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Convergence and Divergence of Brain Network Dysfunction in Deficit and Non-deficit Schizophrenia

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Deficit schizophrenia (DS), characterized by primary and enduring negative symptoms, has been considered as a pathophysiologically distinct schizophrenic subgroup. Neuroimaging characteristics of DS, especially functional brain network architecture, remain largely unknown. Resting-state functional magnetic resonance imaging and graph theory approaches were employed to investigate the topological organization of whole-brain functional networks of 114 male participants including 33 DS, 41 non-deficit schizophrenia (NDS) and 40 healthy controls (HCs). At the whole-brain level, both the NDS and DS group exhibited lower local efficiency (E_{loc}) than the HC group, implying the reduction of local specialization of brain information processing (reduced functional segregation). The DS, but not NDS group, exhibited enhanced parallel information transfer (enhanced functional integration) as determined by smaller characteristic path length (L_p) and higher global efficiency (E_{glob}). The L_p and E_{glob} presented significant correlations with Brief Psychiatric Rating Scale (BPRS) total score in the DS group. At the nodal level, both the NDS and DS groups showed higher functional connectivity in the inferior frontal gyrus and hippocampus, and lower connectivity in the visual areas and striatum than the controls. The DS group exhibited higher nodal connectivity in the right inferior temporal gyrus than the NDS and HC group. The diminished expression of Scale for the Assessment of Negative Symptoms (SANS) subfactors negatively correlated with nodal connectivity of right putamen, while asociality/amotivation positively correlated with right hippocampus across whole patients. We highlighted the convergence and divergence of brain functional network dysfunctions in patients with DS and NDS, which provides crucial insights into pathophysiological mechanisms of the 2 schizophrenic subtypes.

Key words: deficit schizophrenia/resting-state fMRI/functional connectivity/small-world/graph theory

Introduction

Schizophrenia is a highly heterogeneous psychiatric disorder. A major barrier to identify the neurobiological underpinnings of schizophrenia is its current nosology that reflects a clinical syndrome rather than a single disease entity. Deficit schizophrenia (DS)[1] represents a clinically homogeneous subgroup of patients characterized by the presence of primary and enduring negative symptoms which presents as a trait-like feature from the first episode of schizophrenia and lasts during periods of clinical stability. Patients with DS differ from those with non-deficit schizophrenia (NDS) in a variety of clinical aspects such as the higher rate of male[2–4] and summer birth,[5] poorer treatment response[6] and long-term clinical outcome.[7,8]

Numerous efforts have been made to identify focal abnormalities of brain morphology between DS and NDS. While early imaging studies reported the DS-specific alterations of the frontoparietal regions,[9] DS patients were more recently demonstrated to have

significantly reduced temporal gray matter[10–13] and white matter volume[13] compared with NDS patients. However, schizophrenia is thought of as a dysconnectivity disorder in multiple neuronal circuits (eg, frontostriatal and frontotemporal pathways)[14–16] rather than a focal pathology in a single region. In the past 10 years, imaging connectomics studies, which usually models the brain as a complex network in the context of graph theory,[17–19] have revealed topological disorganization in the whole-brain networks in schizophrenia such as reduced local clustering or local network efficiency (which reflects reduced functional segregation), reduced characteristic path length or higher global network efficiency (which reflects enhanced functional integration), and a redistribution of highly connected hubs (eg, frontal and temporal cortical hubs).[20–23] Notably, by measuring inter-regional cortical thickness correlation derived from structural magnetic resonance imaging (MRI) data, a prior structural connectomics study demonstrated that patients with DS exhibited aberrant network organization in comparison with either NDS patients or healthy controls (HCs), as characterized by stronger frontoparietal and frontotemporal couplings.[24] Relative to the brain's structural networks, functional networks are believed to capture the dynamics of information communication among regions.[19,25] However, no studies reported whether the DS patients exhibit topological disorganization in whole-brain functional networks such as abnormal functionally segregated and integrated information processing.

Resting-state functional MRI (R-fMRI), measuring spontaneous or intrinsic brain activity, has been widely used to investigate whole-brain functional connectivity (ie, functional connectomics) in schizophrenia.[20,26–29] Using R-fMRI, the most consistent finding in schizophrenic connectomics involves less local clustering or local efficiency in the whole-brain functional networks as compared to HCs,[21,23,30,31] indicating the relatively sparse local connectedness or reduced functional segregation in schizophrenia.[31,32] However, several independent R-fMRI studies have examined global network integrity in terms of global efficiency metric in patients with schizophrenia and reported inconsistent findings ranging from substantial increases[23,30] to no changes.[21] One of the key factors leading to these discrepancies between studies is clinical heterogeneity of recruited participants. Intriguingly, one R-fMRI study had delineated functional connectivity differences between schizophrenic patients suffering from predominant positive and negative symptoms,[33] which inferred distinct neural correlates of disparate symptoms and disease subtypes in schizophrenia.[34] Consequently, it would be of value to explore the unique characteristics of functional networks in DS patients with prominent and enduring negative symptoms.

To address these issues, in this study, we employed R-fMRI and graph theoretical approaches to study topological organization of whole-brain functional networks in 114 participants including 33 DS patients, 41 NDS patients, and 40 HCs. We sought to determine whether there were commonalities and distinctions in the topological abnormalities of whole-brain functional networks between the DS and NDS groups as compared to the controls. Based on recent studies in schizophrenia,[10,11,21,23,30,31,35] we hypothesized that (1) at the whole-brain level, there would be the common alterations of reduced functional segregation (in terms of local network efficiency) and the specific differences in global network integration (in terms of global efficiency) between DS and NDS patient groups, (2) at the nodal level, specific brain regional alterations would be found in DS patients, with high possibility of localization primarily to temporal regions, and (3) these network abnormalities would be associated with psychiatric symptoms or neurocognitive variables in the patients.

Methods

Participants

The present study consisted of a total of 128 participants including 84 clinically stable schizophrenia patients (40 DS and 44 NDS) and 44HCs. The schizophrenia patients were recruited from the psychiatric rehabilitation unit of Yangzhou Wutaishan Hospital, Jiangsu province, China. The eligibility criteria of the patients included: (1) a diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and confirmed by the Chinese version of the Structured Clinical Interview for DSM-IV (SCID-I)[36]; (2) male right-handed Chinese Han patients and age between 20 and 65 years; (3) having stable psychiatric symptoms and antipsychotic medication for at least 12 months based on the medical record. The exclusion criteria included severe comorbid conditions, neurological disorders, head trauma, mental retardation, alcoholism or substance abuse disorder and a history of previous electroconvulsive therapy. The diagnoses of DS and NDS were made according to the Chinese version of the Schedule for the Deficit Syndrome (SDS).[37] Specifically, the SDS rated the deficit syndrome as present if 2 of the following symptoms (restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive) had been at least moderately severe, persistent over 12 months and not attributable to secondary sources (eg, medication side effects, depression, paranoia, and anxiety). The healthy male controls who were age- and handedness-matched with the patients were recruited from the local community meeting the following criteria: (1) no lifetime history of psychotic, mood, and substance abuse or dependence, ascertained by the Structured Clinical Interview for DSM-IV Non-Patient version (SCID-NP)[38]; (2) no history of organic brain disorder, mental retardation, or severe head trauma; and (3) no family history of psychiatric disorders. Fourteen subjects were excluded after the evaluation of head motion (ie, exceeding 3 mm in translation or 3 degrees in rotation,

4 DS, 3 NDS and 4 HC) or poor quality of image (ie, ghost intensity, 3 DS). Therefore, 33 DS, 41 NDS patients and 40 HCs were finally available for the fMRI analysis. The study was approved by the Institutional Ethical Committee for clinical research of ZhongDa Hospital Affiliated to Southeast University and written informed consent was obtained from all participants.

Clinical Evaluation

The severity of schizophrenic symptoms was evaluated by the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), and the Scale for the Assessment of Positive Symptoms (SAPS). BPRS scale was organized into separate positive, negative, disorganized and affect syndromes based on the findings of the most comprehensive factor analysis of the 18-item BPRS.[39,40] SANS scale was organized into separate Diminished Expression, Inattention-Alogia and Social Amotivation factors based on the findings of the most comprehensive factor analysis of the 19-item SANS to date[41,42] (see the detailed category method in supplementary materials). Since the relevance of the Inattention-Alogia factor to negative symptoms remains controversial, it has been suggested that a 2-domain structure may be appropriate for the exploratory analysis.[42,43] Thus, 4 SANS components were employed for all the following exploratory analyses: SANS 19 items total score (SANS1), SANS diminished expression (SANS2), SANS social amotivation (SANS3) and SANS expression plus amotivation (SANS4).

Neurocognitive Assessments

Participants were evaluated by a battery of classical neurocognitive tests which consisted of Digit Vigilance test (DVT), Animal Naming Test (ANT), Controlled Oral Word Association Test (COWAT), Block Design (Wechsler adult intelligence scale-Chinese Revision [WAIS-RC]), Trail Making Test-A, B (TMT-A,B), Stroop Color-Word test (SCWT) and Spatial Processing (Block design). Based on previous reports regarding cognitive processes assessed by each of the tasks,[44–48] these cognitive measures were further grouped into 4 rationally motivated domains: sustained vigilance/attention (hereinafter labeled as sustained attention), ideation fluency, cognitive flexibility and visuospatial memory. For each domain, the composite score analysis was performed as a data reduction technique on these neurocognitive measures to reduce multiple comparisons and for the correction of the interdependency of neuropsychological measures.[44,48,49] Briefly, for each patient, the raw scores of each test were first transformed to *Z* scores with reference to the means and SDs of the test across all HCs.[8,50,51] Then, the composite scores for each neuropsychological domain were calculated by summation of the *Z*-transformed scores within the cognitive domains as below: sustained attention (4 tests, DVT, TMT-A, Stroop words and Stroop colors), ideation fluency (2 tests, ANT and COWAT), cognitive flexibility (2 tests, TMT-B and Stroop interference) and visuospatial memory (2 tests, Spatial processing [Block Design] and WAIS-RC test). The variables (eg, TMT) in which good performance was represented by lower values were adjusted for sign to ensure that higher *Z*-scores represented better performance for all variables. Cronbach's alpha and Cohen's *d* effect sizes[52,53] were computed for each cognitive domain (table 1).

Data Acquisition

All participants were scanned using a 3T MR system (GE HDx) with an 8-channel phased array head coil in the Subei Hospital of Jiangsu Province, Yangzhou, China. To minimize head motion, each subject's head was immobilized with cushions inside the coil during scanning. R-fMRI data were acquired using a gradient recalled echo echo-planar imaging (GRE-EPI) sequence: repetition time (TR) = 2000 ms, echo time (TE) = 25 ms, flip angle = 90°, number of slices = 35, field of view (FOV) = 240 × 240 mm^2, slice thickness = 4 mm without gap, matrix size = 64 × 64, voxel size = 4 × 4 × 4 mm^3, 240 volumes. During the MRI scan, participants were asked to lie quietly awake in the scanner with their eyes closed. In addition, T1 weighted structural images and diffusion weighted MRI dataset were also acquired, but these data are not used in this study.

Data Preprocessing

Data preprocessing was carried out using the SPM8 package (http://www.fil.ion.ucl.ac.uk/spm/software/SPM8/) and graph theoretical network analysis toolbox (GRETNA, http://www.nitrc.org/projects/gretna/).[54] To allow for magnetization equilibrium, the first 10 volumes were discarded. The remaining 230 volumes were first corrected for the acquisition time delay among different slices, and then the volumes were realigned to the first volume for head-motion correction. The time course of head motions was obtained by estimating the translations in each direction and the rotations in angular motion about each axis for each of the 230 consecutive volumes. Data of 11 subjects (4 DS, 3 NDS and 4 HCs) were discarded as they had head motion for more than 3 mm of translation or 3 degrees of rotation in any direction. The resulting functional images were spatially normalized to the standard space of the Montreal Neurological Institute using an optimum 12-paraeter affine transformation and nonlinear deformations[55] and resampled to a 3 mm cubic voxel. After a linear trend of the time courses was removed, the resulting images were further temporally band-pass filtered (0.01–0.08 Hz) to reduce the effects of low-frequency drift and high-frequency noises. Finally, the nuisance signals involving 6 head motion parameters, cerebrospinal fluid signal, white matter signal and global mean

Table 1. Statistics of Demographics, Raw Neuropsychological Performance, Domain-Specific Composite Scores and Clinical Characteristics Among NDS, DS and HC Groups

	HC (n = 40)	NDS (n = 41)	DS (n = 33)	$F/ES/t/\chi^2$	P
Age (y)	45.95 ± 9.47	46.02 ± 5.35	48.70 ± 7.68	1.464	.236
Education (y)	10.60 ± 2.73	9.20 ± 1.83	8.82 ± 2.02	6.685[a,b]	.002
Sustained vigilance/attention	—	**−4.04 ± 3.27**	**−10.51 ± 6.47**	**1.262**	
Digit vigilance test (s)	137.89 ± 42.86	181.74 ± 64.84	292.23 ± 128.61	25.001[b,c]	<.001
TMT-A (s)	49.92 ± 23.40	81.02 ± 30.80	134.21 ± 68.57	27.238[a,b,c]	<.001
Stroop words only	79.93 ± 16.31	58.88 ± 15.14	44.39 ± 19.99	31.728[a,b,c]	<.001
Stroop colors only	49.87 ± 13.14	36.05 ± 11.27	26.52 ± 12.85	24.428[a,b,c]	<.001
Ideation fluency	—	**−2.16 ± 2.12**	**−3.53 ± 1.79**	**0.698**	
COWAT	9.23 ± 2.33	6.66 ± 3.51	4.91 ± 3.11	14.300[a,b,c]	<.001
Animal naming test	18.10 ± 4.72	12.07 ± 4.50	9.27 ± 3.22	33.546[a,b,c]	<.001
Cognitive flexibility	—	**−2.04 ± 1.36**	**−4.17 ± 2.55**	**1.042**	
TMT-B (s)	122.64 ± 66.13	197.90 ± 53.33	302.45 ± 120.19	34.786[a,b,c]	<.001
Stroop interference	32.90 ± 10.47	21.46 ± 8.56	16.73 ± 10.69	20.329[a,b]	<.001
Visuospatial memory	—	**−2.15 ± 1.39**	**−3.70 ± 2.00**	**0.900**	
Spatial processing (block design)	18.25 ± 3.40	13.29 ± 3.30	11.36 ± 4.47	25.241[a,b]	<.001
WAIS-RC (block design)	27.83 ± 8.31	21.41 ± 6.45	13.42 ± 8.92	22.925[a,b,c]	<.001
Age at onset (y)		22.51 ± 2.62	22.09 ± 3.00	−0.644	.521
Duration of illness (y)		23.51 ± 5.81	26.61 ± 7.06	2.068	.042
BPRS total		27.41 ± 2.42	32.15 ± 3.05	7.450	<.001
Positive syndrome		6.34 ± 1.09	6.09 ± 1.07	−0.992	.324
Negative syndrome		7.46 ± 0.95	12.58 ± 1.70	15.467	<.001
Disorganized syndrome		6.46 ± 0.81	6.61 ± 1.35	0.564	.574
Affect		7.15 ± 1.15	6.88 ± 1.17	−0.988	.327
SANS total (19 items)		22.80 ± 4.42	40.30 ± 6.01	14.416	<.001
diminished expression		7.10 ± 1.76	12.55 ± 2.32	11.493	<.001
social amotivation		9.10 ± 2.49	15.45 ± 2.06	11.773	<.001
expression plus amotivation		16.20 ± 3.54	28.00 ± 3.78	13.821	<.001
SAPS total		9.85 ± 4.32	8.85 ± 3.71	−1.058	.293
Hallucinations		0.54 ± 0.81	0.45 ± 0.51	−0.508	.613
Delusions		1.17 ± 0.50	1.06 ± 0.35	−1.121	.266
Bizarre behavior		1.00 ± 0.59	0.82 ± 0.53	−1.378	.172
Positive thought disorder		1.00 ± 0.63	1.03 ± 0.81	0.176	.861
CPZ-equivalent daily dose (mg)		537.07 ± 209.66	503.18 ± 224.38	−0.670	.505
Smoking ratio (%)		73.20	60.60	1.317	.251*

Note: TMT-B, Trail Making Test-B; COWAT, Controlled Oral Word Association Test; BPRS, Brief Psychiatric Rating Scale; SANS, Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; NDS: non-deficit schizophrenia; DS: deficit schizophrenia; HC: healthy controls; CPZ: chlorpromazine; ES: Effect size (Cohen's *d*); WAIS-RC; Wechsler adult intelligence scale-Chinese Revision. Data are presented as mean ± SD. Unless otherwise indicated, the comparisons of the demographic and raw neuropsychological data among 3 groups were performed with the separate general linear model (GLM) analysis. Post hoc pairwise comparisons were performed by using least-significant difference (LSD) comparisons. The clinical characteristics between DS and NDS groups were compared by using 2 sample 2-tailed t tests (For t values, each negative column represents DS < NDS). The Patients' composite scores (bold words) of the 4 neuropsychological domains were standardized using the HC group data.
[a]Post hoc pairwise comparisons showed significant group differences between NDS vs HC.
[b]Post hoc pairwise comparisons showed significant group differences between DS vs HC.
[c]Post hoc pairwise comparisons showed significant group differences between DS vs NDS.
*The P-value was obtained by using a chi-square test. The significance level was set at $P < .05$.

signal were regressed out from the data. The residuals were used for the following brain network analyses.

Network Construction

In the context of graph theory, the brain was modeled as a network that is composed of nodes and edges linking nodes.[17,18] Herein, nodes represent brain regions and edges represent inter-regional functional connectivity. Specifically, we employed an automated anatomical labeling (AAL) atlas[56] to parcellate the brain into 90 regions of interest (ROIs) (45 in each hemisphere). The names of the ROIs and their corresponding abbreviations are listed in supplementary table S1. The time series of each ROI was estimated by averaging the residual time series of all voxels within that region. To measure functional connectivity among regions, we computed the Pearson correlation coefficients between the regional time series of all possible pairs of brain regions, yielding a correlation matrix (90 × 90) for each subject. Finally, each correlation matrix (Pearson correlation coefficients, absolute values) was thresholded into an undirected

binarized matrix with a fixed sparsity or density value (which was defined as the existing number of edges in a network divided by the maximum possible number of edges). Setting a sparsity-specific threshold ensured that the networks among the 3 groups had the same number of edges or wiring cost. Specifically, we computed the brain network properties over a wide range of network sparsity or network density ($8\% \leq s \leq 50\%$) at the intervals of 0.01 in which small-world parameters (which reflects optimal balance between functional segregation and functional integration) could be properly estimated and the number of spurious edges was minimized, as indicated in previous studies.[57,58] Through this thresholding, a set of 90 × 90 binarized matrices were obtained for each subject.

Network Analysis

For the constructed brain networks, the global and regional network measures were calculated to characterize their whole-brain architecture and regional nodal centrality, respectively.

The global measures included: (1) functional segregation metrics: clustering coefficient (C_p), normalized clustering coefficient (γ) and local efficiency (E_{loc}); (2) functional integration metrics: characteristic path length (L_p), normalized characteristic path length (λ) and global efficiency (E_{glob}); and (3) small-worldness metric: σ ($\sigma = \gamma/\lambda$). Briefly, the Cp of a network is the average of the clustering coefficients of all nodes and indicates the extent of the local density or cliquishness of the network. The E_{loc} of a network is the mean of all the local efficiencies of the nodes in the network and reveals how fast the communication is among the densely interconnected groups of brain regions. Meanwhile, the L_p of a network is the shortest path length (number of edges) required to transfer from one node to another averaged over all pairs of nodes, which is a measure of the extent of average connectivity or overall routing efficiency of the network. The E_{glob} of a network measures the ability of parallel information transmission over the network. Finally, the normalized clustering coefficient (γ) and normalized characteristic path length (λ) are defined as the ratio of the C_p and L_p of the brain network to those of matched random networks respectively, which have been typically used to examine the small-world properties quantitatively. The small-worldness ($\sigma = \gamma/\lambda$) characterizes an optimal balance between functional segregation ($\gamma > 1$) and functional integration ($\lambda \approx 1$), which is essential for high synchronizability and fast information transmission in the brain.

For regional nodal network measures, 2 nodal centrality metrics, nodal degree (k_{nodal}) and nodal efficiency (E_{nodal}), were employed[59] (see the more detailed interpretations of these network measures in supplementary materials).

Furthermore, we calculated the area under the curve (AUC) for each network metric for all the following statistical analysis (for the illustration of AUC, supplementary figure S4). The AUC metric provides a summarized scalar for topological characterization of brain networks independent of single threshold selection. The integrated AUC metric has been used in previous brain network studies and is sensitive at detecting topological alterations of brain disorders.[60–62]

Statistical Analysis

The continuous variables of demographic, clinical and cognitive raw data are presented as mean ± SD and analyzed by the general linear model (GLM) analysis. The categorical variables were analyzed by the chi-square test. Psychiatric symptoms between DS and NDS groups were compared using 2 sample t tests. The composite scores of each cognitive domain were compared between the 2 schizophrenia subgroups by effect size estimation (Cohen's d).

To determine the group differences in global network measures and regional nodal characteristics, statistical comparisons were performed on the AUC of each network metric (functional segregation and integration measures, small-worldness measure and nodal centrality measures) among the 3 groups using univariate 1-way analysis of covariance (ANCOVA). For the nodal centrality analyses, the false discovery rate (FDR) was calculated for multiple comparison correction. Post hoc pairwise comparisons were then performed using a general linear model. Recent literature has suggested that head motion has a confounding effect on resting-state functional connectivity.[63–65] In this study, we did not find significant differences in head motion among the 3 groups (Kruskal-Wallis Test: $\chi^2 = 4.307$, $P = .116$ for mean framewise displacement [FD][64]). Nevertheless, to further exclude possible effects of head motion, we analyzed all the network metrics by including mean FD as the covariate in the statistical models.[66] Therefore, the effects of head motion (mean FD), age and years of education were controlled for all of these analyses. Additionally, we also evaluated the effects of chlorpromazine (CPZ)-equivalent daily dose and illness duration on the network analysis for the post hoc pairwise comparison between DS and NDS. The significance level was set at $P < .05$.

Once significant group differences were observed in any network metric, we conducted 2 exploratory analysis strategies to assess the relationships between these metrics and the clinical and cognitive variables (composite scores of cognitive domains): (1) for the shared abnormal network metrics in patients with DS and NDS as compared to the controls, we first combined the deficit and non-deficit patients to assess these relationships in the "whole" schizophrenia group, performed by multiple linear regression analyses (dependent variables: the AUC

of network metrics showing between-group differences; independent variable: each clinical/cognitive variable. The group effect, mean FD, age, education, drug dose and illness duration were taken into account as covariates). Then, the multiple linear regression analyses were further performed in each patient group respectively with mean FD, age, education, drug dose and illness duration as unconcerned confounding factors. (2) For the distinct abnormal network metrics in each patient group, we explored the relationships between these metrics and the clinical and cognitive variables within the specific group using multiple linear regressions with mean FD, age, education, drug dose and illness duration as covariates.

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics for the subjects are presented in table 1. The ANOVA analysis showed significant differences in education (F[2,111] = 6.685, P = .002) but not age (F[2,111] = 1.464, P = .236) among the 3 groups. Least-significant difference (LSD) post hoc comparisons revealed shorter education periods for DS (P = .001) and NDS (P = .006) patients relative to HC subjects, while the 2 patient subgroups did not differ significantly (P = .473). There was no significant difference (χ^2[2] = 0.937, P = .626) in the type of antipsychotic treatment between the DS and NDS group (conventional antipsychotics: 42.4% [n = 14] and 31.7% [n = 13]; novel antipsychotics: 30.3% [n = 10] and 34.1% [n = 14]; combination: 27.3% [n = 9] and 34.1% [n = 14], respectively).The 2 patient subgroups had no significant differences in the mean age of onset, smoking and antipsychotic medicine dosage (chlorpromazine equivalents) except for a longer illness duration (t[72] = 2.068, P = .042) in the DS group. The DS patients showed more severe psychopathological total symptoms and negative symptoms (all Ps < .001) than NDS but not in positive, affect or disorganized syndromes (all Ps > .172).

Cognitive Characteristics

The GLM analysis revealed significant overall differences among the 3 groups for each individual neuropsychological test with age and education as covariates (all Ps < .001, table 1). LSD post hoc comparisons confirmed that both the DS and NDS patients performed worse than the control group on each of the neuropsychological test (all Ps < .05, except the Digit vigilance test in NDS vs HC [P = .079]). Furthermore, patients with DS, as compared with those with NDS, had significantly more severe impairment in most of the neuropsychological measures (all Ps < .05, except the Stroop interference [P = .135] and spatial processing test [P = .056] in DS vs NDS). The Cronbach's alpha for the 4 cognitive domains ranged from .673 to .824 (sustained attention: 0.824, ideation fluency: 0.690, cognitive flexibility: 0.731 and visuospatial memory: 0.673), indicating relatively high internal consistency among the measures. The range of the Cohen's d effect size was from 0.698 to 1.262 across the 4 cognitive domains (sustained attention: 1.262, ideation fluency: 0.698, cognitive flexibility: 1.042 and visuospatial memory: 0.900), which indicated that the DS–NDS differences of all the cognitive domains achieved moderate to large effect sizes.

Global Topological Organization of Functional Brain Networks

The mean FC strength (absolute value) across all regions exhibited significant difference between the 3 groups (F[2,111] = 5.072, P = .008). Post hoc comparisons showed that there was no significant difference between the NDS and HC group (P = .118) while the DS group showed significantly lower mean FC than the HC group (P = .002) and a tendency to lower FC than the NDS group (P = .091) (figure 1A).

All of the 3 groups exhibited typical small-world network architecture at a sparsity range of 0.08 to 0.50, ie, compared with matched random networks, the functional brain networks had larger clustering coefficients ($\gamma > 1$) and almost identical characteristic path lengths ($\lambda \approx 1$). Therefore, the small-worldness scalar $\sigma > 1$ for all the 3 groups (figure 1B). Nevertheless, ANCOVAs on the AUC of global network properties showed significant group effects in C_p, L_p, λ, E_{loc}, and E_{glob} (table 2 and figure 1C). Further post hoc analysis revealed that: (1) compared with the HC group, the NDS group showed significantly lower E_{loc} (P = .020) and a trend toward lower C_p (P = .068) in the brain networks while there were no differences (all Ps > .387) in L_p, λ, and E_{glob}; (2) compared with the HC group, the DS group showed the significantly lower E_{loc} (P = .003), C_p (P = .003), L_p (P = .046), and λ (P = .013), and the higher E_{glob} (P = .028) in the brain networks; and (3) compared with the NDS group, the DS group exhibited significantly lower λ (P = .048) and trends toward lower L_p (P = .057) and higher E_{glob} (P = .054) in the brain networks (table 2 and supplementary table S2).

Regional Topological Organization of Functional Brain Networks

We further localized the brain regions showing significant group differences in at least 1 nodal property in the patients.[67] ANCOVA analysis (P < .05, FDR corrected) revealed significant group differences in nodal degree primarily in the frontal, temporal, occipital and subcortical regions (table 2 and figure 2A). Post hoc analysis further revealed that: (1) compared with the HC group, the NDS group showed significantly higher nodal degree in the left inferior frontal gyrus (orbital part, ORBinf) and right hippocampus, and lower nodal degree in the right inferior occipital gyrus (IOG), right lingual gyrus (LING), right putamen and

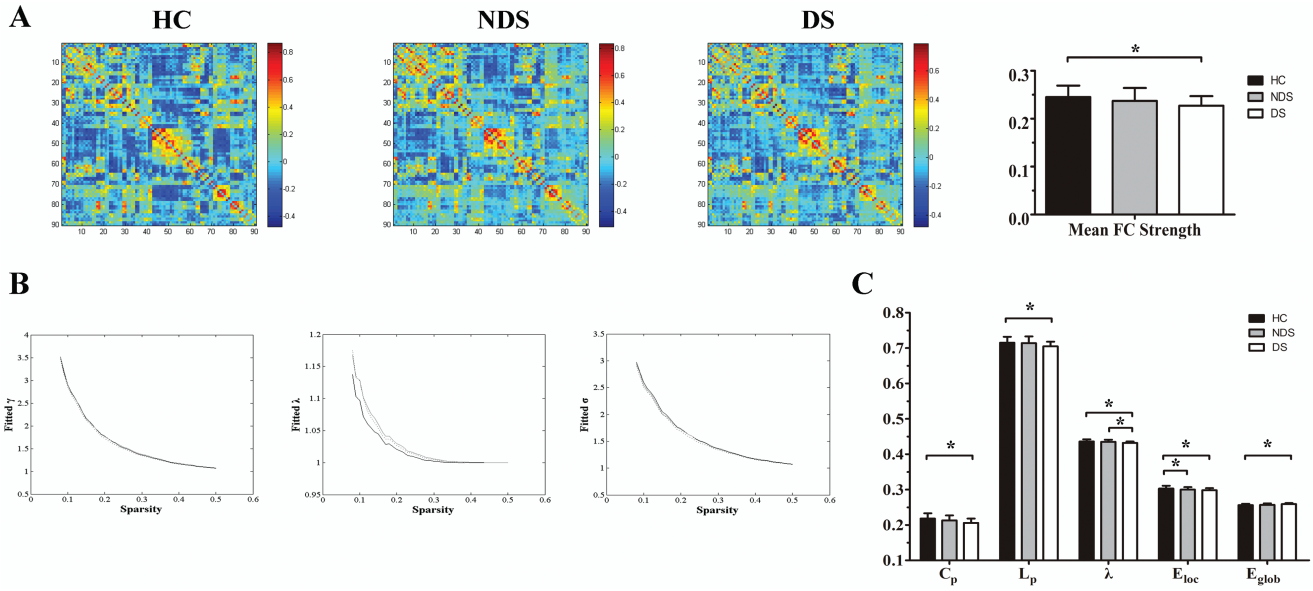

Fig. 1. Mean functional connectivity strengths and global network properties among the NDS, DS and HC groups. (**A**) The mean Pearson correlation matrices of the HC, NDS and DS group. The bar graph shows the mean functional connectivity (FC) strengths (Pearson correlation coefficients, absolute values) across all regions in each group. Error bars denote SDs. Black asterisks indicate significant differences ($P < .05$) in the post hoc comparisons. (**B**) The typical small-world network architectures ($\gamma > 1$, $\lambda \approx 1$ and $\sigma > 1$) across the sparsity among the NDS, DS and HC group with mean FD, age and years of education as covariates. Blue lines represent the NDS group, red lines represent the DS group and green lines represent the HC group. (**C**) The bar graph shows the value of significant AUC of the global network parameters among the 3 groups. Error bars denote SDs. Black asterisks indicate significant differences ($P < .05$) in the post hoc comparisons. Note: NDS: non-deficit schizophrenia; DS: deficit schizophrenia; HC: healthy controls. For color, please see the figure online.

Table 2. Comparisons of Global and Regional Network Metrics Among NDS, DS and HC Groups

		T (*P*) Value of Post hoc Test		
Global Metrics	*F* (*P*)	NDS vs HC	DS vs HC	DS vs NDS
C_p	6.051 (.003)	−1.850 (.068)[a]	−3.139 (.003) (DS < HC)	NS
L_p	3.110 (.049)	NS	−2.033 (.046) (DS < HC)	−1.934 (.057)[a]
γ	0.634 (.533)	NS	NS	NS
λ	3.954 (.022)	NS	−2.539 (.013) (DS < HC)	−2.018 (.048) (DS < NDS)
σ	0.592 (.555)	NS	NS	NS
E_{loc}	5.730 (.004)	−2.375 (.020) (NDS < HC)	−3.039 (.003) (DS < HC)	NS
E_{glob}	3.717 (.027)	NS	2.251 (.028) (DS > HC)	1.965 (.054)[a]
Nodal degree	FDR correction			
IOG.R	10.149 (.00009)	−4.190 (<.001) (NDS < HC)	−2.775 (.007) (DS < HC)	NS
PUT.R	10.020 (.0001)	−3.516 (<.001) (NDS < HC)	−4.521 (<.001) (DS < HC)	NS
ORBinf.L	8.161 (.0005)	3.492 (<.001) (NDS > HC)	3.508 (<.001) (DS > HC)	NS
ITG.R	7.123 (.0012)	NS	3.156 (.002) (DS > HC)	2.227 (.029) (DS > NDS)
PAL.R	6.572 (.002)	−2.504 (.014) (NDS < HC)	−3.406 (.001) (DS < HC)	NS
LING.R	6.436 (.00229)	−3.196 (.002) (NDS < HC)	−2.213 (.030) (DS < HC)	NS
HIP.R	6.420 (.00232)	3.514 (<.001) (NDS > HC)	2.430 (.018) (DS > HC)	NS

Note: NS, Not significant; NDS, non-deficit schizophrenia; DS, deficit schizophrenia; HC, healthy controls; C_p, clustering coefficient; L_p, characteristic path length; γ, normalized clustering coefficient; λ, normalized characteristic path length; σ, small-worldness; E_{loc}, local efficiency; E_{glob}, global efficiency; R: right; L, left; IOG, inferior occipital gyrus; PUT, putamen; ORBinf, inferior frontal gyrus (orbital part); ITG, inferior temporal gyrus; PAL, pallidum; LING, Lingual gyrus; HIP, hippocampus. The comparisons of the AUC of global metrics and nodal degree among the 3 groups were performed by using univariate ANCOVAs. Post hoc pairwise comparisons were then performed using *t* tests. The age, education and mean FD effects were removed in all of these analyses. For the comparison between DS and NDS, the disease duration and drug dose were taken into account as the additional covariates in the 2 sample 2-tailed *t* tests. For the nodal degree analyses, the false discovery rate (FDR) was calculated for multiple comparison correction. For the post hoc tests, $P < .05$ was considered significant.

[a]The significance of the post hoc pairwise comparison was tendency.

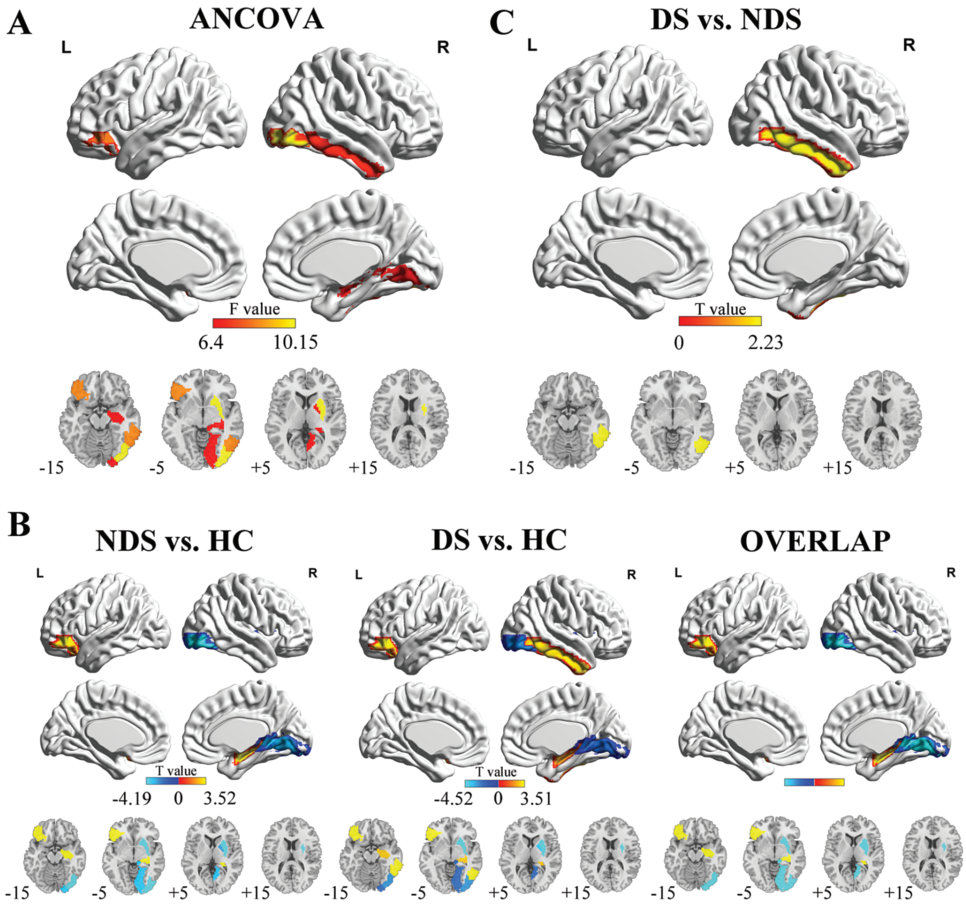

Fig. 2. Brain regions showing abnormal nodal degree in functional bran networks among the NDS, DS and HC groups. (**A**) Regions with significant group differences in nodal degree in the ANCOVA ($P < .05$, FDR corrected) analysis. (**B**) The post hoc pairwise comparisons showed the regions with significant differences in nodal degree in the NDS and DS groups compared with the HC group respectively and their overlap abnormal regions. For the overlap figure, the yellow regions represent higher and blue regions represent lower nodal degree in patient groups compared with the HC group. (**C**) The post hoc pairwise comparison showed the regions with significant differences in nodal degree between DS and NDS. *Note*: NDS: non-deficit schizophrenia; DS: deficit schizophrenia; HC: healthy controls; ANCOVA: 1-way analysis of covariance; L: left; R: right. For color, please see the figure online.

right pallidum; (2) compared with the HC group, the DS group showed greater nodal degree in the left ORBinf, right hippocampus and right inferior temporal gyrus (ITG), and lower nodal degree in right IOG, right LING, right putamen and right pallidum. Notably, both the patient groups showed higher nodal degree in the left ORBinf and right hippocampus (HC < [DS = NDS]), and lower nodal degree in the right IOG, right LING, right putamen and right pallidum (HC > [DS = NDS]) than the controls (figure 2B). Finally, post hoc comparison of the 2 patient groups revealed significantly higher nodal degree in the right ITG in the DS group compared with the NDS group (figure 2C) (DS > [NDS = HC]).

While comparing with nodal efficiency among 3 groups, ANCOVA analysis ($P < .05$, FDR corrected) revealed significant group differences in left ORBinf, right hippocampus, right IOG and right putamen. Post hoc analysis further revealed that both the patient groups showed higher nodal efficiency in the left ORBinf and right hippocampus (HC < [DS = NDS]), and lower nodal efficiency in the right IOG and putamen (HC > [DS = NDS]) than the controls. No DS-specific nodal efficiency alterations were found as compared to NDS patients (supplementary table S3).

Relationships Between Network Measures and Clinical Variables

For the global network measures: (1) the lower E_{loc} in the schizophrenic patients showed no significant correlation with any clinical or cognitive variables (Ps > .05); (2) the lower L_p ($r = -.389$, $P = .041$) and higher E_{glob} ($r = .392$, $P = .039$) in the DS group exhibited significant correlations with the BPRS total score (figure 3A) and the DS-specific lower λ showed a trend toward negative correlation ($r = -.335$, $P = .082$) with the BPRS total score.

For the nodal degree metric: (1) the higher nodal degree in right hippocampus in the schizophrenia patients was positively correlated with the SANS1 and SANS3 factors

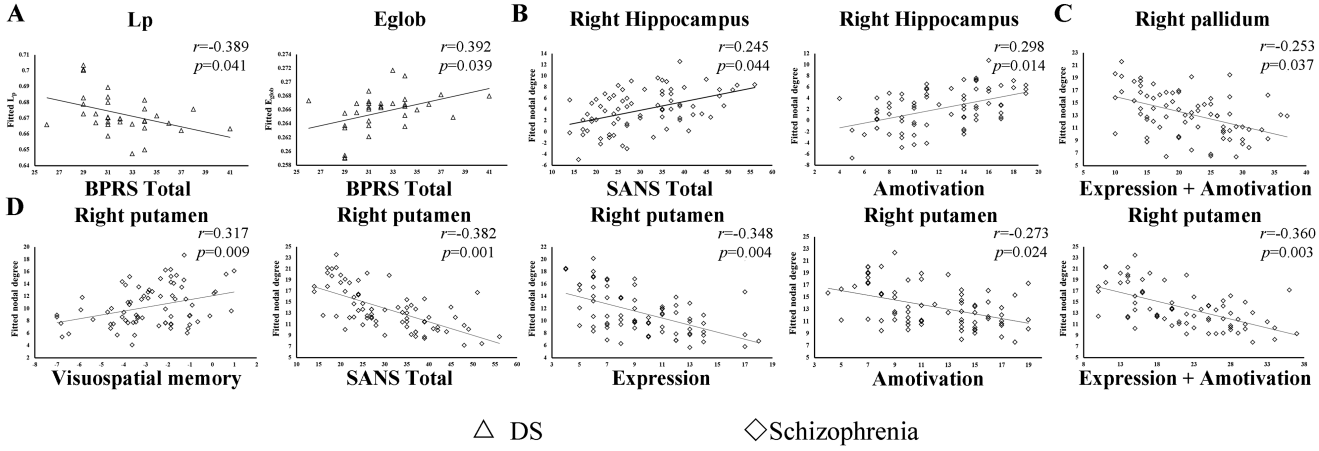

Fig. 3. The relationships between network measures and clinical variables in DS patients and within the schizophrenia group, respectively. (**A**) Scatter plots of the global network metrics (L_p and E_{glob}) and Brief Psychiatric Rating Scale (BPRS) total score in DS group. (**B**) Scatter plots of nodal degree in right hippocampus against SANS total and SANS social amotivation factor in the whole schizophrenia group, (**C**) Scatter plots of nodal degree in right pallidum against SANS expression plus amotivation factor in the whole schizophrenia group. (**D**) Scatter plots of nodal degree in right putamen against clinical and cognition variables in the whole schizophrenia group. Note: The multiple linear regression analyses were performed with group effect (if needed), mean FD, age, education, drug dose and illness duration as unconcerned confounding factors in the patient groups. DS: deficit schizophrenia; L_p: characteristic path length; E_{glob}: global efficiency; SANS: Scale for the Assessment of Negative Symptoms.

(figure 3B, all *P*s < .05). The degree in right pallidum was negatively correlated with the SANS4 factor within the schizophrenia group (figure 3C, $r = -.253$, $P = .037$). Moreover, the lower nodal degree in right putamen in the schizophrenia group was positively correlated with the visuospatial memory, and negatively correlated with the SANS1, SANS2, SANS3, and SANS4 factors (figure 3D, all *P*s < .05). Further analyses were performed to explore the relationships between those common abnormal network metrics and the clinical/cognitive variables in each patient group respectively. The right hippocampus was positively correlated with SANS3 factor in the NDS group ($r = .347$, $P = .038$). The degree in right pallidum were negatively correlated with SANS1, SANS2, and SANS4 factors in the NDS group (all *P*s < .05). Moreover, the right putamen was positively correlated with the visuospatial memory, and negatively correlated with the BPRS total score, SANS1, SANS2, SANS3, and SANS4 factors in the NDS group (supplementary figure S2, all *P*s < .05). Within the DS group, the nodal degree in the left ORBinf and right hippocampus were significantly correlated with the attention and ideation fluency function, respectively (supplementary figure S2, all *P*s < .05). (2) The DS-specific higher nodal degree in right ITG showed no significant correlation with any clinical or cognitive variables (*P*s > .05).

For the nodal efficiency metric, the results were largely compatible with the above-mentioned nodal degree findings except the near-significant correlation between right hippocampus and SANS1 within the schizophrenia patients ($P = .055$), and the relationship between right hippocampus and SANS3 in the NDS group ($P = .115$) was no longer significant (supplementary figure S3, all *P*s < .05).

Discussion

This is the first neuroimaging study using graph theory analysis to explore the topological alterations of functional brain networks in the DS and NDS groups as compared to the HC group. The main findings are as follows: (1) at the whole-brain level, the lower information segregation was commonly demonstrated in both DS and NDS groups, in which the metrics of functional segregation were affected more broadly in DS (ie, lower E_{loc} and C_p) than NDS patients (ie, lower E_{loc}). The higher global information integration was found only in the DS patients (ie, lower L_p and λ, and higher E_{glob}) but not in the NDS patients relative to the controls. The DS patients exhibited higher global integrity in the brain networks (ie, lower λ) compared with the NDS patients. Furthermore, the L_p and E_{glob} were significantly correlated with the BPRS total score in the DS group. (2) At the nodal level, both the NDS and DS groups showed commonly higher nodal connectivity in the inferior frontal gyrus and hippocampus, and commonly lower connectivity in the visual areas and striatum than the controls. The DS group demonstrated a specific regional disturbance in the right ITG compared with the NDS patients. These findings advance our understanding of similarities and differences underlying neural mechanisms between DS and NDS patients from a network perspective.

Functional segregation and functional integration refer to the ability for local specialization and parallel information transfer in the brain network, respectively. Both E_{loc} and C_p are the metrics of functional segregation. E_{loc} reflects the efficiency or "speed" of information transfer among the adjacent nodes, while the C_p reveals

the density of the local interconnectivity within a network.[59] The present study found that both DS and NDS patients exhibited reduced local network efficiency (lower E_{loc}), which was largely compatible with several previous brain network studies suggesting the decreased local information processing in schizophrenia.[20,21,23] These findings indicate that disrupted functional segregation might be a common feature of brain network disorganization in schizophrenia, regardless DS and NDS. It might be plausible that the observed reduced local communication efficiency (functional segregation) of brain functional networks may arise from neurodevelopmental dysfunction such as excessive synaptic pruning in schizophrenia.[16,31] DS patients have previously been shown to have higher risk of neurodevelopment impairments than NDS patients such as worse premorbid adjustment for the early epochs of life.[8,68,69] Accordingly, the present study showed a relatively broader impaired functional segregation of the whole-brain functional networks in the DS patients (ie, lower E_{loc} and C_p) than NDS patients (ie, lower E_{loc}). This hypothesis may be further support by recent studies, in which both lower E_{loc} and lower C_p were found in childhood-onset schizophrenia.[23,31] It is notable that the DS patients studied here not only demonstrated reduced functional segregation (lower E_{loc} and C_p), but also showed abnormal enhanced functional integration (lower L_p and λ, and higher E_{glob}) in the brain network. Functional integration ensures interregional prompt transfer of information in brain networks, which constitutes the basis of higher-order cognitive tasks and conscious processing.[70,71] The lower characteristic path length (L_p and λ) indicates the reduction of the shortest length for information to propagate between any pair of parallel nodes in a network, and the higher global efficiency (E_{glob}) reflects the increased efficiency of information transfer among remote brain regions. Consistent with the present study, the enhanced functional integration has been reported in the analysis of function network in the patient with schizophrenia, which could be due to the dynamic cerebral reorganization of functional connectivity between brain regions.[16,31] Importantly, the greater functional integration in schizophrenia patients has been assumed to have potential benefits, which might represent greater resilience to focal neural damage.[30,72] Furthermore, the present study found the specific correlations between L_p, E_{glob} and the BPRS total score in the DS group, which may represent a possible compensatory response to the functional deficit in DS patients.

Several convergent abnormalities in regional nodal connectivity, involving the hippocampus, striatum (putamen and pallidum), inferior frontal gyrus and visual regions, were found in both the DS and NDS groups compared with the HCs. Most of these regions have been previously reported to have functional disconnections in patients with schizophrenia.[21,30,73–76] The present study also found the right hippocampus hyper-connectivity exhibited positive correlations with the SANS total score and the social amotivation factor in the schizophrenia group. Consistently, a recent R-fMRI study also demonstrated significantly positive associations of the greater intrinsic right hippocampus activity with negative symptoms and cognitive dysfunction in patients with schizophrenia.[26] The putamen and pallidum, regions of reduced connectivity observed in the present study, are important relay stations between the cortex and the basal ganglia nuclei and are involved in the regulation of the reward system. The present finding also indicated that both the putamen and pallidum metrics negatively correlated with the SANS total score and SANS expression plus the amotivation factor in the whole schizophrenia group, especially in the NDS patients. Intriguingly, recent task fMRI studies according well with our findings showed a significantly negative correlation between the reduced putamen/ventral striatum activity and negative symptoms in schizophrenia.[77,78] Additionally, it should be noted that the correlations between negative symptoms and abnormal connectivity of the right hippocampus, putamen and pallidum were not observed in the DS patients. However, these negative findings of correlation do not exclude pathologic involvement of the impaired neural circuits in a specific symptom domain.[79] Whether it could be attributed to ceiling effects of more severe negative symptoms or to pathology in other than the hippocampus and reward system in DS patients remains unclear.

The present findings of particular interest demonstrated divergent regional alteration of the increased nodal degree in the right ITG in DS patients relative to NDS patients. Consistent with our findings, the right ITG, important for language formulation[80] and face perception,[81] has been reported to have volume reduction in DS patients as compared with NDS patients.[12] Previous evidence also suggested a specific nonprogressive impairment of right temporal lobe in early neurodevelopment in DS patients.[10] Interestingly, abnormal increased activation of right ITG was found to be related to the deficits in facial recognition and interpersonal communication seen in autism,[81] which are phenotypically similar to the negative symptoms of schizophrenia. Furthermore, recent study also reported a disrupted integrity of white matter tracts in the right inferior longitudinal fasciculus (ILF) of DS patients relative to NDS patients.[82] The ILF is considered to connect the neuronal circuit from the visual areas (occipital lobe) to the temporal lobe (ITG, amygdale, and hippocampus regions),[83,84] which is essential for face recognition,[85] visuoemotional processing[86] and other functions related to language.[87] DS patients have been reported to have poorer performance than NDS patients on facial affect labeling and basic visuoperceptual face processing tasks.[88] Recent Meta-analysis has demonstrated the highly consistent relationship between facial recognition and negative symptoms.[89] It had been speculated that patients with negative symptoms might

have poorer emotion perception because of reduced emotional experience (ie, anhedonia) or expression (ie, affective flattening).[89–91] Therefore, lesions of this neuronal circuit, including ILF and right ITG, might be implicated in emotion perception deficit and the prominent negative symptoms in the DS patients, which is in accordance with the hypothesis that disruptions of neural circuit structure and function may underlie the specific cluster of behaviors characteristic of a symptom domain.[79] The present hypothesis might be further supported by the evidence showing abnormal temporal volume[10–12,35] and diminished mean regional cerebral blood flow (rCBF) in the temporal region[92] in DS patients. Furthermore, it should be mentioned that abnormalities of fronto-parietal connectivity in DS patients have also been reported by several functional and structural neuroimaging studies.[24,92–94] The present study also found differences of right inferior parietal cortex, bilateral middle temporal gyri and bilateral inferior frontal gyri between DS and NDS at the uncorrected level ($P < .05$, data not shown). The relatively small sample size, the large number of covariates and the FDR correction might decrease the statistical power of the present study. Due to the relatively strict statistical criteria, the right ITG was revealed as the sole positive region of nodal metrics in DS patients, providing valuable evidence to understanding the pathophysiology of deficit symptoms of schizophrenia.

Limitations and methodological issues of our study should be considered. Firstly, all the patients received antipsychotic treatment, which might contribute to the alterations of the functional connectivity and network parameters by antagonism at dopamine, and perhaps other, receptors.[60,95] However, the type and dosage of antipsychotic drug was consistent between the 2 patient groups, and antipsychotic dosage was not significantly correlated with any of the connectivity or network metrics. Secondly, chronic schizophrenia patients were recruited in the present study to guarantee the status of clinical stability as a requirement of DS categorization. Illness duration in patients with schizophrenia might import potential confounders for neuroimaging analysis. Thirdly, the present study, an exploratory analysis with the relative small sample, did not include correcting the correlations between nodal parameters and clinical variables for multiple comparisons. In order to increase the homogeneity of the participants, the present study attempted to restrict variance by eliminating or minimizing confounders including gender, fluctuations of psychiatric symptoms and social environment. This would present difficulties in the recruitment of both DS and NDS patients. The present study enrolled DS sample relatively large compared to other published neuroimaging studies of this group. However, it should be emphasized that the present sample size has limited power, which means that we are unable to accurately determine the different contributions of cognitive impairments, psychiatric symptoms and subgroup effects on neuroimaging network parameter alterations. Future studies are required to increase the statistical power with a larger sample size. Moreover, multiple neuroimaging measures might be also needed to compensate for the relative imprecision and low sensitivity of any single-modality neuroimaging technique.[79]

In summary, our findings provided empirical evidence for convergent and divergent patterns of network dysfunctions between patients with DS and NDS. Specifically, abnormalities between the 2 patient groups emphasize the core neural circuitry essential for the visuoemotional and social functions characteristically impaired in DS patients. Collectively, the present study indicates that the subjects with deficit syndrome might be a specific subgroup within schizophrenia.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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