also be strengthened by our findings, which showed positive associations between BDI-II scores and self-inhibitory connections of DAN. Patients with MDD showed no different self-connections of DAN, compared to patients with BD, which suggested that BD was closer to MDD than to HC, or SCZ in externally oriented attention processing. In contrast, BD had an increased self-inhibitory connection of SAN compared to HCs, SCZ, and MDD. Reduced within-connectivity of SAN has been consistently reported in patients with BD,[21,85,88,89] which could be explained by the stronger self-inhibitory connection of SAN. We also found that self-inhibitory effects on SAN were associated with the YMRS scores in BD, thereby suggesting that SAN has an important role in mood regulation.

The current study has several limitations. First, the sample size of patients with BD was smaller than that of the other groups. Second, we had limited medication data for the datasets and did not test for nonmedicated patients. Third, we found that the DCM parameter of the self-connection of LIN was negatively associated with the CPZ dose in SCZ and the IMP dose in MDD and BD. Furthermore, we could not estimate the accurate effects of benzodiazepines on DCM parameters because we only obtained information on whether the patients took benzodiazepines. Therefore, the difference in the DCM parameter of self-connection of LIN between HC, and patients with SCZ, MDD, and BD may be because of medication effects. Fourth, our spatial resolution was quite low because each network adopted by the 7-network Yeo parcellation consisted of several smaller functionally different regions. Fifth, we did not have any data of the illness duration or data of the clinical states (ie, acute vs. remitted); therefore, we did not estimate their effects on the causal connections.

DCM has revealed that LIN is a common abnormal network in psychiatric disorders. Furthermore, DCM showed disorder-specific abnormal causal relationship patterns across 7 networks. Thus, DCM is useful for elucidating the dynamic aspects of the aberrancy of causal relationships among large-scale networks of multiple psychiatric disorders.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

Acknowledgment

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