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Grey matter connectome abnormalities and age-related effects in antipsychotic-naive schizophrenia

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ABSTRACT

Background: Convergent evidence is increasing to indicate progressive brain abnormalities in schizophrenia. Knowing the brain network features over the illness course in schizophrenia, independent of effects of antipsychotic medications, would extend our sight on this question.
Methods: We recruited 237 antipsychotic-naive patients with schizophrenia range from 16 to 73 years old, and 254 healthy controls. High-resolution T1 weighted images were obtained with a 3.0T MR scanner. Grey matter networks were constructed individually based on the similarities of regional grey matter measurements. Network metrics were compared between patient groups and healthy controls, and regression analyses with age were conducted to determine potential differential rate of age-related changes between them.
Findings: Nodal centrality abnormalities were observed in patients with untreated schizophrenia, particularly in the central executive, default mode and salience networks. Accelerated age-related declines and illness duration-related declines were observed in global assortativity, and in nodal metrics of left superior temporal pole in schizophrenia patients. Although no significant intergroup differences in age-related regression were observed, the pattern of network metric alternation of left thalamus indicated higher nodal properties in early course patients, which decreased in long-term ill patients.
Interpretations: Global and nodal alterations in the grey matter connectome related to age and duration of illness in antipsychotic-naive patients, indicating potentially progressive network organizations mainly involving temporal regions and thalamus in schizophrenia independent from medication effects.
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1. Introduction

Approximately 70 percent of patients with schizophrenia suffer from long-term psychiatric disabilities [1]. To date, it remains unclear whether brain changes found in the early stage of illness deteriorate during the course of illness and in which way they may contribute to persistent disabilities. Although substantial evidence demonstrates that some patients manifest progressive deterioration of social functioning [2–5] as well as grey/white matter volume reduction [6–8] after illness onset, the nature of connectome level changes and the

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Research in context

Evidence before this study

How brain changes at the network level progress with age remains elusive in schizophrenia. Previous evidence indicated deterioration of network connectivity in schizophrenia in functional network and structural network that derived from diffusion tensor imaging, but confounded by drug effects. Recently, an approach for constructing individual grey matter networks was introduced but has not been examined in this regard. Cross-sectional studies on antipsychotic-naïve schizophrenia, especially including those with duration of untreated illness over decades, would be a reasonable approach to explore the brain changes in relation to age and illness course free from the effects of antipsychotics.

Added value of this study

This study included patients with duration of untreated psychosis from months to decades. The alternations of network metrics in relation to age and illness course would provide adminicular evidence regarding illness deterioration, as well as potential different patterns of brain changes.

Implications

Implications of all the available evidence anatomical brain connectome indicated potential illness deterioration in grey matter network involving left thalamus and left superior temporal pole, while the decreased nodal metrics in central executive network and default mode network at both early and later illness course might represent a disease trait that is maintained over the illness course. This study provides a biomarker profile that advances understanding of progression of schizophrenia from the perspective of whole brain grey matter network organization without the confounding effects of antipsychotic medication.

degree to which drug effects contribute to such changes are not clear [8–13]. Furthermore, the follow-up period of previous longitudinal studies is usually restricted to the first few years after illness onset, so longer-term effects are unclear. While longitudinally following untreated patients for many years would address this challenge scientifically, it is not possible to withhold treatment over a lifetime for ethical reasons. Cross-sectional studies of brain changes in relation to duration of untreated illness represent a reasonable approach for searching adminicular evidence regarding different patterns of brain changes related to illness course.

By studying long-term ill but antipsychotic-naive patients with an average illness duration of more than twenty years, our previous research identified accelerated age-related cortical thinning in prefrontal and temporal regions [14], and greater age-related decline of white matter microstructure in the genu of the corpus callosum [15]. These findings suggest progressive changes of brain structures during the lifespan course of schizophrenia. As schizophrenia is characterized as a disorder of brain dysconnectivity [16–19], structural changes need to be considered not only in terms of region-by-region analysis, but also at the connectome network level [20,21]. Regarding the brain network analysis, deterioration of network connectivity in schizophrenia were reported both in functional network [22] and structural network that derived from diffusion tensor imaging (DTI) [23,24], but confounded by drug effects. However, our previous functional study included both treated and untreated patients with long illness duration reported negative observation on network deterioration [25], indicating inconsistent findings of network progression in schizophrenia. In comparison to networks extracted from functional MRI or DTI, structural grey matter networks have higher stability, which is important in a cross-sectional correlational study [26]. Therefore, studying untreated schizophrenia with large age span from the perspective of grey matter network might provide more insights on deterioration of schizophrenia.

Classical grey matter networks have been constructed by calculating the covariance of grey matter measurements across participants, resulting in brain networks only at the group level. The derived network metrics are therefore not able to reflect the variability between individuals or to estimate correlations with clinical variables such as illness duration and symptom severity. A newer approach constructs grey matter networks at the individual level, which based on the morphometric similarities of grey matter between brain regions [27].

In this study, we evaluated individual network properties in a large sample of antipsychotic-naive patients with schizophrenia across a large age span, including patients with duration of untreated psychosis (DUP) from months to decades, and further exploring the effects of age and DUP, as they are relevant indicators in the development of schizophrenia, in which onset age of schizophrenia mainly distributed between 16 and 30 years old [28], longer duration of illness usually accompanied by older age. We aimed to find evidence on the deterioration of brain in schizophrenia at relatively complete disease course from the view of grey matter network.

2. Methods

2.1. Ethics

This study was approved by the research ethics committee of West China Hospital of Sichuan University; study number 2019 (1016), and written informed consent was obtained from participants or their legal guardians if they were under 18 years old.

2.2. Participants

All participants were right-handed with age between 16 and 76 years, and recruited at the West China Hospital from September 2005 to May 2014. A total of 237 never-treated patients with schizophrenia were recruited (age: 16–73 years, age of onset: 14–47 years, illness duration: 1 week-48 years), including 202 first episode drug-naïve schizophrenia patients and 35 patients who remained untreated for over 5 years. The first episode patients were typical and well described in our previous work [29]. Regarding those who were chronically ill but received no treatment, these patients lived mostly in small villages with tight social networks in West China, and others in urban or suburban areas. They had not received any antipsychotic medication before participation due to reasons including (1) parental concern about family stigma associated with mental illness, (2) a lack of understanding or recognition of the severity of mental illness in parents or spouse, (3) poor socioeconomic conditions that limited travel and funds for medical care, and (4) emotional rejection of medical care by the family for conflicting with physicians when the patient brought to medical attention close to the time of illness onset [14]. Their diagnoses were confirmed before participation by a Mental Health Screening Program supported by West China Hospital, a project aiming to provide psychiatric care to people living in the community with serious mental illness but who had not had access to or previously sought psychiatric treatment. Diagnosis of schizophrenia was determined by consensus of two experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID)-Patient Version. The duration of untreated illness was determined using the Nottingham Onset Schedule [30], with information provided by patients, family members, and other sources. Current symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) [31]. However, the DUP information was missing for 46 patients due

to the fact that some patients and family members could not provide precise details about the illness onset especially for those who lived in rural areas.

A total of 254 healthy individuals (age: 16–76 years) were recruited from the community where the patients resided through advertisements. The SCID-Non-Patient Version was used to exclude healthy participants with any major psychiatric disorders, and any known major psychiatric illness in their first-degree relatives. The exclusion criteria for all participants included: (1) contraindications for an MRI examination (i.e., braces or claustrophobia); (2) a history of neurological diseases; (3) alcohol or drug abuse/dependence; (4) a positive pregnancy test; and (5) a history of any systemic disease, including cardiovascular and metabolic diseases.

2.3. Image acquisition

High-resolution T1-weighted images were acquired on a 3.0 T GE Signa EXCITE scanner (General Electric, Milwaukee) with an 8-channel head coil. Details of the scanning protocol are as follows: repetition time (TR)=8.5 ms, echo time (TE)=3.4 ms, flip angle=12°, sagittal orientation, matrix=256 × 256, number of slices=156, and slice thickness=1 mm. A flexible cushion was applied to minimize head motion during scanning. Two experienced neuro-radiologists separately inspected images to ensure that there were no image artifacts or gross brain abnormalities.

2.4. Extraction and normalization of brain networks

The construction of individual grey matter networks followed the methodology proposed by Tijms et al. [27]. In brief, the whole brain grey matter was segment into $2 \times 2 \times 2$ mm^3 voxel cubes using Statistical Parametric Mapping software (SPM, http://www.fil.ion.ucl.ac.uk/spm). Each cube was defined as a node of the network, and the "connections" between cubes were determined by statistical similarities of their grey matter morphologies, where similarity was determined by the maximal correlation between two cubes over different rotations. Weighted network maps were constructed after setting a threshold for each individual map, keeping connections with significant positive correlations after correction for multiple comparisons [32].

Given that the size of grey matter networks obtained using these procedures differed across individuals [33], we normalized them based on the unified Automated Anatomical labeling (AAL) parcellation template with the methodology proposed by Batalle et al. [34]. The normalized connection strength was bounded between 0 and 1. Self-connections were excluded. Details of normalization are provided in Supplementary Materials. These procedures yielded a 90×90 normalized weighted grey matter similarity network for each subject.

2.5. Network property analysis

Six global property metrics (global efficiency, E_g; local efficiency, E_{loc}; assortativity; the small world scalar, σ; cluster coefficient, Cp; characteristic path length, Lp) and three nodal property metrics (betweenness, degree, nodal efficiency) were calculated for each participant [35,36]. The E_g reflects network integration and mathematically equals the average inverse of Lp, while E_{loc} measures information transfer capacity of a node and its neighbors. Assortativity quantifies the extent that nodes with similar degree are connected to each other [37]. The σ is a metric that reflects the relation of information transfer to network density. The Cp is a metric of network segregation, measuring the local interconnectivity of the network, while the Lp is a metric of network integration, reflecting the average of the shortest path length. Betweenness, defined as the fraction of all shortest paths in the network that pass through a given node, characterizes the node's effect on information flow. Degree is the number of links connected to a node, which reflects its information communication ability, whilst Ne measures the ability of one node to propagate information with its connected nodes [38].

The GRETNA toolbox (version Master, https://www.nitrc.org/projects/gretna/) was used for the calculation of network properties [39]. Network properties were calculated at the range of sparsity (S) thresholds of 0.05–0.40 with an interval of 0.01. This threshold was determined by the size of network matrix (90 nodes), which ensured that the thresholded networks met the small worldness scalar $\sigma > 1.0$, based on (1) the average degree on all nodes of each threshold network being $>2 \times \log$ (N) (with N indicating the number of nodes, $N = 90$ here); and (2) the σeof the thresholded network of all subjects is > 1.1 [35]. The area under the curve (AUC) was calculated for each network metric, providing a summary metric for characterizing topological properties of brain networks independent of any single threshold selection [40].

2.6. Statistics

2.6.1. Differences in network metrics between diagnostic groups

The group differences between patients and controls in network metrics, both at the global and nodal level, were examined with analysis of covariance (ANCOVA) with age, sex and education years as covariates. As the global and nodal network metrics reflect network organization at different levels in non-independent ways, they were corrected for multiple comparisons independently with Bonferroni correction. Thus, global network metrics were corrected with $p < 0.05/6$, while nodal network metrics were corrected with $p < 0.05/270$ (90 regions and 3 metrics for each region). For those network metrics that do not obey the normal distribution, a non-parametric test was further conducted to test whether inter-group differences were replicated, details were presented in Supplementary Materials.

Given that the patient group included patients that were at the adolescent stage and those who were old, an additional age-wise subgrouping analysis in network metrics of patient group in relation to controls was conducted to see whether those changes replicated at different age range. All participants were divided into three age levels:$<$ 20 years old, 20–45 years old and $\geq$ 45 years old (adolescent, adult, elderly, Table S1), and the network metrics were compared between patients and healthy controls at the three age levels to examine whether the findings observed in the primary analysis were replicated.

2.6.2. Age-related regression analysis of altered network metrics

To identify differential relationships between grey matter connectome measures and age in metrics where group differences had been detected, the global and nodal network metrics with significant inter-group differences were extracted for each subject, and modelled with age using a quadratic model for each group. This was done because the age effects on the brain are known to follow a non-linear trajectory [41,42]. The models that achieved statistical significance in either group were compared between groups to determine whether there exists a significant differential rate of age-related changes between patients and controls (details were presented in Supplementary Materials).

2.6.3. Associations between altered network metrics and DUP

As the age and DUP were closely related in patients, the association between altered network metrics and DUP in schizophrenia patients was also examined in those with available data, simply with a linear regression model to confirm the age-related findings. Notably, the age range of 46 patients with missing DUP was 16–58 years and most of them were younger than 40 years old, which was basically consistent with the age distribution of the whole sample of

patients, thus the results were also representative. Findings were corrected with Bonferroni. In exploratory analysis, network abnormalities were additionally correlated to age of onset and findings were presented in the Supplementary Materials.

2.6.4. Separate analyses of abnormal network metrics in DUP-wise subgroups

As noted in above analyses, some network metrics were increased across all schizophrenia patients (e.g., nodal metrics in left STP and left thalamus), but exhibited age-related decline or DUP-negative changes. We postulated that different pathophysiological processes might be implicated in these altered network metrics at different stages of illness. To further test this postulation, separate following case/control comparisons were calculated in the groups that patients with DUP shorter or longer than 5 years, described as short-term and long-term group respectively, for those network metrics which had been identified as being abnormal across all patients. Such time point of 5 years was determined according to our previous findings that patients with DUP longer than 5 years showed progressive changes [14,15], while shorter than 5 years did not [43,44]. This was done to see whether patients at different illness course would display different patterns of changes. Since the 5-year DUP cutoff subgrouping is somewhat arbitrary, similar subgroup analyses were conducted with DUP cutoff at 1 and 2 years respectively (Supplementary Materials, Table S2). Details were presented in Supplementary Materials.

2.6.5. Correlation analysis with clinical variables

Partial correlation was used for evaluating relationships between abnormal network metrics and PANSS scores in schizophrenia patients, with age, sex, and education years being controlled. Nominal significance thresholds with uncorrected $p < 0.05$ were used for these heuristic analyses.

2.7. Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Demographics

Sex or years of education did not significantly differ between patients and controls ($p > 0.05$). The patient group had significant lower age in comparison with the control group, with an average difference of 3.5 years ($p < 0.05$, T-test, Table 1).

Table 1
Demographic and clinical features of antipsychotic-naive patients with schizophrenia and healthy controls.

Group	Patients ($N = 237$)	Controls ($N = 254$)	T/χ^2	p
	Mean (SD)			
Age, year	28.05 (12.62)	31.56 (12.83)	3.51	0.002
Sex, Male/Female	105/132	128/126	1.82	0.205
Education, year	11.30 (3.72)	11.83 (3.55)	1.65	0.100
Onset age, year	23.81 (7.72)			
Duration, month	50.96 (110.75)			
PANSS total score				
Total score	89.82 (15.84)			
Positive score	24.59 (6.31)			
Negative score	19.90 (7.98)			

Abbreviations: SD, standard deviation; PANSS, the positive and negative symptom scale.

3.2. Inter-group differences in network metrics

3.2.1. Global properties

In comparison to healthy subjects, patients showed significantly higher assortativity, i.e. a stronger tendency of nodes being connected to similar nodes ($p = 0.004$, F test). There were no significant differences in the small world scalar, global efficiency, local efficiency, characteristic path length, or clustering coefficient between patient and controls after Bonferroni correction.

3.2.2. Nodal properties

Relative to the control group, the patient group showed significantly higher betweenness in left parahippocampal gyrus (PHG), caudate, and inferior temporal gyrus (ITG), and right anterior cingulate gyrus (ACG) and middle cingulate gyrus (MCG); higher degree in bilateral caudate, left PHG, thalamus, superior temporal pole (STP) and ITG, and right putamen, ACG and MCG; and higher Ne in left caudate, PHG, STP, thalamus, and right putamen, ACG and MCG.

The patient group additionally showed significantly lower betweenness in bilateral insula, left pars orbitalis, and right orbital superior frontal gyrus (SFG), orbital middle frontal gyrus (MFG), posterior cingulate gyrus (PCG), middle occipital gyrus (MOG) and pallidum; significantly lower degree in bilateral insula, left superior temporal gyrus (STG) and pars orbitalis, and right orbital SFG, orbital MFG, medial SFG, PCG, MOG and pallidum; and significantly lower nodal efficiency in bilateral insula, left STG, pars orbitalis, pars triangularis, and right dorsolateral SFG, orbital SFG, PCG, MOG and pallidum. All p values for these comparisons survived from Bonferroni correction (all with $p < 0.05/270$, Fig. 1, Table 2). Notably, regions manifesting decreased nodal properties in patients included medial PFC, PCG and STG, which are within the DMN. The dorsolateral SFG, MFG, pars triangularis and the pars orbitalis are within the CEN, whereas the insula is within the SN [45,46] (Supplementary Materials, Table S3).

The non-parametric test examining inter-group differences in network metrics that did not obey the normal distribution replicated the findings showed above (Table S4). All the three age-level comparisons also showed the same findings as the primary patient vs control differences as noted above (Table S5), implying high stability of our findings.

3.3. Age-related regression of abnormal network metrics

Comparison of regression models between abnormal network metrics and age, which achieved statistical significance in either participant group, revealed accelerated age-related declines in assortativity at the global level ($p = 0.040$, F test), and degree of left STP ($p = 0.009$, F test) in patients relative to healthy controls with nominal significance thresholds (Fig. 2, Table 3).

3.4. Associations between abnormal network metrics and DUP

In regions with significant group differences, significant negative associations were observed between DUP and assortativity at the global level ($p < 0.001$, Pearson correlation), as well as between DUP and degree and Ne of left thalamus and STP at the nodal level (all $p < 0.05/50$, Bonferroni corrected), and these findings were consistent with the age-related regression findings.

Meanwhile, significant positive associations with DUP were observed in betweenness of right PCG, betweenness and degree of left ITG, as well as degree and Ne of right putamen at the nodal level after Bonferroni correction.

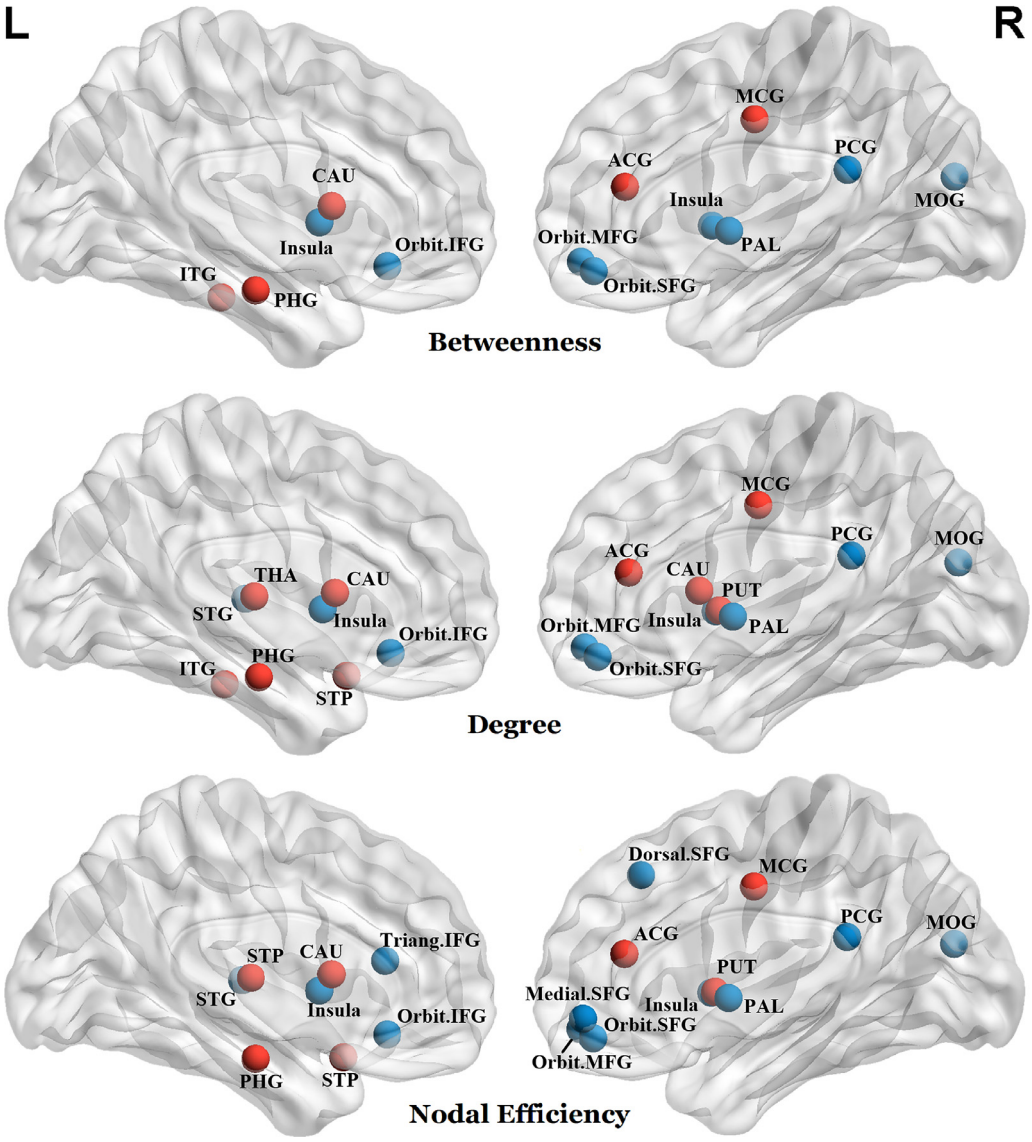

Fig. 1. Regions with altered nodal properties in grey matter network in antipsychotic-naive schizophrenia patients compared to controls.

Abbreviations: L, left; R, right.

Legend: nodes with decreased nodal properties are in blue, and nodes with increased nodal properties are in red.

Abbreviations: L, left hemisphere; R, right hemisphere; SFG, superior frontal gyrus (dor.=dorsolateral, orbit.=orbital, med.=medial); MFG, middle frontal gyrus; IFG, inferior frontal gyrus (triang.= triangularis, orbit.=orbitalis); ACG, anterior cingulate gyrus; MCG, middle cingulate gyrus; PCG, posterior cingulate gyrus; PHG, para hippocampal gyrus; MOG, middle occipital gyrus; CAU, caudate; PUT, putamen; PAL, pallidum; STG, superior temporal gyrus; STP, superior temporal pole; ITG, inferior temporal gyrus.

3.5. Separate analyses of abnormal network metrics in DUP-wise subgroups

In nodal metrics increased in overall patients, we observed that the nodal degree and efficiency of left thalamus were significantly higher in short-term patients (degree $p < 0.001$, Ne $p < 0.001$), but become lower in long-term patients (degree $p = 0.385$, Ne $p = 0.515$), relative to healthy comparisons. Relative to healthy controls, the nodal efficiency of left STP were significantly higher in short-term patients ($p < 0.001$), but become comparable in long-term patients ($p = 0.064$) (Fig. 3). The nodal network metrics of left ITG did not significantly differed from controls in short-term patients (betweenness $p = 0.171$, degree $p = 0.079$) but exhibited higher in long-term patients (betweenness $p = 0.001$, degree $p = 0.003$) than controls, while the increased nodal properties of right putamen in short-term patients than controls (degree $p = 0.034$, Ne $p = 0.080$) became much higher in long-term patients (degree $p = 0.013$, Ne $p = 0.009$) (Supplementary Materials, Fig. S1 and Table S6a). *P*-value were obtained by F test. The nodal network metrics of bilateral caudate, right ACG and MCG remained higher in both short-term and long-term patients compared to healthy control groups. With regard to nodal metrics found decreased in overall patients, the patterns of changes were mostly similar in both short-term and long-term patients (Supplementary Materials, Table S6b).

The alteration patterns indicated above were also confirmed in subgroup analyses at the DUP cutoff of 1 and 2 years respectively (Supplementary Materials, Tables S7 and S8).

3.6. Correlations between abnormal network metrics and PANSS scores

In heuristic analyses of network metrics considered with nominal significance threshold, some modest symptom severity correlations were suggested. At the nodal level, the degree of left PHG ($r=-0.15$, $p = 0.036$) and left thalamus ($r=-0.17$, $p = 0.024$) was negatively correlated with PANSS negative symptom scores, while none altered network metrics were found correlated to PANSS positive scores. The

Table 2
Brain regions with significantly altered nodal properties in antipsychotic-naive schizophrenia patients relative to healthy controls.

Regions with alterednetwork metrics	*Betweenness*		*Degree*		*Nodal Efficiency*	
	MD	***F (p)***	***MD***	***F (p)***	***MD***	***F (p)***
R. dorsolateral SFG	/	/	/	/	-4.71×10^{-3}	6.43 (<0.0001)
R. orbital SFG	−1.30	5.75 (0.00016)	−0.78	7.20 (<0.0001)	-6.41×10^{-3}	8.00 (<0.0001)
R. orbital MFG	−2.66	10.10 (<0.0001)	−1.90	18.58 (<0.0001)	-1.27×10^{-2}	16.95 (<0.0001)
L. pars triangularis	/	/	/	/	-3.68×10^{-3}	6.05 (<0.0001)
L. pars orbitalis	−3.72	14.29 (<0.0001)	−0.96	13.71 (<0.0001)	-6.69×10^{-3}	14.08 (<0.0001)
R. medial SFG	/	/	/	/	-4.07×10^{-3}	6.56 (<0.0001)
L. insula	−4.03	10.05 (<0.0001)	−1.89	14.42 (<0.0001)	-1.25×10^{-2}	14.40 (<0.0001)
R. insula	−1.37	6.58 (<0.0001)	−1.33	10.16 (<0.0001)	-8.43×10^{-3}	9.26 (<0.0001)
R. ACG	4.85	37.75 (<0.0001)	2.18	42.40 (<0.0001)	1.19×10^{-2}	34.61 (<0.0001)
R. MCG	1.66	8.03 (<0.0001)	1.32	12.53 (<0.0001)	7.46×10^{-3}	9.38 (<0.0001)
R. PCG	−7.29	11.26 (<0.0001)	−0.84	12.25 (<0.0001)	-5.44×10^{-3}	13.98 (<0.0001)
L. PHG	1.20	7.84 (<0.0001)	2.16	19.38 (<0.0001)	1.20×10^{-2}	18.19 (<0.0001)
R. MOG	−1.30	6.21 (<0.0001)	−0.95	8.86 (<0.0001)	-6.43×10^{-3}	11.10 (<0.0001)
L. caudate	6.16	9.32 (<0.0001)	0.64	10.97 (<0.0001)	2.94×10^{-3}	8.41 (<0.0001)
R. caudate	/	/	0.87	5.90 (0.00012)	/	/
R. putamen	/	/	0.70	6.77 (<0.0001)	4.33×10^{-3}	8.05 (<0.0001)
R. pallidum	−15.07	13.51 (<0.0001)	−0.74	9.38 (<0.0001)	-4.77×10^{-3}	10.39 (<0.0001)
L. thalamus	/	/	0.47	7.86 (<0.0001)	2.13×10^{-3}	5.97 (0.00011)
L. STG	/	/	−0.22	6.97 (<0.0001)	-1.22×10^{-3}	9.90 (<0.0001)
L. STP	/	/	0.96	21.42 (<0.0001)	1.09×10^{-2}	23.01 (<0.0001)
L. ITG	0.72	8.46 (<0.0001)	0.43	6.88 (<0.0001)	/	/

Abbreviations: MD, mean difference between patient and controls; L, left; R, right; SFG, superior frontal gyrus; MFG, middle frontal gyrus; ACG, anterior cingulate gyrus; MCG, middle cingulate gyrus; PCG, posterior cingulate gyrus; PHG, Para hippocampal gyrus; MOG, middle occipital gyrus; STG, superior temporal gyrus; STP, superior temporal pole; ITG, inferior temporal gyrus.
P-value were obtained by F-test.

degree and Ne of left thalamus were negatively correlated with PANSS total scores (r=−0.19, p = 0.010; r=−0.20, p = 0.007).

The altered global assortativity was not significantly correlated to PANSS scores.

4. Discussion

By analysing age- and DUP-related grey matter changes in a sample including patients living untreated in the community for more than 5 years, we observed global and nodal connectome abnormalities mainly involving the default mode network (DMN), salience network (SN), and central executive network (CEN). Notably, some network metrics that increased in patients showed negative associations with DUP or an accelerated decline in relation to age. These findings add to the literature in two important ways. First, the accelerated changes in anatomical features with age and negative associations with longer illness course were seen in antipsychotic-naive patients indicating that these are longer course of illness related deterioration effects on the brain. Second, analyses at the level of the whole brain connectome, and of brain regions (nodes) in the network, provide insights into the presence of alterations of the anatomical connectome of the brain in short- and long-term ill schizophrenia.

One interesting finding was that nodal properties of left thalamus showed age-related decline, while increased early in age but decreased at late age relative to controls, which also presented in subgroup analysis of short- and long-term patients. The increase in nodal properties of left thalamus involved the nodal degree and Ne, but not betweenness. The increase of degree and Ne of a node suggests increased connectivity with adjacent nodes to the node, and increased communication amongst them [38]. Such increases did not involve increased betweenness, indicating that the shortest path communication of their connectivity within the brain network remained comparable to controls. These changes of nodal properties might indicate a phenomenon of heightened coactivation between aberrant nodes and their neighbors early in the illness course, which might be related to regional brain hyperexcitability in schizophrenia.

The thalamus acts as a relay station for large scale integration of brain activity, and its connections to neocortex have been shown to be important for cognition in schizophrenia [47,48], which also showed age-related decline, but with increased nodal properties at early age, such increase in patient group at early age might represent increased connectivity and coactivation of brain regions during illness onset. A parallel course in the pattern of grey matter volume of thalamus has also been reported, with increased volumes in high-risk subjects for schizophrenia [49], but decreased volume in patients ill for many years [50]. Increased activity of thalamus was also reported in early stages of schizophrenia [51,52], but this has not been consistently reported in later stages of illness. Our findings in the nodal properties of the thalamus in the brain connectome included its association with symptom severity. Decreased nodal properties of thalamus were observed in long-term untreated schizophrenia patients only, who had greater impairment of social function and cognitive ability as reported previously [2–5]. This pattern of altered brain activity may be an important contributing factor to the anatomical alterations observed early in the illness, and its reduction with age and the negative changes related to longer DUP may reflect a reduction of functional connectivity later in the illness course [25]. Our finding adds important evidence indicating a distinct pattern of effects in thalamus in the early course of illness that shifts from increased to decreased involvement of these regions in the brain connectome later in the illness course with adverse effects on clinical symptom severity.

A similar pattern of early increase but later normalization, in this case becoming comparable to healthy subjects in late illness course, was observed in the global metric of assortativity and nodal efficiency of left STP. Nodes with high degree tended to connect those with low degree in typical patterns of the brain network, in other words, the brain network would be in disassortative stage, and the value of assortativity of brain network would be negative [37]. Thus, the higher assortativity in patients with shorter-term illness may indicate a less disassortative state of the brain anatomical network of schizophrenia at the early stage of illness. In the age-related regression analysis of assortativity, we observed that the curve of healthy controls remained relatively consistent over the examined age range,

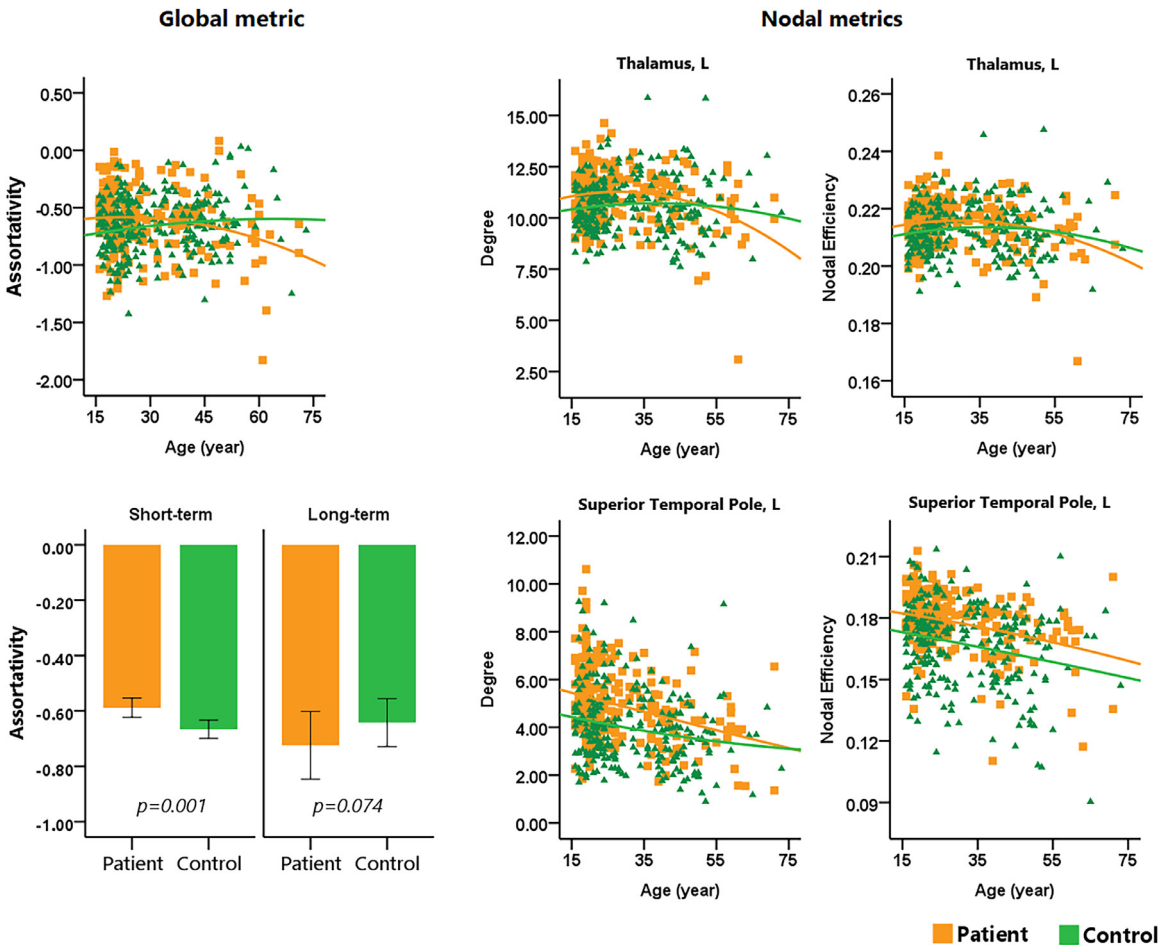

Fig. 2. Quadratic models of network metrics in relation to age with significant differences between antipsychotic-naive schizophrenia and healthy comparisons. Left panel: regression curves of global metric and DUP-subgroup comparisons; Right panel: regression curves of nodal metrics.

while patients showed an accelerated decline and a tendency toward lower values than controls later in the illness course (Fig. 2). This suggests that a trajectory from inadequate disassortativity toward one of excessive disassortativity in network of patients.

In terms of temporal lobe alterations, our age and DUP related effects are consistent with previous findings indicating that alterations in temporal regions show an age-related decline in schizophrenia [53–55]. The STP is part of the paralimbic system, which serves as a transition region between neocortex and allocortex, and supports functions of emotion processing and motivation [56]. The anatomical and functional abnormalities of superior temporal regions, have been well-established in schizophrenia [57–59]. This hyperactivity of this region early in the illness has been considered a contributing factor leading to thought disorder and hallucinations [60–62], as well as memory and attention deficits [63]. This pattern of altered brain activity may be an important contributing factor to the anatomical alterations observed early in the illness, and its reduction with age and the negative changes related to longer DUP may reflect a reduction of functional connectivity later in the illness course [25].

Changes involving nodal properties of the ITG showed increased trajectory in relation to DUP and age, and in subgroup analysis, we seen increased nodal properties relative to controls in long-term ill patients but not in short-term ill patients, notably being present in untreated patients. A similar pattern of nodal alterations was seen in right putamen, also increasing in relation to DUP and age, being then increased in both short- and long-term patients. Previous reports of hyper-perfusion of the striatum at the resting state [64], along with increased dopamine synthesis [65] and metabolites [66], and resting-state activity analysis [67] in drug-naïve patients suggested enhanced striatal function and integration in the brain connectome both early and later in the illness course. Our findings, along with previous reports of increased volume of right putamen in long-term ill patients with schizophrenia [14], suggest that the alterations in the role of the striatum in the brain connectome not only were persistent but increased over the illness course in untreated patients, and thus likely represent intrinsic developing features of the illness.

With regards to decreased nodal properties in patients, alterations were seen in medial PFC, PCG and the STG, which were within the DMN; and the dorsolateral SFG, orbital MFG, pars triangularis and the pars orbitalis within the CEN, as well as the insula, which within the SN. The DMN is involved in internal information processing and self-reflection [68], while the CEN directs the processing of external information [69], which is functionally anti-correlated to DMN activity. Functional MRI studies have reported dysfunction and aberrant interactions of them in schizophrenia [70] and subjects at risk for psychosis [71], with SN intermediating them, indicating a crucial role of aberrant DMN and CEN in schizophrenia. Furthermore, the changes in these networks almost maintained consistent along the course of illness and age. Along with previous findings, our grey matter connectome analysis enhances understanding of these abnormalities at the level of the anatomical relations amongst brain regions that support optimal brain function, and further indicates that these network disorganizations might represent illness traits that occur preceding the illness onset. Besides regions within specific networks, the decreased network metrics of right MOG and pallidum across illness course were also observed. The MOG assumes the function of

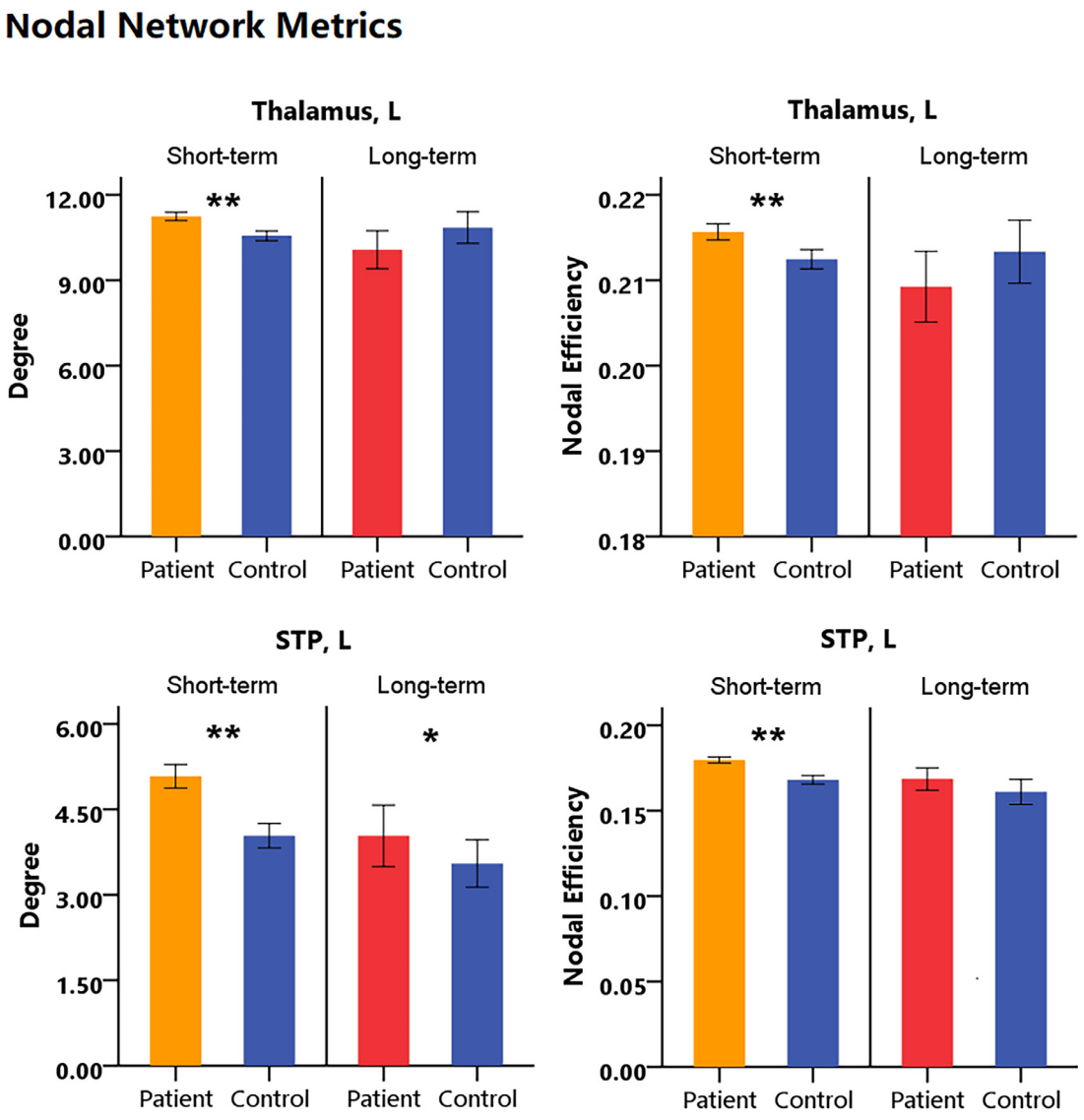

Fig. 3. Different alteration patterns of nodal network metrics with age-related decline in short-term and long-term ill schizophrenia patients (subgrouping by DUP cutoff at 5 years) when compared to healthy controls respectively.

Legend: * = $p < 0.05$, ** = $p < 0.001$.

Abbreviations: L, left; R, right; STP, superior temporal pole.

Table 3
Comparisons of quadratic curves of age-related network metric changes between schizophrenia patients and healthy controls.

Nodes with significant age-related metric changes	Patient*p value* (R^2) [a]	Control*p value* (R^2) [a]	F	p [b]	Nodes with significant age-related metric changes	Patient*p value* (R^2) [a]	Control*p value* (R^2) [a]	F	p [b]
Global Assortativity									
	0.0084 (0.040)	0.050 (0.024)	3.21	0.040					
Nodal Betweenness									
R. PCG	0.027 (0.027)	0.060 (0.022)	0.13	0.815	L. ITG	<0.0001 (0.100)	0.100 (0.018)	1.41	0.246
Nodal Degree									
R. PCG	0.023 (0.031)	0.016 (0.032)	0.67	0.512	L. STP	<0.0001 (0.103)	0.0044 (0.042)	9.19	0.0086
R. putamen	<0.0001 (0.120)	0.093 (0.019)	0.19	0.830	L. ITG	0.0011 (0.057)	0.171 (0.014)	1.76	0.173
L. thalamus	<0.0001 (0.078)	0.0067 (0.005)	0.45	0.639					
Nodal Efficiency									
R. PCG	0.010 (0.039)	0.103 (0.018)	0.83	0.438	L. thalamus	0.0033 (0.048)	0.0093 (0.010)	0.67	0.513
R. putamen	<0.0001 (0.123)	0.026 (0.029)	0.59	0.553	L. STP	<0.0001 (0.106)	0.00069 (0.056)	0.61	0.550

Abbreviations: L, left; R, right; PCG, posterior cingulate gyrus; STP, superior temporal pole; ITG, inferior temporal gyrus.
a: *p*-value for the regression models of network metrics with age; b: *p*-value for the difference of age-regression models of network metrics between patients and controls.

language and visual cognition [72], in which the decreased network properties might associated visual cognitive impairment and verbal dysfunction. As the relay nuclear of moto function [73], the decreased network properties of pallidum might be related to abnormal movements in patients.

In correlation analysis, network properties of left thalamus, which had age- and DUP-related decline, were negatively correlated to PANSS scores, which suggested a possible deterioration of symptom severity along illness course. A negative association between network connectivity of left PHG and negative symptom were also observed. Considering the pivotal role of PHG in cognition and emotion, such negative association might result from the disturbed medial limbic circuit, involving PHG, thalamus and cingulate in current study.

Several limitations should be noted with regard to this work. First, the study design has the advantage of testing for age- and DUP-related anatomical alterations independent of drug treatment effects, but the disadvantage of being a cross-sectional rather than longitudinal study. While this limits inferences, studying untreated patients over years longitudinally of treatment cannot be done for ethical reasons, so our approach is perhaps the best or only option for modelling age- and DUP-related changes in untreated patients with schizophrenia beyond the initial phase of illness. Second, although the sample size of untreated schizophrenia patients we included was larger than previous studies, both for early and later course of illness patients, most of the patients were early rather than later in their course of illness. This limits comparable statistical power for detecting effects in the early and later course of illness and for precise modelling DUP-related effects. Third, in order to ensure the consistency in network size across individuals, we conducted a normalization procedure with anatomical templates as done in previous studies. This procedure might induce template-dependant effects. Forth, the imaging study was completed outside of acute episodes of schizophrenia patients, potentially limiting clinical-pathological correlations. Fifth, there was significant age differences between patients and healthy controls, and also between short-term patients and matched healthy controls, but it was also controlled as a covariate during the primary and subgroup analyses. Finally, since we focused more on brain network changes without confounding effects of antipsychotics in the current study, the systematical characterization of treatment effects, which is also very important, requires future investigation.

In conclusion, age- and DUP-related alterations in the anatomical brain connectome, indicated a distinct pattern of effects in thalamus, which were most typically in the form of increased nodal roles in the brain connectome early in the illness course and declines in nodal connections later in the illness course. The decrease of nodal metrics in CEN and DMN seen at both early and later illness course might represent a disease trait that is maintained over the illness course.

Contributors

Mr. Beisheng Yang and Dr. Wenjing Zhang contribute equally to this paper. Su Lui conceived and designed the study. Bo Tao, Biqiu Tang, Jing Yang, Siyi Li, and Jiaxin Zeng participated in data collection and data analysis, while Beisheng Yang and Wenjing Zhang analysed, interpreted the data and drafted the manuscript. Rebekka Lencer, Hengyi Cao, John Sweeney, Qiyong Gong and Su Lui revised the paper critically. Beisheng Yang, Wenjing Zhang, Bo Tao and Su Lui have verified the underlying data, and all authors approved the final version to be submitted.

Data sharing statement

The data and code that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions of West China Hospital.

Declaration of Competing Interest

Drs. John Sweeney, Wenjing Zhang and Siyi Li consult to VeraSci. The other authors declare no competing interests.

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Supplementary materials

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References

[1] Barbato A. Psychiatry in transition: outcomes of mental health policy shift in Italy. Aust N Z J Psychiatry 1998;32(5):673–9.
[2] Kotov R, Fochtmann L, Li K, Tanenberg-Karant M, Constantino EA, Rubinstein J, et al. Declining clinical course of psychotic disorders over the two decades following first hospitalization: evidence from the suffolk county mental health project. Am J Psychiatry 2017;174(11):1064–74.
[3] Velthorst E, Fett AJ, Reichenberg A, Perlman G, van Os J, Bromet EJ, et al. The 20-year longitudinal trajectories of social functioning in individuals with psychotic disorders. Am J Psychiatry 2017;174(11):1075–85.
[4] Austin SF, Mors O, Budtz-Jorgensen E, Secher RG, Hjorthoj CR, Bertelsen M, et al. Long-term trajectories of positive and negative symptoms in first episode psychosis: a 10year follow-up study in the OPUS cohort. Schizophr Res 2015;168(1–2):84–91.
[5] Stone WS, Cai B, Liu X, Grivel MM, Yu G, Xu Y, et al. Association between the duration of untreated psychosis and selective cognitive performance in community-dwelling individuals with chronic untreated schizophrenia in rural China. JAMA Psychiatry 2020.
[6] Cropley VL, Klauser P, Lenroot RK, Bruggemann J, Sundram S, Bousman C, et al. Accelerated gray and white matter deterioration with age in schizophrenia. Am J Psychiatry 2017;174(3):286–95.
[7] Gutiérrez-Galve L, Chu EM, Leeson VC, Price G, Barnes TR, Joyce EM, et al. A longitudinal study of cortical changes and their cognitive correlates in patients followed up after first-episode psychosis. Psychol Med 2015;45(1):205–16.
[8] Ahmed M, Cannon DM, Scanlon C, Holleran L, Schmidt H, McFarland J, et al. Progressive brain atrophy and cortical thinning in schizophrenia after commencing clozapine treatment. Neuropsychopharmacology 2015;40(10):2409–17.
[9] Konopaske GT, Dorph-Petersen KA, Sweet RA, Pierri JN, Zhang W, Sampson AR, et al. Effect of chronic antipsychotic exposure on astrocyte and oligodendrocyte numbers in macaque monkeys. Biol Psychiatry 2008;63(8):759–65.
[10] Konopaske GT, Dorph-Petersen KA, Pierri JN, Wu Q, Sampson AR, Lewis DA. Effect of chronic exposure to antipsychotic medication on cell numbers in the parietal cortex of macaque monkeys. Neuropsychopharmacology 2007;32(6):1216–23.
[11] Szeszko PR, Robinson DG, Ikuta T, Peters BD, Gallego JA, Kane J, et al. White matter changes associated with antipsychotic treatment in first-episode psychosis. Neuropsychopharmacology 2014;39(6):1324–31 official publication of the American College of Neuropsychopharmacology.
[12] Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch Gen Psychiatry 2011;68(2):128–37.
[13] Vita A, De Peri L, Deste G, Barlati S, Sacchetti E. The effect of antipsychotic treatment on cortical gray matter changes in schizophrenia: does the class matter? A Meta-analysis and meta-regression of longitudinal magnetic resonance imaging studies. Biol Psychiatry 2015;78(6):403–12.

[14] Zhang W, Deng W, Yao L, Xiao Y, Li F, Liu J, et al. Brain structural abnormalities in a group of never-medicated patients with long-term schizophrenia. Am J Psychiatry 2015;172(10):995–1003.
[15] Xiao Y, Sun H, Shi S, Jiang D, Tao B, Zhao Y, et al. White matter abnormalities in never-treated patients with long-term schizophrenia. Am J Psychiatry 2018;175(11):1129–36.
[16] Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? Clin Neurosci 1995;3(2):89–97 New York, NY.
[17] Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, et al. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr Res 2011;127(1−3):46–57.
[18] van den Heuvel MP, Kahn RS. Abnormal brain wiring as a pathogenetic mechanism in schizophrenia. Biol Psychiatry 2011;70(12):1107–8.
[19] Fornito A, Zalesky A, Breakspear M. The connectomics of brain disorders. Nat Rev Neurosci 2015;16(3):159–72.
[20] van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol 2010;20(8):519–34.
[21] Avena-Koenigsberger A, Misic B, Sporns O. Communication dynamics in complex brain networks. Nat Rev Neurosci 2017;19(1):17–33.
[22] Zhang F, Qiu L, Yuan L, Ma H, Ye R, Yu F, et al. Evidence for progressive brain abnormalities in early schizophrenia: a cross-sectional structural and functional connectivity study. Schizophr Res 2014;159(1):31–5.
[23] Di Biase MA, Cropley VL, Baune BT, Olver J, Amminger GP, Phassouliotis C, et al. White matter connectivity disruptions in early and chronic schizophrenia. Psychol Med 2017;47(16):2797–810.
[24] Sun Y, Chen Y, Lee R, Bezerianos A, Collinson SL, Sim K. Disruption of brain anatomical networks in schizophrenia: a longitudinal, diffusion tensor imaging based study. Schizophr Res 2016;171(1−3):149–57.
[25] Yao L, Li F, Liu J, Liao W, Li X, Li M, et al. Functional brain networks in never-treated and treated long-term lll schizophrenia patients. Neuropsychopharmacology 2019;44(11):1940–7.
[26] Zalesky A, Fornito A, Seal ML, Cocchi L, Westin CF, Bullmore ET, et al. Disrupted axonal fiber connectivity in schizophrenia. Biol Psychiatry 2011;69(1):80–9.
[27] Tijms BM, Seriès P, Willshaw DJ, Lawrie SM. Similarity-based extraction of individual networks from gray matter MRI scans. Cereb Cortex 2012;22(7):1530–41 New York, NY: 1991.
[28] Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet 2016;388(10039):86–97.
[29] Xiao Y, Yan Z, Zhao Y, Tao B, Sun H, Li F, et al. Support vector machine-based classification of first episode drug-naïve schizophrenia patients and healthy controls using structural MRI. Schizophr Res 2019;214:11–7.
[30] Singh SP, Cooper JE, Fisher HL, Tarrant CJ, Lloyd T, Banjo J, et al. Determining the chronology and components of psychosis onset: the Nottingham onset schedule (NOS). Schizophr Res 2005;80(1):117–30.
[31] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13(2):261–76.
[32] Weese J, Rosch P, Netsch T, Blaffert T, Quist M. Gray-value based registration of CT and MR images by maximization of local correlation editors. In: Taylor C, Colchester A, editors. Proceedings of the Medical Image Computing and Computer-Assisted Intervention, Miccai'99, Proceedings. Lecture Notes in Computer Science. 16791999; 2021. p. 656–63.
[33] van Wijk BCM, Stam CJ, Daffertshofer A. Comparing brain networks of different size and connectivity density using graph theory. PLoS ONE 2010;5(10).
[34] Batalle D, Munoz-Moreno E, Figueras F, Bargallo N, Eixarch E, Gratacos E. Normalization of similarity-based individual brain networks from gray matter MRI and its association with neurodevelopment in infants with intrauterine growth restriction. Neuroimage 2013;83:901–11.
[35] Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. Nature 1998;393(6684):440–2.
[36] Latora V, Marchiori M. Efficient behavior of small-world networks. Phys Rev Lett 2001;87(19):198701.
[37] Newman ME. Assortative mixing in networks. Phys Rev Lett 2002;89(20):208701.
[38] Freeman LC. A set of measures of centrality based on betweenness. Sociometry 1977;40(1):35–41.
[39] Wang J, Wang X, Xia M, Liao X, Evans A, He Y. GRETNA: a graph theoretical network analysis toolbox for imaging connectomics. Front Hum Neurosci 2015;9:386.
[40] Zhang J, Wang J, Wu Q, Kuang W, Huang X, He Y, et al. Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. BiolPsychiatry 2011;70(4):334–42.
[41] Alexander-Bloch AF, Reiss PT, Rapoport J, McAdams H, Giedd JN, Bullmore ET, et al. Abnormal cortical growth in schizophrenia targets normative modules of synchronized development. Biol Psychiatry 2014;76(6):438–46.
[42] Ziegler G, Dahnke R, Jäncke L, Yotter RA, May A, Gaser C. Brain structural trajectories over the adult lifespan. Hum Brain Mapp 2012;33(10):2377–89.
[43] Ren W, Lui S, Deng W, Li F, Li M, Huang X, et al. Anatomical and functional brain abnormalities in drug-naive first-episode schizophrenia. Am J Psychiatry 2013;170(11):1308–16.
[44] Xiao Y, Lui S, Deng W, Yao L, Zhang W, Li S, et al. Altered cortical thickness related to clinical severity but not the untreated disease duration in schizophrenia. Schizophr Bull 2015;41(1):201–10.
[45] Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 2011;15(10):483–506 Regul. Ed..
[46] Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008;1124:1–38.
[47] Giraldo-Chica M, Rogers BP, Damon SM, Landman BA, Woodward ND. Prefrontal-thalamic anatomical connectivity and executive cognitive function in schizophrenia. Biol Psychiatry 2018;83(6):509–17.
[48] Huang AS, Rogers BP, Woodward ND. Disrupted modulation of thalamus activation and thalamocortical connectivity during dual task performance in schizophrenia. Schizophr Res 2019;210:270–7.
[49] Oertel-Knochel V, Knochel C, Matura S, Rotarska-Jagiela A, Magerkurth J, Prvulovic D, et al. Cortical-basal ganglia imbalance in schizophrenia patients and unaffected first-degree relatives. Schizophr Res 2012;138(2−3):120–7.
[50] van Erp TG, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, et al. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol Psychiatry 2016;21(4):547–53.
[51] Tregellas JR, Davalos DB, Rojas DC, Waldo MC, Gibson L, Wylie K, et al. Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. Schizophr Res 2007;92(1−3):262–72.
[52] Bor J, Brunelin J, Sappey-Marinier D, Ibarrola D, d'Amato T, Suaud-Chagny MF, et al. Thalamus abnormalities during working memory in schizophrenia. An fMRI study. Schizophr Res 2011;125(1):49–53.
[53] Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull 2008;34(2):354–66.
[54] Lee SH, Niznikiewicz M, Asami T, Otsuka T, Salisbury DF, Shenton ME, et al. Initial and progressive gray matter abnormalities in insular gyrus and temporal pole in first-episode schizophrenia contrasted with first-episode affective psychosis. Schizophr Bull 2016;42(3):790–801.
[55] van Erp TGM, Walton E, Hibar DP, Schmaal L, Jiang W, Glahn DC, et al. Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the enhancing neuro imaging genetics through meta analysis (ENIGMA) consortium. Biol Psychiatry 2018;84(9):644–54.
[56] By Al-Baradie R, Marser Mesulam M. Principles of behavioral and cognitive neurology. 2nd Ed. Oxford University Press, Inc; 2002. p. 51..
[57] Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry 2005;162(12):2233–45.
[58] Bandeira ID, Barouh JL, Bandeira ID, Quarantini L. Analysis of the superior temporal gyrus as a possible biomarker in schizophrenia using voxel-based morphometry of the brain magnetic resonance imaging: a comprehensive review. CNS Spectr 2020:1–7.
[59] Mwansisya TE, Hu A, Li Y, Chen X, Wu G, Huang X, et al. Task and resting-state fMRI studies in first-episode schizophrenia: a systematic review. Schizophr Res 2017;189:9–18.
[60] Suzuki M, Yuasa S, Minabe Y, Murata M, Kurachi M. Left superior temporal blood flow increases in schizophrenic and schizophreniform patients with auditory hallucination: a longitudinal case study using 123I-IMP SPECT. Eur Arch Psychiatry Clin Neurosci 1993;242(5):257–61.
[61] David AS. Auditory hallucinations: phenomenology, neuropsychology and neuroimaging update. Acta Psychiatr Scand Suppl 1999;395:95–104.
[62] Alonso-Solís A, Vives-Gilabert Y, Portella MJ, Rabella M, Grasa EM, Roldán A, et al. Altered amplitude of low frequency fluctuations in schizophrenia patients with persistent auditory verbal hallucinations. Schizophr Res 2017;189:97–103.
[63] Crossley NA, Mechelli A, Fusar-Poli P, Broome MR, Matthiasson P, Johns LC, et al. Superior temporal lobe dysfunction and frontotemporal dysconnectivity in subjects at risk of psychosis and in first-episode psychosis. Hum Brain Mapp 2009;30(12):4129–37.
[64] Malaspina D, Harkavy-Friedman J, Corcoran C, Mujica-Parodi L, Printz D, Gorman JM, et al. Resting neural activity distinguishes subgroups of schizophrenia patients. Biol Psychiatry 2004;56(12):931–7.
[65] Lindström LH, Gefvert O, Hagberg G, Lundberg T, Bergström M, Hartvig P, et al. Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. Biol Psychiatry 1999;46(5):681–8.
[66] Kumakura Y, Cumming P, Vernaleken I, Buchholz HG, Siessmeier T, Heinz A, et al. Elevated [18F] fluorodopamine turnover in brain of patients with schizophrenia: an [18F]fluorodopa/positron emission tomography study. J Neurosc Off J Soc Neurosci 2007;27(30):8080–7.
[67] Huang XQ, Lui S, Deng W, Chan RC, Wu QZ, Jiang LJ, et al. Localization of cerebral functional deficits in treatment-naive, first-episode schizophrenia using resting-state fMRI. Neuroimage 2010;49(4):2901–6.
[68] Sormaz M, Murphy C, Wang HT, Hymers M, Karapanagiotidis T, Poerio G, et al. Default mode network can support the level of detail in experience during active task states. Proc Natl Acad Sci USA 2018;115(37):9318–23.
[69] Goulden N, Khusnulina A, Davis NJ, Bracewell RM, Bokde AL, McNulty JP, et al. The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. Neuroimage 2014;99:180–90.
[70] Supekar K, Cai W, Krishnadas R, Palaniyappan L, Menon V. Dysregulated brain dynamics in a triple-network saliency model of schizophrenia and its relation to psychosis. Biol Psychiatry 2019;85(1):60–9.
[71] Wotruba D, Michels L, Buechler R, Metzler S, Theodoridou A, Gerstenberg M, et al. Aberrant coupling within and across the default mode, task-positive, and salience network in subjects at risk for psychosis. Schizophr Bull 2014;40(5):1095–104.
[72] Grill-Spector K, Kourtzi Z, Kanwisher N. The lateral occipital complex and its role in object recognition. Vision Res 2001;41(10−11):1409–22.
[73] Gillies MJ, Hyam JA, Weiss AR, Antoniades CA, Bogacz R, Fitzgerald JJ, et al. The cognitive role of the Globus pallidus interna; insights from disease states. Exp Brain Res 2017;235(5):1455–65.