

Research Article

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Identification of common neural substrates with connectomic abnormalities in four major psychiatric disorders: A connectome-wide association study

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Abstract

Background: Recent imaging studies of large datasets suggested that psychiatric disorders have common biological substrates. This study aimed to identify all the common neural substrates with connectomic abnormalities across four major psychiatric disorders by using the data-driven connectome-wide association method of multivariate distance matrix regression (MDMR).

Methods: This study analyzed a resting functional magnetic resonance imaging dataset of 100 patients with schizophrenia, 100 patients with bipolar I disorder, 100 patients with bipolar II disorder, 100 patients with major depressive disorder, and 100 healthy controls (HCs). We calculated a voxel-wise $4,330 \times 4,330$ matrix of whole-brain functional connectivity (FC) with 8-mm isotropic resolution for each participant and then performed MDMR to identify structures where the overall multivariate pattern of FC was significantly different between each patient group and the HC group. A conjunction analysis was performed to identify common neural regions with FC abnormalities across these four psychiatric disorders.

Results: The conjunction of the MDMR maps revealed that the four groups of patients shared connectomic abnormalities in distributed cortical and subcortical structures, which included bilateral thalamus, cerebellum, frontal pole, supramarginal gyrus, postcentral gyrus, lingual gyrus, lateral occipital cortex, and parahippocampus. The follow-up analysis based on pair-wise FC of these regions demonstrated that these psychiatric disorders also shared similar patterns of FC abnormalities characterized by sensory/subcortical hyperconnectivity, association/subcortical hypoconnectivity, and sensory/association hyperconnectivity.

Conclusions: These findings suggest that major psychiatric disorders share common connectomic abnormalities in distributed cortical and subcortical regions and provide crucial support for the common network hypothesis of major psychiatric disorders.

Introduction

Making a diagnosis based on a cluster of clinical symptoms according to the diagnostic classification system and prescribing appropriate psychotropics play a central role in modern psychiatric practice. However, the overlap of clinical symptoms in patients with different disorders suggests that psychiatric disorders may share common neural substrates. For example, affective symptoms are common in patients with schizophrenia; depressive and mania symptoms were reported in 80 and 20% of patients with schizophrenia, respectively [1]. A cross-sectional study also revealed a high prevalence of current hallucinations in hospitalized psychiatric patients with mixed bipolar depression (22.9%), bipolar manic depression (11.2%), bipolar depression (10.5%), and unipolar depression (5.9%) [2]. Nevertheless, most previous structural or functional imaging studies have focused on patients with one psychiatric disorder and have rarely tested the aforementioned hypothesis directly in the same study. Meta-analysis of imaging studies across different diagnostic groups is an important approach for testing the hypothesis of the common neural substrates. A meta-analysis of 193 voxel-based morphometry studies comprising 15,892 individuals across 6 diverse diagnostic groups (schizophrenic disorder [SZ], bipolar disorder [BD], major depressive disorder [MDD], substance addiction, obsessive-compulsive disorder, and anxiety disorder) with matched controls revealed that gray matter loss converged across

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diagnoses in three regions: dorsal anterior cingulate cortex and bilateral insula [3]. Functional connectivity (FC) analysis indicated that these three regions form a tightly interconnected network called the salience network. Another meta-analysis of 283 whole-brain functional magnetic resonance imaging (fMRI) studies during cognitive control tasks [4] in 5,493 patients with various disorders (SZ, BD, MDD, anxiety disorders, and substance abuse disorders) found transdiagnostic abnormal activations in several frontal and parietal regions in the multidemand network and salience network. Another meta-analysis of 226 task-related functional imaging studies on mood disorders, posttraumatic stress disorder, and anxiety disorders also revealed that the most consistent transdiagnostic abnormalities in task-related brain activity converge in regions that are primarily associated with inhibitory control and salience processing [5]. These results provided preliminary evidences for the hypothesis of common neural substrates in major psychiatric disorders.

Recently, increasing numbers of studies adopted a transdiagnostic approach, which recruited patients with various psychiatric disorders and controls in the same study, and showed the potential to identify the common neural substrates across various psychiatric disorders directly. Several studies have successfully identified common deficits of cognitive controls [6], dopamine synthesis [7], gray matter volume [8], and network-level FC [9] among various psychiatric disorders. Our previous FC study focused on the thalamus and identified the common patterns of thalamocortical dysconnectivity in four major psychiatric disorders (SZ, BD-I, BD-II, and MDD) [10]. However, it is unclear whether common FC abnormalities also exist in structures other than the thalamus. To determine all the common structures with FC abnormalities in major psychiatric disorders by using FC analyses, a brain-wise map of FC abnormalities in each disorder is required. In this study, we proposed that the recently developed connectome-wide association method of multivariate distance matrix regression (MDMR) [11] was suitable for the purpose and able to identify all common neural substrates with FC abnormalities across major psychiatric disorders. MDMR analysis was developed for high-dimensional data sets related to genetics or imaging, and it enables researchers to relate p variables to additional m factors collected from N individuals, where $p > N$ [12]. Shehzad *et al.* [11] applied MDMR to a connectome-wide association study and provided a detailed evaluation of its statistical properties. Following the initial introduction of the method, MDMR has been used to identify connectivity deficits in youths with psychosis-spectrum symptoms [13], individuals at a clinically high risk of psychosis [14], and those with a transdiagnostic risk of mental illness [15]. This method was also used to identify the FC features in different groups according to data-driven phenotypic categories [16]. In these studies, a pair-wise FC matrix of each voxel with variable resolutions was first calculated, and MDMR was then performed to identify voxels whose FC patterns with all other voxels were significantly associated with a clinical phenotype of interest. Subsequently, a follow-up seed-based FC analysis of the structures identified by using MDMR was usually adopted to understand the nature of FC abnormalities and to compare them with those in the literature. Importantly, as the analysis is based on the statistical inference of voxels and typically provides a complete brain-wise map of connectomic abnormalities for the effect of interest, neural substrates with FC abnormalities across different psychiatric disorders can be identified.

Here, this study aimed to demonstrate a brain-wise map of common neural structures with connectomic abnormalities in four major psychiatric disorders, namely SZ, BD-I, BD-II, and MDD, through a data-driven connectome-wide association study. We

focused on these four psychiatric disorders because FC abnormalities in these disorders were the major research interests of our laboratory and we had collected a single-site resting fMRI dataset of these disorders with enough sample sizes for MDMR analysis. First, we performed MDMR to identify regions where the overall multivariate pattern of FC was significantly different between the patients of these four groups and controls. A conjunction analysis was performed to identify common neural structures with connectomic abnormalities in the four groups of patients. Then, we focused on the pair-wise FCs of these identified regions and conducted a follow-up analysis to understand the major pattern of FC abnormalities. The results of this study may provide a brain-wise map of common connectomic abnormalities in the four major psychiatric disorders and further evidence for the common network hypothesis of major psychiatric illness.

Methods

Participants

This study included 100 patients with SZ, 100 patients with BD-I, 100 patients with BD-II, 100 patients with MDD, and 100 healthy controls (HCs) (Table 1). The diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. These participants were selected from a single-site resting fMRI dataset (see Supplementary Table 1 for demographic properties of the dataset) to match the age and sex of the five groups as much as possible. The mean ages of the patients with SZ, BD-I, BD-II, MDD, and HC were 36.0, 38.3, 37.5, 37.7, 36.4, and 36.4 years, respectively, and no significant difference was noted among these five groups. However, the BD-II group in the dataset was the smallest, and hence, our BD-II sample could not be matched to the other groups by sex. The mean illness durations of the patients with SZ, BD-I, BD-II, and MDD were 12.5, 12.4, 12.1, and 7.9 years, respectively. The SZ, BD-I, and BD-II groups were matched by the illness duration. The MDD group has shorter illness duration than the other three groups because of the late onset. All participants were recruited from outpatient and inpatient units of Taipei Veterans General Hospital in Taiwan. The participants with the following conditions were excluded: (a) substance abuse or dependence over the preceding 6 months; (b) a history of head injuries that resulted in sustained loss of consciousness, cognitive sequelae, or both; and (c) neurological illnesses or any other disorder that affects cerebral metabolism. HCs were recruited through advertisements. An experienced psychiatrist used the MINI for screening to exclude candidates with major psychiatric illnesses. Furthermore, healthy candidates whose first-degree relatives had axis-I disorders, including SZ, MDD, and BD, were excluded. The clinical status of the patients with SZ was characterized using the Positive and Negative Syndrome Scale (PANSS). The clinical assessments used for the BD-I, BD-II, and MDD patients were the Young Mania Rating Scale (YMRS) and Montgomery Åsberg Depression Rating Scale (MADRS) (Table 1). However, some of patients with BD-I and BD-II only used self-rated visual analog mood scales to rate their mood states, and their MADRS and YMRS ratings were not available. These patients were receiving treatment with various atypical antipsychotics, antidepressants, and mood stabilizers before participating in the experiment. All procedures were approved by the Institutional Review Board of Taipei Veterans General Hospital in accordance with the Declaration of Helsinki, and all participants provided written informed consent after they were informed of the experimental procedures.

Table 1. The enrolled participants' demographic data.

N = 500	SZ	BD-I	BD-II	MDD	HC	F	p
Sex (M/F)	50/50	50/50	30/70	50/50	50/50	0.00	1.00
Age (years)	35.99 ± 9.04	38.30 ± 9.97	37.52 ± 12.36	37.69 ± 12.39	36.36 ± 8.50	0.83	0.51
Education (years)	13.58 ± 2.70	13.73 ± 2.94	14.03 ± 2.94	13.55 ± 3.30	15.16 ± 1.86	5.77	0.00
Age at onset	23.39 ± 6.55	25.44 ± 10.00	25.85 ± 10.99	29.80 ± 12.00			
Length of illness	12.47 ± 9.35	12.44 ± 8.59	12.09 ± 10.41	7.85 ± 7.10			
PANSS	(n = 100)	(n = 74)	(n = 68)	(n = 56)			
Total scores	62.66 ± 15.95	28.95 ± 20.58	42.36 ± 8.90	48.30 ± 14.92			
Positive subscale	13.88 ± 4.92	5.96 ± 4.21	8.25 ± 1.85	7.36 ± 2.38			
Negative subscale	16.46 ± 5.28	6.52 ± 4.82	8.69 ± 2.72	9.29 ± 4.74			
Psychopathology	32.02 ± 8.54	16.47 ± 12.10	25.42 ± 6.23	28.25 ± 10.24			
HAMD-17	(n = 100)	(n = 46)	(n = 39)	(n = 99)			
Total scores	7.80 ± 5.15	8.11 ± 6.43	6.95 ± 7.31	17.46 ± 7.73			
MADRS		(n = 53)	(n = 54)	(n = 90)			
Total scores		13.32 ± 8.89	14.63 ± 10.73	26.09 ± 9.80			
YMRS		(n = 74)	(n = 68)	(n = 100)			
Total scores		4.77 ± 5.06	4.07 ± 4.32	1.79 ± 1.95			
WM (2-back)	(n = 100)	(n = 72)	(n = 49)	(n = 99)	(n = 100)		
Reaction time	815.23 ± 197.32	802.57 ± 230.75	824.20 ± 249.84	791.60 ± 199.58	646.62 ± 161.17	12.07	0.00
Correct	10.82 ± 3.51	10.99 ± 3.93	11.33 ± 3.31	11.56 ± 3.44	13.60 ± 2.40	10.96	0.00
Antipsychotics	n = 95	n = 59	n = 55	n = 23			
Antidepressants	n = 38	n = 23	n = 53	n = 59			
Mood stabilizers	n = 52	n = 74	n = 61	n = 42			
Lithium	n = 3	n = 28	n = 11	n = 1			

Abbreviations: BDI, Beck Depression Inventory; HAMD-17, 17-item Hamilton Depression Scales; MADRS, Montgomery Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale for Schizophrenia; WM, working memory; YMRS, Young Mania Rating Scale.

Magnetic resonance image acquisition

Magnetic resonance images were acquired using a 3.0-Tesla GE Discovery 750 whole-body high-speed imaging device with an 8-channel high-resolution brain coil. Head stabilization was achieved with cushioning, and all the participants wore earplugs (29-dB rating) to attenuate noise. Automated shimming procedures were performed, and scout images were obtained. The resting-state functional images were collected using a gradient echo T2* weighted sequence (repetition time [TR]/echo time [TE]/Flip = 2,500 ms/30 ms/90°). Forty-seven contiguous horizontal slices parallel to the intercommissural plane (voxel size: 3.5 × 3.5 × 3.5 mm) were acquired and interleaved. These slices covered the cerebellum of each participant. During the functional scans, the participants were instructed to keep their eyes open (each scan lasted for 8 min and 24 s across 200 time points). In addition, a high-resolution structural image was acquired in the sagittal plane using a high-resolution sequence (TR = 2,530 ms, echo spacing = 7.25 ms, TE = 3 ms, and flip angle = 7°) and an isotropic 1 mm voxel (FOV 256 × 256).

Quality check of functional images

Regarding head motion during image acquisition, we used the method of scrubbing within regression (spike regression) suggested

in a previous study [17] to minimize the effect of head motion on the FC measurement. This method identifies “bad” time points using a threshold of framewise displacement > 0.2 mm as well as 1 back and 2 forward neighbors (as reported by [18] and then models each “bad” time point as a separate regressor in the regression models [19, 20]. We also calculated the number of contaminated volumes in each group, and no significant difference was observed between the groups (Supplementary Table 2).

FC preprocessing

All preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (<http://www.restfmri.net>), which is based on Statistical Parametric Mapping (<http://www.fil.ion.ucl.ac.uk/spm>) and the Resting-State fMRI Data Analysis Toolkit (<http://www.restfmri.net>). The functional scans received slice-timing correction and motion correction and were normalized to a standard anatomical space (Montreal Neurological Institute). To prepare the data for FC analysis, the following additional preprocessing steps were used: (a) spatial smoothing by using a Gaussian kernel (6-mm full width at half-maximum), (b) temporal filtering (0.009 Hz < f < 0.08 Hz), and (c) removal of spurious or nonspecific sources of variance through the regression of the following variables: (a) Six head motion parameters and autoregressive models of motion: Six head motion parameters, Six head motion parameters

one time point before, and the 12 corresponding squared items [21] (Friston 24-parameter model); (b) the mean whole-brain signal; (c) the mean signal within the lateral ventricles; and (d) the mean signal within a white matter mask. Furthermore, the regressors used in the method of scrubbing within regression were included to minimize the effect of head motion on the FC measurement. The regression of each of these signals was computed simultaneously, and the residual time course was then retained for the correlation analysis.

Connectome-wide association analysis by using MDMR

We created a brain mask including all cortical and subcortical structures of the Montreal Neurological Institute (MNI152) atlas, except regions in the ventricles. The brain mask was subsampled twice into 4,330 isotropic voxels with 8-mm resolutions to decrease the computation load. The connectome-wide association analysis for each patient group was conducted in three steps [11]. First, we calculated a voxel-wise whole-brain $4,330 \times 4,330$ FC matrix based on Pearson's correlation coefficient of low-frequency fMRI fluctuations with Fisher's r -to- z transformation [22]. In the second step, for each voxel in the connectome, we calculated the similarity between the connectivity maps for all possible pairings of the participants by using a spatial correlation and converted them to a distance metric $\sqrt{2*(1-r)}$, yielding a 200×200 matrix (100 patients and 100 controls). Finally, MDMR was used to test how well the diagnosis of interest explained the relation between each participant's pattern of connectivity, with age, sex, and education level added as the covariates of no interest. For each voxel's connectivity pattern, MDMR yielded a pseudo-F statistic whose significance was assessed using 100,000 iterations of a permutation test. The threshold was set at $p < 0.01$ (corrected for false discovery rate). Any voxel exceeding the threshold was considered significant. An MDMR analysis was separately performed for each diagnostic group of patients. Then, we adopted a conjunction analysis to identify common areas that showed significant FC abnormalities across the four major psychiatric disorders. The clusters in conjunction analysis were selected as regions of interest (ROIs) for follow-up analysis.

Follow-up analysis

Although MDMR identified clusters where the overall multivariate pattern of connectivity is dimensionally related to SZ diagnosis, it did not provide the specific pattern of connectivity driving the significant result. We conducted post hoc ROI-based analyses from the clusters through conjunction analysis. The pair-wise FC values were calculated and compared between each group of patients and HCs by using independent sample t -tests, with age, sex, and education level as the covariates of no interest. The FC abnormalities with a significance of $p < 0.05$ (uncorrected) were demonstrated to visualize the major patterns of FC abnormalities. Importantly, the follow-up analysis was performed to show the major patterns of FC abnormalities between these ROIs and did not focus on the statistical significance of the specific FCs between ROI pairs.

Result

Demographic results

The demographic data and clinical ratings of the participants are shown in Table 1. Except for the BD-II group, all the other groups were age and sex matched. The BD-II group had more women. In all the four groups, the patients had a low-education level.

MDMR analysis

Compared with HC, the four groups of patients showed FC abnormalities in distributed cortical and subcortical regions (Figure 1). The conjunction analysis identified the common neural substrates showing connectomic abnormalities in all the four patient groups (Figure 1, Table 2). The structures with the largest cluster size were the left and right postcentral gyrus. Other sensorimotor-related cortices included precentral gyrus, lingual gyrus, lateral occipital cortex, and fusiform cortex. Furthermore, large clusters in the subcortical structures of the cerebellum and thalamus were also found. At last, the common structures also included several smaller clusters in fronto-parietal association cortices, including bilateral frontal pole, supramarginal gyrus, precuneus, and posterior cingulate. We also quantified the numbers of voxels showing FC abnormalities in each diagnostic group and observed severity in the order of SZ > BD-I > BD-II > MDD (Figure 1B).

Follow-up analysis

The results of follow-up analyses based on pair-wise FCs of these structures were provided in Figure 2. We grouped ROIs according to the functional classification of subcortical structures, sensory-related cortices, and association cortices. The 4 groups of patients showed a similar pattern of FC abnormalities characterized by sensory/subcortical hyperconnectivity, association/subcortical hypoconnectivity, and sensory/association hyperconnectivity. In addition to the three major dysconnectivity patterns, hypoconnectivities among the structures belonging to the same category were also observed. The intracalcarine gyrus was an exception and showed hyperconnectivities with other sensory-related cortices despite its role in visual processing.

Control analysis

Because shorter duration of illness in patients with MDD was a major confounder in this study, we performed a control analysis to evaluate the effect of illness duration on our findings. We selected 100 patients with MDD (age: 41.8 ± 12.5 years; duration of illness: 11.4 ± 8.5 years) with a similar duration of illness as the other three diagnostic groups from our resting fMRI dataset and performed the same MDMR and conjunction analysis. The control analysis revealed slightly more voxels with connectomic abnormalities and additional clusters in the bilateral superior temporal gyrus (see Supplementary Table 3 for detailed structures and cluster size); however, the pattern of graded severities (Figure 1B) and the characteristic patterns of dysconnectivities (Figure 2) did not change significantly.

Discussion

What are the core neural substrates with FC abnormalities in major psychiatric disorders? And what is the major pattern of FC abnormalities? This study attempted to answer the questions through a large-scale connectome-wide association study. We used a fully data-driven survey of the functional connectome to identify common neural substrates with connectomic abnormalities across the four major psychiatric disorders. These structures included the thalamus, cerebellum, sensorimotor-related cortices, and association cortices in the frontal and parietal regions. The follow-up analysis demonstrated that the four major psychiatric disorders also shared a similar pattern of FC abnormalities among these structures; the abnormalities were characterized by

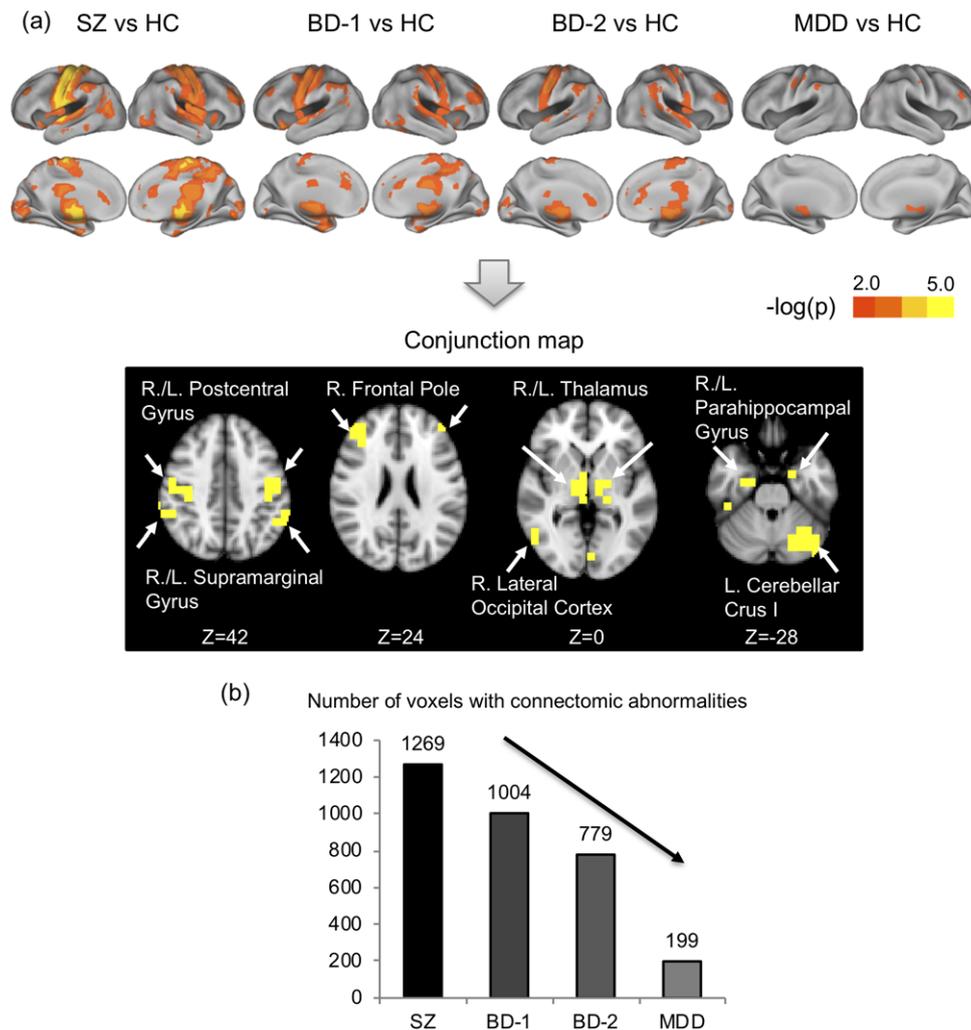


Figure 1. (A) The neural substrates with connectomic abnormalities in each diagnosis were identified by MDMR. Then, the common structures with connectomic abnormalities among the four diagnostic groups were identified through conjunction analysis and included the thalamus, cerebellum, postcentral gyrus, and association cortices in frontal and parietal regions. (B) The total numbers of voxels with connectomic abnormalities in each diagnostic group were calculated and the results showed a graded severity of schizophrenia (SZ) > bipolar I disorder (BD-1) > bipolar II disorder (BD-2) > MDD.

sensory/subcortical hyperconnectivity, association/subcortical hypoconnectivity, and sensory/association hyperconnectivity. The hypoconnectivity among structures within the same category was also observed. The results extended our previous findings of common FC abnormalities in thalamus in four major psychiatric disorders and successfully delineated all the common neural substrates with connectomic abnormalities across these major psychiatric disorders.

Cognitive dysmetria theory is the first to theoretically emphasize the role of cortico-thalamic-cerebellar-cortical (CCTC) circuits in the pathogenesis of patients with SZ [23]. Our finding that the thalamus and cerebellum are the common subcortical structures involved across psychiatric disorders is in accordance with the theory and suggests that the CCTC circuit deficits are shared across the four major psychiatric disorders we investigated. Moreover, intrinsic abnormalities in the cerebello-thalamo-cortical circuitry were also observed in individuals at a clinically high risk of psychosis in a previous study based on the North American Prodrome Longitudinal Study [24]. In our follow-up analysis, these two subcortical structures showed a similar pattern of bidirectional FC changes, marked by hyperconnectivity with sensory-related

cortices and hypoconnectivity with the association cortex. The bidirectional changes were first found in FC studies of thalamocortical connectivity in SZ [25, 26], but also applied to other subcortical structures of basal ganglion and cerebellum in a recent study [27]. Although the subcortical structures of the putamen, hippocampus, and midbrain were not identified in our conjunction analysis, MDMR revealed that they exhibited connectomic abnormalities in those with SZ or BD; these three structures also shared the same pattern of bidirectional FC changes. These findings suggested that the patterns of sensory/subcortical hyperconnectivity and association/subcortical hypoconnectivity are fundamental to FC abnormalities of subcortical structures in major psychiatric disorders.

The largest cortical cluster of the common neural substrate is the postcentral gyrus, which extends to the precentral gyrus and involves the whole primary sensorimotor cortex. In addition to primary sensorimotor cortices, the MDMR analysis identified common neural substrates in other sensory-related areas, including structures in the occipital and temporal cortex for primary and higher visual processing. The follow-up analysis demonstrated that the two major patterns of FC abnormalities were sensory/subcortical and sensory/association hyperconnectivity. Our findings that

Table 2. Conjunction analysis of functional connectivity patterns for four groups.

Index	Voxels	MNI coordinate (mm)			Harvard–Oxford structural atlas
		x	y	z	
27	1,450	36	–21	56	R. Postcentral gyrus
26	1,055	–44	–19	49	L. Postcentral gyrus
25	791	–30	–69	–29	L. Cerebellar Crus I
24	704	–15	–15	6	L. Thalamus
23	701	11	–16	5	R. Thalamus
22	539	–52	–51	44	L. Supramarginal gyrus
21	425	39	39	27	R. Frontal pole
20	373	57	–44	43	R. Supramarginal gyrus
19	192	50	–3	16	R. Central opercular cortex
18	192	53	–62	6	R. Lateral occipital cortex
17	154	–25	–82	–45	L. Cerebellar crus II
16	128	25	–11	–29	R. Parahippocampal gyrus
15	128	–11	–23	75	L. Precentral gyrus
14	100	–43	45	22	L. Frontal pole
13	99	40	–40	–23	R. Temporal occipital fusiform cortex
12	64	5	–27	35	R. Cingulate gyrus, posterior division
11	64	13	–67	35	R. Precuneous cortex
10	64	53	–43	11	R. Middle temporal gyrus
9	64	–43	–67	11	L. Lateral occipital cortex
8	64	–3	–83	3	L. Intracalcarine cortex
7	64	13	–75	–21	R. Cerebellum, crus I
6	64	–19	–3	–29	L. Parahippocampal gyrus

Abbreviations: L, left; R, right.

four major psychiatric disorders shared connectomic abnormalities in primary sensorimotor cortex and other sensory-related cortices suggested the important role of sensorimotor processing in pathogenesis of major psychiatric disorders. It is in accordance with a recent transdiagnostic study that associated three latent components of psychopathology with connectivity alterations within the somatosensory-motor network and its connectivity with subcortical structures and association cortices in several cortical executive networks [28]. Functional deficits in visual and primary sensorimotor processing received more clinical attentions recently. The deficits at different levels of visual processing were found in patients with SZ [29] and BD-I [30, 31]. The excitability deficit in primary sensorimotor deficit measured using transcranial magnetic stimulation has been well studied, and a review suggested a general alteration in motor cortical inhibition in mental illness, rather than disease-specific changes [32]. Although the auditory-related superior temporal gyrus reached significance only in SZ and BD-I in the MDMR analysis and therefore was not identified in the conjunction analysis, they also shared a similar pattern of FC abnormalities as the primary sensorimotor cortex.

Despite smaller cluster size, our analysis also identified several fronto-parietal structures, majorly in lateral frontal and parietal regions. The FC deficits in the association cortices of frontal and parietal regions have received special interest in the past 10 years in FC studies of SZ and other psychiatric disorders because of their

important roles in cognitive controls. One crucial functional classification of the association cortices is the distinction between task-negative and task-positive networks. The task-negative network was less active during various cognitive-demanding tasks and consisted of the default mode network [33], whereas task-positive networks were more active during various cognitive-demanding tasks and majorly included the dorsal attention network [34], salience network, and executive control network [35, 36]. Among them, the FCs of the task-negative default mode network initially received great research interest and has been widely studied in major psychiatric disorders; however, the results have not been completely consistent. Hyperconnectivity [37] and hypoconnectivity [38, 39] have both been reported in FC studies of schizophrenia. By contrast, numerous studies have reported that task-positive control networks have FC impairments [40–43]. In this study, the structures in association cortices identified in our MDMR analysis included major clusters in the lateral frontal and parietal cortices and a small cluster in the precuneus. As the lateral frontal parietal cortices were functionally connected to the task-positive salience or executive control networks, our findings suggest that the common neural substrates in major psychiatric disorders may involve the task-positive networks. It is consistent the two meta-analyses that suggested structural deficits in the salience network and functional activation deficits in task-positive multi-demand network in major psychiatric disorders [3, 4].

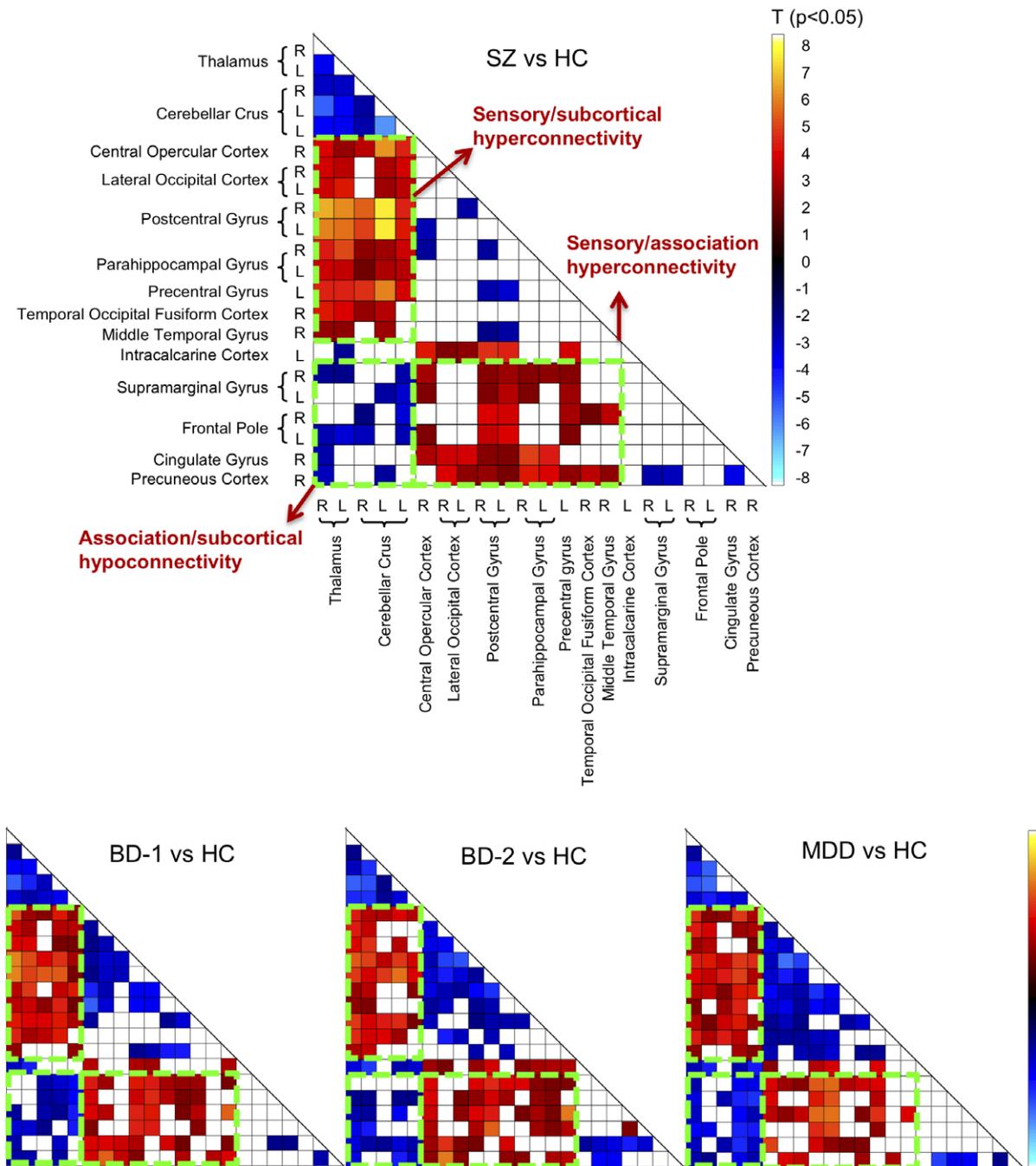


Figure 2. The result of the follow-up analysis based on pair-wise FCs of the common structures identified using MDMR. The order of structures in the figure was arranged according to the classification of subcortical structures, sensory-related cortices, and association cortices. The four groups of patients shared similar patterns of FC abnormalities, characterized by sensory/subcortical hyperconnectivity, association/subcortical hypoconnectivity, and sensory/association hyperconnectivity. Furthermore, a decrease in FC was observed within each structure category were noted.

Our findings have several methodological limitations and alternative conceptualizations. First, the illness durations were not matched in MDD patients. Due to a late illness onset in the MDD group, controlling the age and illness duration simultaneously was impossible. We performed a control analysis by selecting the MDD groups with a similar duration of illness and the main findings were not significantly changed. Second, our patient groups were exposed to various psychotropic medications. Since previous studies have demonstrated the effects of antipsychotics [44, 45], anti-depressants [46–48], and mood stabilizers [49] on brain FCs,

the use of various psychotropics in participants with psychiatric disorders may be confounding our findings in this study. Third, not all of the patients with BD-1 and BD-II received full evaluations of clinical severity by using the MADRS and YMRS. Although these patients were all in euthymic states clinically, the lack of complete evaluations may have limited our interpretations in this study. Lastly, our follow-up analysis focused only on the structures identified using the MDMR analysis. Shehzed et al. [11] compared the method of MDMR and traditional seed-based FC analysis and demonstrated an overlap, but the findings of these two methods

were not in total agreement. Traditional univariate FC analysis may reveal other connectomic abnormalities that were not identified through the MDMR analysis in this study.

Conclusion

This data-driven connectome-wide analysis successfully identifies the common neural substrates with connectomic abnormalities, majorly in thalamus, cerebellum, sensorimotor-related cortices, and fronto-parietal association cortices in four major psychiatric disorders. These disorders also share a similar pattern of dysconnectivities among these identified neural structures. These findings provide considerable support for the common networks hypothesis of major psychiatric disorders.

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Data Availability Statement. The data that support the findings of this study are available upon request, Prof. Pei-Chi Tu (pctu@vghtpe.gov.tw).

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