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Dysfunction of Large-Scale Brain Networks in Schizophrenia: A Meta-analysis of Resting-State Functional Connectivity

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Schizophrenia is a complex mental disorder with disorganized communication among large-scale brain networks, as demonstrated by impaired resting-state functional connectivity (rsFC). Individual rsFC studies, however, vary greatly in their methods and findings. We searched for consistent patterns of network dysfunction in schizophrenia by using a coordinate-based meta-analysis. Fifty-six seed-based voxel-wise rsFC datasets from 52 publications (2115 patients and 2297 healthy controls) were included in this meta-analysis. Then, coordinates of seed regions of interest (ROI) and between-group effects were extracted and coded. Seed ROIs were categorized into seed networks by their location within an a priori template. Multilevel kernel density analysis was used to identify brain networks in which schizophrenia was linked to hyper-connectivity or hypo-connectivity with each a priori network. Our results showed that schizophrenia was characterized by hypo-connectivity within the default network (DN, self-related thought), affective network (AN, emotion processing), ventral attention network (VAN, processing of salience), thalamus network (TN, gating information) and somatosensory network (SS, involved in sensory and auditory perception). Additionally, hypo-connectivity between the VAN and TN, VAN and DN, VAN and frontoparietal network (FN, external goal-directed regulation), FN and TN, and FN and DN were found in schizophrenia. Finally, the only instance of hyper-connectivity in schizophrenia was observed between the AN and VAN. Our meta-analysis motivates an empirical foundation for a disconnected large-scale brain networks model of schizophrenia in which the salience processing network (VAN) plays the core role, and its imbalanced communication with other functional networks may underlie the core difficulty of patients to differentiate self-representation (inner world) and environmental salience processing (outside world).

Key words: schizophrenia/meta-analysis/brain networks/resting-state/salience network/disconnected model

Introduction

Schizophrenia is a disabling mental disorder that affects about 1 percent of the world's adult population.[1,2] Through a century of studying the disorder, the pathophysiological cause of schizophrenia remains unclear. Understanding the bio-markers of schizophrenia from a new perspective is likely to be key for the development of more effective treatments; thus, investing in this type of work has become a research priority. In recent years, our understanding of how schizophrenia affects brain networks has been greatly advanced by attempts to map inter-regional interactions comprising the brain's intrinsic connectivity.[3–6] So far, neuroimaging has provided abundant evidence supporting the view that schizophrenia is characterized as a disorder of disorganized communication among large-scale brain networks,[4–6] but a robust conclusion has not yet been obtained. Existing research using seed-based resting-state functional connectivity (rsFC) analysis, which was the most commonly used analysis to investigate abnormal rsFC in schizophrenia, varies considerably in the location of the seed regions of interest (ROIs); therefore, it is challenging to integrate these results into a coherent model. Kaiser et al[7]

proposed a theoretically informed strategy for categorizing seed ROIs into an a priori brain network (eg, by the location of seed ROIs within functional networks), which would help unify the diverse set of findings to evaluate replication across studies. Although rsFC alterations in schizophrenia have been reviewed[4–6,8] and meta-analyses of regional resting-state activity,[9] abnormal activation from a network perspective,[10] multivariate pattern recognition of brain functional and structural changes,[11] and graph-analytical measures of the whole brain[12] in schizophrenia have been conducted, a meta-analysis of these rsFC alterations has never been investigated.

To address this gap, we conducted a meta-analysis of seed-based rsFC studies and then integrated the findings into a disconnected model of schizophrenia. Because recent researchers have focused on the following brain networks putatively related to schizophrenia, including the default network (DN) related to internally oriented attention,[3] the frontoparietal network (FN) involved in top–down regulation of attention and emotion,[13] the affective network (AN)[14] and the ventral attention network (VAN) (according to some studies, the VAN and AN together can be called the salience network[15]) involved in monitoring salient events,[16] the thalamus network (TN) involved in gating information,[17] and the somatosensory network (SS) involved in sensory and auditory perception,[18] our main goal was to seek the accurate and consistent location of the abovementioned brain networks that demonstrate hyper-connectivity or hypo-connectivity with seed ROIs in schizophrenia, which in turn were categorized into the a priori network. It should be noted that one conceptual framework proposed to explain the core deficits of the illness has been gathering progressive support: the "dysconnection" hypothesis. Specifically, the "dysconnection" hypothesis suggests that the core symptoms of schizophrenia can be described in terms of an abnormal (including reduced and increased) functional integration between distinct brain regions.[19–21] The main trend that has emerged so far is that schizophrenia is associated with reductions in connectivity, as opposed to increases, relative to healthy controls (HC).[8] On the basis of the above evidence, we predicted that schizophrenia would show decreased connectivity within or between the main brain networks, as opposed to increased connectivity, relative to HC. Furthermore, we tested whether rsFC abnormalities were moderated by seed locations or demographic or clinical factors.

Methods

Study Selection

A step-wise procedure was used to identify the relevant experimental articles. First, studies published before October 30, 2015 were selected through a standard search in PubMed (http://www.pubmed.gov) and ISI Web of Science (http://apps.isiknowledge.com) with keywords rest*(-ing), connect*(-ivity), and schizophrenia. Next, additional studies were collected by reviewing the reference list of the relevant papers, publications that cited those articles found in the first step, and through the "related article" function of the PubMed database. Finally, the reference lists of those review articles were inspected for adding more relevant studies. Original magnetic resonance imaging studies using whole-brain seed-based rsFC to compare schizophrenia with HC were included (other rsFC methods utilizing a distinct statistical approach, such as independent components analysis, could not be included). Exclusion criteria were as follows: (1) non-peered-reviewed study; (2) no HC group; (3) whole-brain results could not be obtained or did not survive multiple comparison correction (studies that reported group differences in rsFC were eligible for inclusion) or (4) entirely overlapping samples and the same seed ROIs reported in another publication. Importantly, studies reporting on the same samples but using different seed ROIs were coded as separate studies; papers in which distinct schizophrenia groups were each compared with a single HC group were coded as distinct studies.[7] To achieve a high standard of reporting, we have adopted the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines[22] (supplementary eFigure 1). These literature searches yielded a sample of 56 studies from 52 publications[3,13,14,16–18,23–68] for a total of 2115 schizophrenia patients and 2297 HC (table 1 and supplementary eTable 1). Within the 56 datasets, there were 4 studies[23,24,31,54] in which distinct schizophrenia groups were compared with the same HC group and 6 studies[3,17,25,26,50,51] that used the same samples but different seed ROIs. There was no study that used entirely overlapping samples and the same seed ROIs reported in another publication.

Data Organizing

The current meta-analysis was based on coordinates showing the locations of significant group differences in rsFC. Data were extracted and coded as follow. First, coordinates for the center of mass of each seed ROI (131 seeds) and the peak of each significant between-group effect (752 effects) were extracted and converted to Montreal Neurological Institute space. If the seed ROI was a sphere ROI or an anatomical region from a standard brain atlas or available prior mask, the center of mass was calculated to obtain a representative coordinate. Then, each ROI was categorized into a brain-network based on its location of center of mass or peak coordinate (for unavailable prior masks) within a priori network created by a previous whole-brain network segmentation (including DN, AN, FN, SS, dorsal attention network [DAN], VAN and visual network) from 1000 health participants (supplementary eTable 2).[69–71] The TN was treated as a single network given it was poorly defined into different rsFC networks; importantly, its special role in gating

Table 1. Summary of Demographic of Studies Included in Meta-analysis

Reference	HC (*N*)	SCZ (*N*)	Age (Mean)	Patient Details	Ill Duration (y)	Meds	CPZ-Equivalents	PANSS PS (Mean)	PANSS NS (Mean)	PANSS GP	PANSS Total (Mean)
Alonso-Solís et al[23] auditory verbal hallucinations	20	19	40.05	Chronic	16.11	100%	NAN	17.89	21.47	34.22	72.47
Alonso-Solís et al[23] non auditory verbal hallucinations	20	14	36.43	Chronic	8	100%	NAN	11.43	14.36	27.36	55.23
Anticevic et al[24] chronic	96	20	31.43	Chronic	5.37	95%	240	NAN	NAN	NAN	25.56
Anticevic et al[24] early course	96	28	25	FE	0.45	43%	96.40	NAN	NAN	NAN	36.67
Anticevic et al[17]	90	90	32.93	Chronic	NAN	83.30%	229	15.8	14.34	30.48	60.51
Anticevic et al[25]	90	90	32.93	Chronic	NAN	91%	229	15.8	14.34	30.48	60.51
Bluhm et al[3]	17	17	33.54	Chronic	9.78	88.20%	231.8	9.06[a]	20.35[b]	NAN	NAN
Bluhm et al[26]	17	17	33.54	Chronic	9.78	88.20%	231.8	9.06[a]	20.35[b]	NAN	NAN
Chai et al[27]	15	16	41.6	Chronic	20	100%	504.7	NAN	NAN	NAN	84.7
Chen et al[29]	36	36	32.9	Chronic	10	97.20%	NAN	14.6	15.3	30.5	60.4.
Chen et al[28]	31	29	36.53	Chronic	12	100%	NAN	16.54	19.61	27.71	63.89
Cole et al[30]	22	22	36.54	Chronic	NAN	100%	589.88	1.941[a]	2.472[a]	NAN	NAN
Duan et al[32]	31	28	36.53	Chronic	12	100%	NAN	16.54	19.61	27.71	63.85
Duan et al[31] baseline	62	68	36.3	FE	3.8	94.10%	NAN	24.6	25.3	33.6	82.3
Duan et al[31] follow-up	62	68	36.3	FE	3.8	86.80%	NAN	24.6	25.3	33.6	82.3
Fan et al[33]	15	27	39.7	Chronic	16.5	100%	443.1	11.8	19.9	27.7	63
Fischer et al[34]	12	12	34.18	Chronic	NAN	100%	300	NAN	NAN	NAN	NAN
Guo et al[18]	19	19	23.95	FE	0.78	100%	162.30	19.47	20.26	38.05	77.79
Guo et al[35]	46	49	22.69	FE	1.87	0	NAN	22.27	22.82	NAN	91.31
Hadley et al[36]	21	21	36	Chronic	13.3	60%	NAN	11.9[a]	6.5[b]	NAN	44.4
He et al[37]	113	115	25.36	FE	0.82	0	NAN	NAN	NAN	NAN	92.14
Hoffman et al[38]	23	56	39.1	Chronic	NAN	94.60%	554	16.5	14.9	38.9	70.3
Holt et al[39]	18	18	35.7	Chronic	12.6	83.30%	329.5	12.4	12.3	24.3	49.1
Hoptman et al[14]	21	25	36.7	Chronic	NAN	100%	1157.8	18.9	20.9	NAN	78.7
Hoptman et al[40]	31	33	38.2	Chronic	16.5	100%	1112.8	19.5	19.2	NAN	74.7
Jiang et al[41]	25	26	14.51	FE	0	0	NAN	12.29	12.83	28.71	57.88
Jung et al[42]	23	16	24.7	Chronic	4.8	100%	NAN	14.2	17	28.6	57
Knöchel et al[43]	21	21	38.38	Chronic	8.45	100%	NAN	15.4	15.11	32.6	63.2
Kraguljac et al[44]	22	22	33.77	Chronic	9.32	0	NAN	9.09[a]	6.73[b]	NAN	47.77
Liu et al[45]	10	10	25.6	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
Lui et al[46]	59	37	36	Chronic	14.81	100%	483	18.2	18.31	34.69	71.2
Moran et al[47]	28	18	37.7	Chronic	NAN	100%	NAN	NAN	NAN	NAN	NAN
Moran et al[48]	24	20	37.4	Chronic	NAN	100%	319.5	NAN	NAN	NAN	33.3
Moran et al[49]	44	44	35.2	Chronic	NAN	100%	411	NAN	NAN	NAN	NAN
Oertel-Knöchel et al[50]	24	24	37.9	Chronic	13.52	100%	610	15.45	15.19	NAN	63.29
Oertel-Knöchel et al[51]	24	24	37.9	Chronic	13.52	100%	610	15.45	15.19	NAN	63.29
Salvador et al[52]	40	40	41.45	Chronic	20	97.50%	578	NA	NAN	NAN	NAN
Schilbach et al[53]	82	75	33.46	Chronic	9.03	94.70%	NAN	NAN	NAN	NAN	NAN
Shinn et al[54] auditory verbal hallucinations	28	27	40	Chronic	18	100%	611	NAN	NAN	NAN	NAN
Shinn et al[54] non-auditory verbal hallucinations	28	14	37	Chronic	14	100%	435	NAN	NAN	NAN	NAN
Su et al[55]	25	25	42.5	Chronic	8.7	100%	263	16.6	15.2	32.6	64.4
Tian et al[56]	30	30	22.63	Chronic	3.25	100%	407.6	19.37	16.13	NAN	67.27
Tu et al[16]	30	30	30.8	Chronic	8.29	96.70%	NAN	15.83	17.83	34.63	67.5
Tu et al[57]	36	36	32.9	Chronic	10	97.20%	NAN	14.6	15.3	30.5	60.4.
Wang et al[60]	60	60	38	Chronic	NAN	100%	NAN	NAN	NAN	NAN	NAN
Wang et al[58]	102	94	33.6	Chronic	10	93.60%	450.4	16.6	20.3	NAN	NAN
Wang et al[59]	74	72	38.17	Chronic	16.03	100%	NAN	14.96	14.53	29.22	58.6
Welsh et al[61]	12	11	40.9	Chronic	20.2	100%	NAN	9.9[a]	7.5[b]	NAN	34
Woodward et al[62]	60	42	36.9	Chronic	15.3	97.60%	NAN	19.2	13.8	32.2	65.2

Table 1. *Continued*

Reference	HC (*N*)	SCZ (*N*)	Age (Mean)	Patient Details	Ill Duration (y)	Meds	CPZ-Equivalents	PANSS PS (Mean)	PANSS NS (Mean)	PANSS GP	PANSS Total (Mean)
Xu et al[63]	76	66	33	Chronic	9.5	92.40%	437.4	17	21.1	NAN	72.6
Yan et al[64]	30	30	23.1	Chronic	3.25	100%	407.7	19.4	16.1	31.8	67.3
Zhang et al[65]	31	39	15.5	FE	1.33	0	NAN	20.42	20.91	33.28	74.62
Zhou et al[13]	17	17	22.9	FE	2	76.50%	NAN	NAN	NAN	NAN	85.9
Zhou et al[67]	14	17	23.7	Chronic	3.69	70.60%	570.8	21.4	21.5	NAN	87.6
Zhou et al[66]	100	91	33.8	Chronic	10	100%	447.4	16.6	20	NAN	NAN
Zhu et al[68]	94	100	33.6	Chronic	10.24	91%	453.2	17	20.1	NAN	71.3
	Sum = 2297	Sum = 2115	*M* = 33.34		*M* = 9.57	*M* = 85.69%					

Note: Fifty-six studies from 52 publications compared HC participants to participants with schizophrenia (SCZ). SCZ groups were coded as first episode (FE) and chronic SCZ. Medication status was coded as yes or no based on whether or not participants in the SCZ group were taking psychoactive medications at the time of neuroimaging. "GP" refers to the score of the general psychiatric symptoms based on the Positive and Negative Syndrome Scale (PANSS). NAN cells indicate only that a procedure was not reported.
[a]The positive symptom (PS) score on the Brief Psychiatric Rating Scale (BPRS).
[b]Negative symptom (NS) score on the BPRS. "CPZ" refers to chlorpromazine (mg/day).

information.[72] Additionally, midbrain was also regarded as a single network because no study was conducted to divide midbrain into different brain networks. Finally, effects were also categorized into hypo-connectivity or hyper-connectivity condition. Based on previous studies, hypo-connectivity was defined as reduced positive or increased negative rsFC in schizophrenia compared with HC; hyper-connectivity was defined as reduced negative or increased positive rsFC in schizophrenia compared with HC.

Data Analysis

Our meta-analysis was performed using the multilevel kernel density analysis (MKDA) toolbox (http://wagerlab.colorado.edu), a Matlab toolbox. For 2 conditions of connectivity with each prior network: hyper-connectivity and hypo-connectivity, we conducted 2 separate meta-analyses. When performing this analysis, the peak coordinates from each study[73,74] and the seed-network comparison were first separately convolved with a spherical kernel (r = 15 mm)[7,75] and then thresholded at a maximum value of 1, resulting in an indicator map (IM) where a value of 1 indicated a significant effect in the neighborhood, while 0 indicated the absence of a significant effect. Then, these IMs were subsequently weighted based on the number of participants.[73,74] Subsequently, the weighted IMs were averaged together, producing density maps. The density maps reflected the weighted proportion of studies in which hypo-connectivity or hyper-connectivity with each prior network was observed in schizophrenia within 15 mm of each voxel.

To correct for multiple comparisons and identify voxels whose *P*-statistic exceeds the frequency expected by chance, a Monte Carlo simulation was conducted to determine thresholds (15 000 iterations). According to a previous meta-analysis study, density maps can be thresholded by 2 complementary approaches: height-based (density of voxels that exceed the maximum value expected by chance over the whole brain) and extent-based (density of groups of contiguous voxels that exceed the maximum cluster size expected by chance).[7,73]

Post Hoc Tests

To evaluate the potential disturbance of the variance of datasets (seed anatomy location and demographic and clinical factors), 3 post hoc tests inspired by a previous similar study[7] were performed. First, to assess whether any single study had a substantial impact on the meta-analytic results, jackknife statistics were conducted. Specifically, the density statistic for each significant cluster was iteratively recalculated leaving out each study; then, a chi-square test was performed to compare the likelihood ration of each significant cluster between the original density map and the leave-one-out density map.[76] Given that there was no single study whose being left out changed the result at the alpha level ($P < .05$), the present findings included all studies. Second, we calculated Fisher exact tests to investigate whether there were anatomical region effects to our findings; ie, one anatomical region may contribute more to a significant effect than other anatomical regions within the same network. Therefore, we compared the difference in effect likelihood among different regions within the same network. Third, considering the possible moderation of clinical variables to our results, we also conducted Fisher exact tests to explore the moderation of these effects, including age (elder > median age [35.2]; younger < median age) and duration of illness (short-duration = 1–5 y; middle-duration = 5–10 y; long-duration > 10 y). For these analyses, the proportion of studies within each clinical or demographic group reporting the effect was calculated, and differences in proportions were tested between groups. The medication and the categories of schizophrenia (first episode; chronic schizophrenia) were

not considered in this analysis because of the low ratio between studies without and with medication (5/51) and between first-episode patient studies and chronic patient studies (9/47).

Results

Within-Network Dysfunctions

Hypo-connectivity Within the DN. Schizophrenia was linked to hypo-connectivity between the DN seeds and regions of the anterior cingulate cortex (ACC) and medial prefrontal cortex (MPFC) (figure 1A and table 2). These areas are related to the internal mental state (eg, self-referential thinking).[77] Hypo-connectivity within the DN has been reported to be related to a decrease in positive connectivity in schizophrenia.[3,23,26,31,58,67] Post hoc tests indicated that seeds in the hippocampus (Hipp) were more likely than those in the MPFC and posterior cingulate cortex to exhibit hypo-connectivity with the ACC (supplementary eTable 3). Compared with the younger age group, the elder group showed a greater reduction in connectivity between the DN seeds and ACC. In addition, trends showed a greater likelihood of hypo-connectivity between the DN seeds and the ACC in those with a middle-duration of illness than those with a short-duration (supplementary eTable 4).

Hypo-connectivity Within the AN. Schizophrenia was associated with hypo-connectivity between the AN seeds and regions of the MPFC (figure 1B and table 2) involved in emotion regulation.[78] When reported in the original studies, hypo-connectivity was associated with a weaker positive connectivity.[14,24,33,56] Post hoc tests did not reveal differences among anatomical seed effects (supplementary eTable 3) or moderation by age or illness duration variables (supplementary eTable 4).

Hypo-connectivity Within the SS. Hypo-connectivity was observed between the SS seeds and regions of the superior temporal gyrus (STG) (figure 1D and table 2) involved in speech perception and comprehension.[79,80] When reported in the original papers, such hypo-connectivity was related to a weaker positive connectivity in schizophrenia.[18,50,51,54] Post hoc analyses did not reveal differences among anatomical seed effects (supplementary eTable 3) or moderation by age or illness duration variables (supplementary eTable 4).

Hypo-connectivity Within the VAN. Schizophrenia was characterized by hypo-connectivity between the VAN seeds and regions of the putamen and ACC (figure 1E and table 1) involved in salience monitoring.[15] When reported in the original papers, the hypo-connectivity within the VAN was related to a weaker positive connectivity in schizophrenia.[16,47,48,58,64] The likelihood of hypo-connectivity did not differ among anatomical regions of the VAN (supplementary eTable 3).

Hypo-connectivity Within the TN. Hypo-connectivity was observed between the TN seeds and regions of the bilateral thalamus (figure 1F and table 2) believed to be critical for gating function.[81,82] According to the original studies, hypo-connectivity with the TN was associated with a weaker positive connectivity between the TN seeds and the thalamus.[17,25,59] The moderation by age was not significant (supplementary eTable 4).

Between-Network Dysfunctions

Hypo-connectivity Between the DN and Regions of the VAN or FN Involved in Salience Monitoring or Goal-directed Regulation. Hypo-connectivity was observed between the DN seeds and key regions of the VAN, including the ACC and insula, involved in salience monitoring.[15] (figure 1A). In addition, schizophrenia was also associated with hypo-connectivity between the DN seeds and a region of the left DLPFC that is critical for goal-directed regulation[83] (figure 1A). Examining the original paper revealed that hypo-connectivity between the DN seeds and the ACC, insula, and DLPFC was associated with increased negative connectivity.[23,29,31,35,45,58,60] Post hoc tests indicated that seeds in the ACC were more likely than those in the Hipp and PCC to exhibit hypo-connectivity to the insula with marginal significance (supplementary eTable 3). Additionally, the Hipp showed greater hypo-connectivity with the insula than the MPFC, and the MPFC was more likely than the PCC to show hypo-connectivity with the insula (supplementary eTable 3). The hypo-connectivity between the DN seeds and the insula gradually increased across the 3 durations of illness (short-duration < middle-duration < long-duration, supplementary eTable 4).

Hyper-connectivity Between the AN and Regions of the VAN Involved in Salience Monitoring. Surprisingly, schizophrenia was linked to hyper-connectivity between the AN seeds and regions of the putamen extending to the caudate (figure 1B) that are involved in monitoring extraneous stimuli.[15,84] The hyper-connectivity was originally reported to be associated with increased positive functional connectivity.[24,56] The likelihood of insula hyper-connectivity did not differ among anatomical regions of the AN (supplementary eTable 3) and was not moderated by the illness duration variable (supplementary eTable 4).

Hypo-connectivity Between the FN and Regions of the TN or VAN Involved in Gating Information or Salience Monitoring. Hypo-connectivity was observed between the FN seeds and regions of the thalamus (figure 1C) involved in relaying and gating information. In addition, hypo-connectivity was also observed between the FN seeds and a region of the insula extending to the putamen (figure 1C),

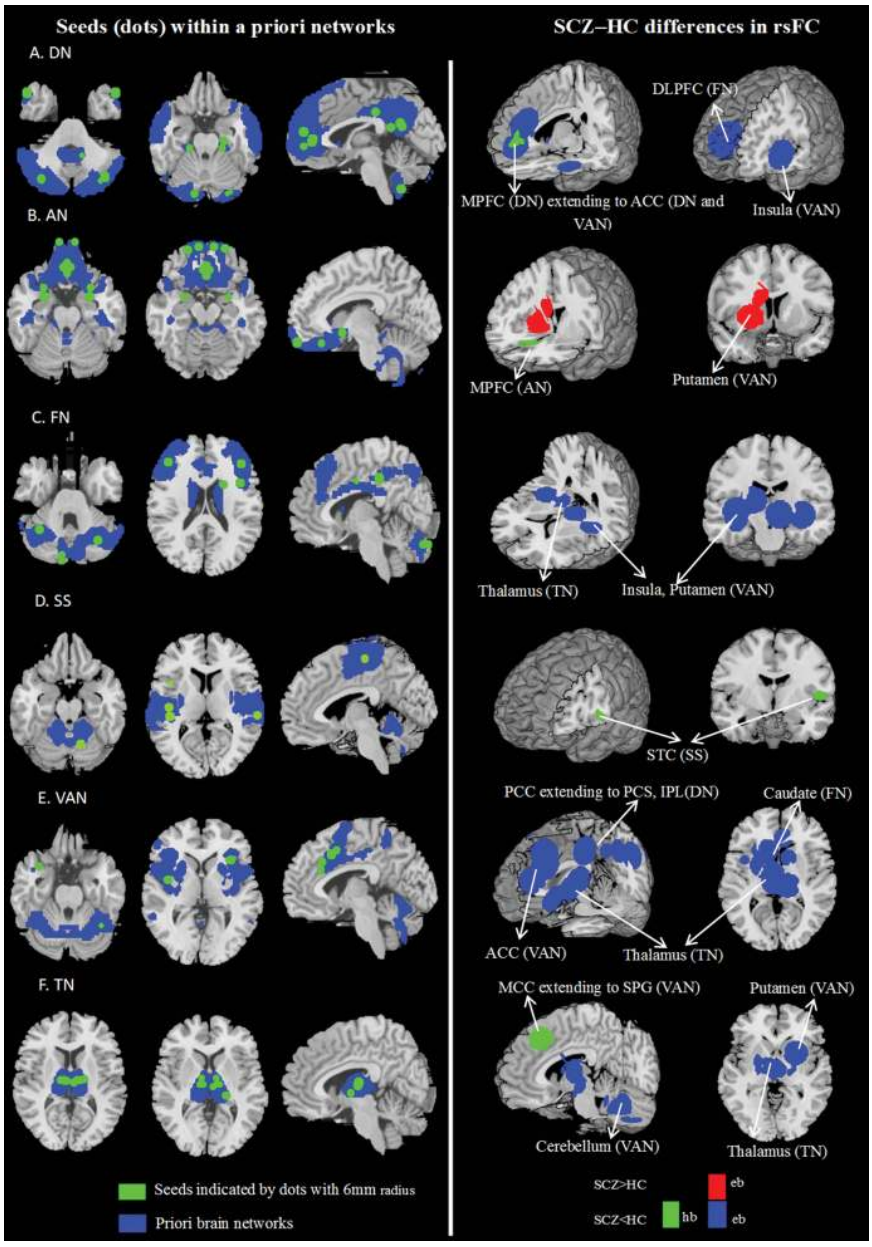

Fig. 1. Meta-analysis of abnormal resting-state functional connectivity (rsFC) in schizophrenia (SCZ). The first 3 columns represent the seed regions of interest (ROI) indicated by dots with 6 mm radius and categorized by an a priori functional network. The last 2 columns represent altered rsFC in SCZ. (A) SCZ exhibited hypo-connectivity within the default network (DN) between the DN seeds and the medial prefrontal cortex (MPFC) extending to the anterior cingulate cortex (ACC) and hypo-connectivity between the DN seeds and 2 regions within the ventral attention network (VAN), the ACC and insula; hypo-connectivity was also observed between the DN seeds and the dorsolateral prefrontal cortex (DLPFC), a key hub of the frontoparietal network (FN). (B) SCZ was related to hypo-connectivity within the AN between the AN seeds and the MPFC and hyper-connectivity between the AN seeds and a region of the putamen extending to a region of the caudate within the VAN. (C) SCZ was associated with hypo-connectivity between the FN seeds and the thalamus network (TN) and extending into regions of the insula and putamen within the VAN. (D) SCZ was linked to hypo-connectivity within the somatosensory network (SS), mainly in the language network between the SS seeds and the superior temporal cortex (STC). (E) SCZ exhibited hypo-connectivity between the VAN seeds and a region of the posterior parietal cortex (PPC) extending to the precuneus (PCS) and inferior parietal lobule (IPL) within the DN, hypo-connectivity between the VAN seeds and a region of the caudate within the FN, hypo-connectivity between the VAN seeds and the TN, and hypo-connectivity within the VAN between the VAN seeds and the regions of the putamen and ACC. (F) Individuals with schizophrenia had hypo-connectivity between the TN seeds and regions of the MCC extending to the superior frontal gyrus (SFG) and cerebellum within the VAN, hypo-connectivity within the TN between the TN seeds and thalamus, and hypo-connectivity between the TN seeds and regions of the cerebellum within the VAN. The results are shown with both height-based (hb) thresholding (the proportion of studies reporting an effect at that voxel exceeds chance) and extent-based (eb) thresholding (the proportion of studies reporting an effect at the contiguous voxels exceeds chance). All results are significant at $P < .05$, corrected for family-wise error rate.

Table 2. Results of the Meta-analysis of Resting-state Functional Connectivity in Schizophrenia

Seed-Network & Thresholding	Seed Anatomy	Effect Network	Effect Anatomy	*x*	*y*	*z*[a]	Voxels	Max. *P*
DN	ACC, Cerebellum, MPFC, MTG/STG, Para/Hipp, PCC/RSP							
SCZ < HC (hb)		DN	Right ACC	4	42	12	73	.66
SCZ < HC (eb)		DN, VAN, FN	Right MPFC extending to ACC/DLPFC	0	50	2	4112	.49
SCZ < HC (eb)		VAN	Left insula	−40	8	−6	2040	.45
AN	ACC, Amygdala, FP, MPFC, NACC							
SCZ < HC (hb)		AN	Left MPFC	10	40	−2	298	.75
SCZ > HC (eb)		VAN	Right putamen extending to insula, caudate	20	−4	8	2379	.42
FN	DLPFC, Caudate, Cerebellum, MCC							
SCZ < HC (eb)		TN,VAN	Right thalamus extending to insula, putamen	6	−12	6	4025	.62
SCZ < HC (eb)		TN,VAN	Left thalamus extending to MID, cerebellum, insula, putamen	−4	−8	−8	5036	.57
SS	Post/ Precentral, STG							
SCZ < HC (hb)		SS	Left STG	−50	−8	−2	65	.62
VAN	ACC, insula, MCC							
SCZ < HC (eb)		DN	Left PCC extending to precuneus, IPL	−2	−56	24	8385	.47
SCZ < HC (eb)		FN, TN, VAN	Left caudate extending to thalamus, putamen, ACC	−16	16	−10	14 870	.43
TN	Thalamus							
SCZ < HC (hb)		VAN	Left MCC extending to SFG	0	26	32	1051	.93
SCZ < HC (eb)		VAN	Right cerebellum	8	−70	−52	2943	.51
SCZ < HC (eb)		TN,VAN	Left thalamus extending to Mid, putamen	−7	−10	6	5789	.67

Note: ACC, anterior cingulate cortex; AN, affective network; DLPFC, dorsolateral prefrontal cortex; DN, default network; FN, frontoparietal network; FP, frontal pole; HIPP, hippocampus; IPL, inferior parietal cortex; MPFC, medial prefrontal cortex; MCC, middle cingulate cortex; NACC, nucleus accumbens; PCC, posterior cingulate cortex; Postcent, postcentral cortex; RSP, retrosplenial cortex; SFG, superior frontal gyrus; SS, somatosensory network; STG, superior temporal gyrus; TN, thalamus network; VAN, ventral attention network.

[a]Coordinates are from the Montreal Neurological Institute standard stereotaxic spaces. Voxels indicate the number of $2 \times 2 \times 2$ mm^3 voxels. Maximum *P* is the maximum proportion of studies exhibiting the effect at the peak density weighted by sample size. The results are shown with both height-based (hb) thresholding (the proportion of studies reporting an effect at that voxel exceeds chance) and extent-based (eb) thresholding (the proportion of studies reporting an effect at contiguous voxels exceeds chance). All results are significant at $P < .05$, corrected for family-wise error rate.

an area involved in monitoring information regarding salience and somatosensation.[15,85] This hypo-connectivity was reported to be related to weaker positive connectivity in schizophrenia.[13,29,49,57,58] The likelihood of hypo-connectivity of FN seeds did not differ among anatomical regions of the AN (supplementary eTable 3). The elder group showed a greater reduction in connectivity between the FN seeds with the thalamus than those in the younger group. A trend showed a greater likelihood of hypo-connectivity between the FN seeds and the thalamus with a long-duration of illness than with a middle-duration (supplementary eTable 4).

Hypo-connectivity Between the VAN and Regions of the DN, FN, and TN Involved in Internal Thought, Goal-directed Regulation and Gating Information. Schizophrenia was associated with hypo-connectivity between the VAN seeds and the PCC extending to the precuneus and inferior parietal cortex (figure 1E), a functionally consistent set of regions involved in internal thought.[77] When reported in the original papers, this hypo-connectivity was associated with increased negative connectivity in schizophrenia.[49,58,64] Additionally, hypo-connectivity was found between the VAN seeds and the caudate (figure 1E), which is involved in goal-directed regulation.[83] Hypo-connectivity was also observed between the VAN seeds and the thalamus (figure 1E), an area involved in gating information. Such hypo-connectivity was related to weaker positive connectivity in schizophrenia in

the original studies.[29,47,48,58,64] Post hoc analyses did not reveal differences among the anatomical seed effects (supplementary eTable 3). The elder group showed more increased connectivity between the VAN seeds with the PCC, a hub of the DN (supplementary eTable 4).

Hypo-connectivity Between the TN and Regions of the VAN Involved in Salience Monitoring. Schizophrenia showed hypo-connectivity between the TN seeds and regions of the cerebellum, putamen and middle cingulate cortex extending to the superior frontal gyrus (figure 1F), a set of regions belonging to the VAN and involved in monitoring information about salience.[15,85] The hypo-connectivity was related to a weaker positive connectivity in schizophrenia in the previous studies.[17,25,46,61,68]

Discussion

To our knowledge, this is the first meta-analysis to integrate these diverse results after systematically identifying 56 studies from 52 publications reporting seed-based whole-brain rsFC in schizophrenia. Our findings provide a comprehensive picture and strong evidence for the "dysconnection" hypothesis in schizophrenia. More specifically, schizophrenia consistently displayed reduced connectivity within and between brain networks involved in internally oriented attention (DN), processing of emotion (AN) and salience (VAN), gating information (TN), goal-directed regulation of these functions (FN) and auditory processing (SS), with an exception for the hyper-connectivity observed between the AN and VAN (figure 2). These consistently decreased hypo-connectivities motivate the proposition of a disconnected large-scale brain network model of schizophrenia in which network dysfunction is tightly linked to deficits in regulating salient information and maintaining the integrated self. In this disconnected model, the decreased communication within brain systems critical for salience processing (VAN) and gating information (TN) and brain systems responsible for internal thought (DN) or emotion processing (AN), the altered hypo-connectivity among the system involved in goal-directed regulation (FN) and the VAN, DN and AN, and the altered hyper-connectivity between the VAN and AN may help understand the dissociation between self-representation and environmental salience processing, which is a core feature of schizophrenia.[86]

According to our meta-analysis, schizophrenia showed hypo-connectivity in the VAN, a network involved in processing salience, which presented imbalanced communication with brain networks engaged for internal thought and brain systems involved in external goal-directed regulation. These findings cater to an influential model, the unifying triple network model in psychopathology,[87] which states that there is an aberrant intrinsic organization and interconnectivity of the salience network (VAN in this study), frontoparietal central executive network

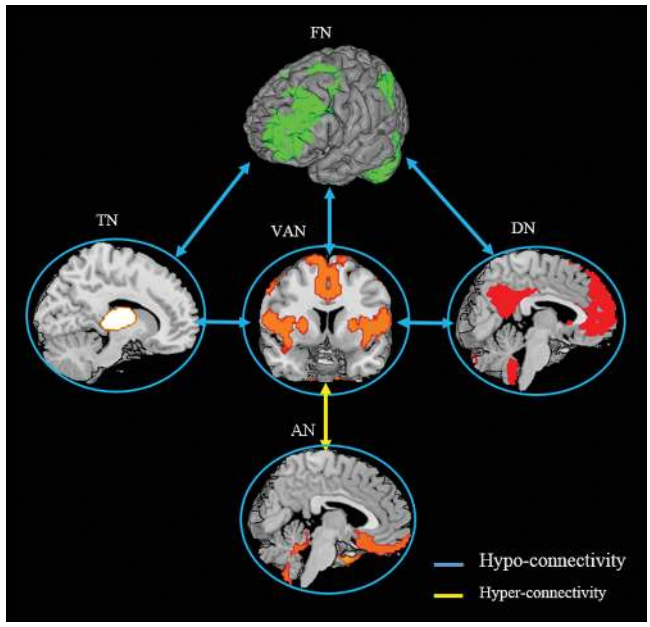

Fig. 2. A disconnected large-scale brain networks model of schizophrenia. Reduced connectivity within the salience monitoring systems (ventral attention network [VAN]; thalamus network [TN]) and imbalanced connectivity among the salience systems and networks involved in internal thought (default network [DN]) and external goal-direction regulation (frontoparietal network [FN]) may reflect a weakness in salience processing that contributes to the general deficits in both external goal-directed behavior and self-awareness. Meanwhile, reduced connectivity between the FN and TN, which are involved in gating information, may underlie the loss of salient information management control. Furthermore, decreased connectivity within neural systems involved in emotion processing and hyper-connectivity between the emotion system (AN) and the salience processing system (VAN) may relate to the deficits in emotion perception and regulation. Circles refer to reduced connectivity within the corresponding networks.

(FN in this study) and DN in psychiatric disorders. The model proposed that in schizophrenia, a weak detection and performance of salience stimuli lead to the inappropriate assignment of saliency to goal-relevant external stimuli and internal mental events. For example, patients with schizophrenia display aberrant salience attribution to external stimuli.[88] At the neural level, the compelling evidence came from several studies that used Granger causal analysis to illustrate a dysfunctional salience-network interaction with the FN and DN in schizophrenia.[49,89,90] These neuroimaging studies collectively provide evidence that schizophrenia patients exhibit a reduction in the strength of the causal influences from the VAN to the FN (goal-oriented or externally directed cognition) and DN (self-related or internally directed cognition). That is, the VAN cannot appropriately mediate the balance between activity of self-produced and activity of externally directed cognition to direct the right response to salient stimuli. This point was confirmed by our meta-analysis showing decreased connectivity between the

VAN and DN and the VAN and FN. In addition, the DN is involved in self-related activity per se (eg, self-referential processing), and the reduced connectivity within this network indicated the lack of integration of inner activity.[91] Meanwhile, the goal-directed regulation system (FN), showing hypo-connectivity with the DN and VAN, may be further involved in the confusion about self-related and unrelated information observed in schizophrenia due to the dysfunctional control of the FN on internal thought and salient stimuli, resulting in taking unrelated information as salient stimuli.[88] Therefore, the present patterns of imbalanced communication within and between these functional networks in schizophrenia may illustrate the weakness in salience processing (the perception of environmental stimuli as abnormally salient) leading to general deficits in both external goal-directed behavior and self-awareness.[87,89,90]

In general, the reduced positive FC may reflect a reduced integrative ability subserving similar goals.[92] It, however, should be noted that increased negative FC could be conceptualized as stronger connectivity, albeit in the opposite direction.[93,94] Therefore, hypo-connectivities for negative FC (schizophrenia has more negative FC than HC) between the DN seeds and the regions of VAN and FN, and between the VAN seeds and the regions of DN found in the present study may represent stronger integration in schizophrenia compared to HC. While there is no clear conclusion to the interpretation of increased negative FC, one plausible explanation would seem to be that increased negative FC may reflect increased completion for processing resources from a limited "central executive."[92–94] Therefore, the increased competition between the DN and VAN and FN, and between the VAN seeds and the DN may suggest that the dynamic equilibrium of the 3 brain systems was disrupted in schizophrenia. However, it is remarkable that, in ROI-based functional connectivity analyses, the global signal regression method and the interpretation of a negative correlation are still an open issue,[95,96] and the findings should be treated with caution.

We regard the TN and VAN as a whole unit monitoring internal and external salient information, although we divided them into 2 separate networks due to no prior segmentation of the thalamus. Although the role of the thalamus in the pathological mechanism of schizophrenia remains unclear,[72] given the fact that the thalamus displayed synchronized activity with the nodes of the VAN, recent brain network evidence has regarded the thalamus as a critical part of the VAN.[15,85] In the present meta-analysis, reduced connectivity within the thalamus system and between the TN and VAN may imply a possible mechanism of dysfunction of salience processing in schizophrenia. In addition, the present study found that schizophrenia showed reduced connectivity between the FN and TN. This point is consistent with recent evidence of thalamic nuclei anatomically and functionally disconnecting from the prefrontal cortex.[61,97] This finding may imply a loss of salient information management control.[72]

We also found that schizophrenia exhibited hypo-connectivity within the AN, especially in the ventral MPFC. Studies have proven that effective emotional regulation depends on communication between an area of the MPFC involved in cognitive control and limbic regions involved in affective response, eg, the amygdala.[98] Therefore, the observed decreased FC between the MPFC and amygdala in schizophrenia[24,56] may reflect the loss of coordination between control and affective systems. Meanwhile, the only instance of hyper-connectivity was observed between the ROIs of the AN and the putamen of the VAN in the present meta-analysis. Numerous pieces of evidence have strongly indicated that the putamen plays an important role in the processing of highly salient information,[15,84] especially negative emotion.[99] Increased connectivity may suggest that the patients with schizophrenia regard emotional information as the salient stimuli rather than the emotion per se. This provides a further explanation for the difficulty of the brain network to perceive negative emotion[100] and the dysfunction of emotion regulation in schizophrenia.[101]

Additionally, reduced connectivity among the SS system was revealed in our meta-analysis, especially in the left superior temporal gyrus (STG) of the auditory network, which is involved in speech perception and comprehension.[79,80] The STG has been thought to play a central role in inducing hallucinations in schizophrenia.[102] Previous studies of functional connectivity have indicated that reduced functional connectivity of the left STG of the auditory network was a trait marker of hallucinations in schizophrenia.[50,51] Combined with the reduced connectivity within the salience system, we speculate that the altered salience processing may further facilitate the perception of the "inner voice," although future studies are needed to validate this point of view.

Our exploratory moderation analyses revealed that moderation effects of illness duration and age were observed in several networks. Within the DN, connectivity was found to be gradually decreased with the increase in illness duration and age. The negative connectivity between the DN seeds and the insula, a hub of the VAN, was increased across illness duration. Meanwhile, elder group showed more increased connectivity between the VAN seeds and the PCC, a hub of DN. This result implies that difficulties in differentiating self-relevant from self-irrelevant information may render the perception of more environmental stimuli as abnormally salient across the illness duration and age.[88] The situation may become worse as prefrontal–thalamic coupling was gradually reduced across the duration of illness and age,[72,97] possibly reflective of top–down control disturbances.[17]

In summary, the disconnected large-scale brain networks model of schizophrenia mainly highlights the

dysfunctional role of the VAN (figure 2), which serves as the integral hub mediating the interactions between large-scale brain networks involved in externally oriented attention and internally oriented self-related mental processes. This model further outlined the disability of the VAN to assist target brain regions in the generation of appropriate behavioral responses to salient stimuli in schizophrenia.[85,103] From the perspective of a large-scale brain networks, this model provided the explanation for the triple network model of aberrant saliency mapping in schizophrenia[87]; ie, dysfunctional connectivity within the salience processing system and its further dysregulation of self-related activity and external goal-oriented attention lead to the aberrant assignment of salience to one's own experience in schizophrenia. Interestingly, the dysfunction mode of the large-scale networks in schizophrenia complimented our support for the "dysconnection" hypothesis[19]; the main trends to emerge are that the reduction in communication within and between different networks exacerbated the disruption of originally integrated mental function in schizophrenia.

Notwithstanding these implications, the main limitations of this study should be acknowledged while also indicating suggestions for future research consideration. First, the present meta-analysis was only limited to seed-based rsFC because this was the method most used in FC studies of schizophrenia. Due to the relatively few prior independent components analysis studies and their inconsistent numbers of components, it was not possible to separate the analysis for this method. However, when numerous independent components analysis studies have accumulated, computing the replicability of disorganized functional networks across different methods would be an important future direction. Second, although this meta-analysis provided overall consistency in the locations of the effects, the exclusion of negative findings built into the MKDA methodology may have biased the results. Future similar studies should use advanced methods and take negative findings into account. Third, although we did a general quality assessment of the individual studies (supplementary eTable 5), reports of the individual studies might also be affected by a priori assumptions of the authors, especially given that the ROI seeds were developed 2 ways: the authors either have prior ROIs or have ROIs that are data-driven, ie, the author calculated the rsFC based on regions from another imaging index; this might represent a potential bias in the present results. However, it must be mentioned that all of the individual studies of rsFC were whole-brain reports, and we treated them equally, dividing the ROI seeds into each prior network. Fourth, we attempted to integrate the present rsFC findings in schizophrenia using a meta-analysis; however, the limited studies for each network, especially the 7 studies for the TN network, might affect the stability of the results. This should motivate a future study to test the stability and repeatability of our results. In addition, because there were just 2 studies reporting effects in visual network and one study investigating the midbrain network (see supplementary eTable 2 and supplementary eFigure 2 for the seed ROIs within these 2 networks), it did not allow us to conduct meta-analyses for these 2 networks. In light of considerable deficits of visual processing in schizophrenia,[104] we predicted schizophrenia would show altered rsFC in visual network, and future studies should systematically investigate the pathophysiological cause behind it, especially when considering early visual deficits affect subsequent integrative processes in schizophrenia.[105]

Although the analysis of the moderating effect provided some significant results, we should remain cautious as these exploratory analyses could only compare differences in the likelihood (but not magnitude) of network abnormalities between clinical and demographic groups and only for groups that were consistently identified across the original studies.[7] Although it was not possible to test the moderating effects of medication and patient type because of the low frequency of studies with medication and patient categories, this motivates future investigations. In addition, imaging parameters (eg, magnetic field strength) and pre-processing varied greatly across the publications (supplementary eTable 1). For example, whether we should do global signal regression or ask participants to rest with eyes open vs closed may affect the results.[106] Due to the low proportion of studies in every methodological group, a moderating analysis was impossible. Future studies should take these methodological issues into consideration. Finally, although the full repertoire of functional networks utilized by the brain is continuously and dynamically "active" even when at "rest,"[107] it is not clear to what extent schizophrenia-related alterations in rsFC would exist during the performance of other tasks. The results presented here surely provide motivation for further investigations regarding this important issue and provide a more comprehensive view for neurobiological abnormalities in schizophrenia.

Conclusions

To the best of our knowledge, this is the first meta-analysis to comprehensively illustrate disconnection in large-scale brain networks in individuals with schizophrenia. More specifically, reduced connectivity within the VAN, TN, AN, and DN and imbalanced connectivity between the VAN and TN and networks involved in internal thought (DN) and external goal-direction regulation (FN) may underlie schizophrenia biases toward salient information because of the difficulty in differentiating self-produced and external world stimuli. Meanwhile, decreased connectivity within the neural systems involved in emotion processing and hyper-connectivity between emotion systems and salience processing systems may relate to the deficits in emotional perception and regulation. These

findings motivate a disconnected large-scale brain networks model of schizophrenia in which disconnected coordination among large-scale networks may underlie the dissociation between self-representation and environmental salience processing that is the core feature of schizophrenia.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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