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# Effect of second-generation antipsychotics on brain network topology in first-episode schizophrenia: A longitudinal rs-fMRI study

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ABSTRACT

*Objective:* We aimed to evaluate the functional network properties in first-episode schizophrenia (SZ) patients at baseline and after 4-months treatment with second-generation antipsychotic drugs.
*Methods:* Resting-state functional magnetic resonance imaging and graph theory approaches were utilized to evaluate the functional integration and segregation of brain networks in 36 first-episode patients (20 male/16 female) with SZ and 36 age and sex matched healthy controls (20 male/16 female).
*Results:* Compared with healthy controls, SZ at baseline showed lower clustering coefficient ($C_p$) and local network efficiency ($E_{loc}$), and this abnormal pattern was modulated with treatment of antipsychotic drugs at follow-up. Longitudinally, the increase of $C_p$ was associated with the improvement of negative symptom. We found that the strength of functional connectivity between brain regions were significantly increased in three connections after treatment, mainly involving the frontal, parietal and occipital lobes.
*Conclusion:* The current study suggested that antipsychotic drugs could modulate the faulty local clustering of the functional connectome in SZ. Furthermore, $C_p$, the parameter that reflects local clustering of topological organization, demonstrated the potential to be a connectome-based biomarker of treatment response to second-generation antipsychotics in patients with SZ.



## 1. Introduction

Schizophrenia (SZ) is a debilitating psychiatric disease with a lifetime morbid risk of 1%, carrying a profound impact on both patients and society (Whiteford et al., 2013). After years of exploration, the underlying pathophysiological mechanism for SZ remains largely unknown. Numerous studies have increasingly supported the hypothesis that SZ is a disorder of aberrant functional connectivity at the whole brain scale in the context of neuroimaging (Alexander-Bloch et al., 2013). This hypothesis indicates that SZ is not characterized by isolated damage of a few brain regions, but rather by pathological impairments of brain networks throughout interconnected neural systems (van den Heuvel and Fornito, 2014).

Functional brain imaging studies focusing on the disrupted network of SZ commonly used resting-state functional magnetic resonance imaging (rs-fMRI). Applying graph theory-based approaches on rs-fMRI could quantitatively describe the topological architecture of human brain as a highly interconnected network. This kind of network is capable of efficient information transfer at a low wiring cost as formatting a highly modulated small-world architecture (Bullmore and Sporns, 2009; Tononi et al., 1994), and could offer optimized balance between functional integration and segregation (Tononi et al., 1994). This topological approach also allows examination of topological reconfiguration of network in reaction to pathological attacks or anti-psychotic treatment (Bassett et al., 2008).

Previous studies that used this method in SZ have found reduced network segregation (i.e., decreased clustering) and increased or unchanged integration (i.e., global efficiency) (Alexander-Bloch et al., 2010; Alexander-Bloch et al., 2013; Liu et al., 2008; Lynall et al., 2010). However, it remains difficult to determine to what extent such abnormalities were influenced by antipsychotic drugs, as thus far most functional studies enrolled chronic SZ patients and the treatment could already affect the topological architecture at baseline. To advance understanding of the effects of antipsychotic drugs, a recent study utilizing graph theoretical methods in unmedicated SZ patients at baseline and 6-week endpoint found reduced global clustering and increased global

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efficiency after treatment of risperidone (Hadley et al., 2016). Nevertheless, although this study detected modulation of global topological metrics in SZ after treatment with a short follow-up interval, the change of other topological metrics and specific connectivity pattern after a relatively long interval remains unclear.

Here, we employed rs-fMRI to examine the topological change of SZ patients at two time points: baseline and after 4-months treatment with second-generation antipsychotic drugs. We analyzed the change of topological parameters and specific functional connections between brain regions in SZ patients. We hypothesized that the topological parameters could manifest a trend to return to normal status after treatment, and such topological alterations could reflect the improvement of clinical symptoms.

## 2. Materials and methods

### 2.1. Subjects

This longitudinally designed study included 36 first-episode SZ patients who were enrolled from inpatient of Psychiatric department, as well as age and sex-matched 36 healthy controls (HC) who were recruited through advertisement from local community. All patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and were at the first-episode (including currently in acute episode, currently in partial remission and currently in full remission according to DSM-5) of SZ with exposure to antipsychotic treatment within 2 weeks. Some patients with <6 months illness duration were diagnosed as SZ after 6-months follow-up according to diagnostic criteria. The exclusion criteria for patients included: pregnancy, major medical and neurological diseases, history of significant head trauma and drug or alcohol abuse or dependence. Additional exclusion criteria for HC comprised current or a past history of psychiatric disorders. At baseline, the psychometric assessments and scan were carried out in the same day, so as the psychometric assessments and scan at 4-months follow-up. The psychometric assessments were performed by two senior clinical psychiatrists using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) scores were available in 14 patients. Drug dose across patients was calculated as olanzapine equivalence according to the method proposed by Leucht et al. (2016). During the follow-up, all patients received second generation anti-psychotic drugs, including paliperidone (9 patients), risperidone (16 patients), olanzapine (11 patients), amisulpride (3 patients), and aripiprazole (1 patient) (partial patients received multi-drug therapy). All patients (or guardians when the patient was under 18) gave written informed consent approved by the local Research Ethics Committee (Xijing Hospital, the Fourth Military Medical University) after a complete description of this study. This study was in accordance with the Declaration of Helsinki.

### 2.2. Image acquisition

All subjects were scanned on a 3.0 T GE Discovery 750 MR scanner with an eight-channel phased array head coil (Milwaukee, Wisconsin, USA). During the scanning, subjects were asked to stay still and keep their eyes closed without falling asleep.

Detailed parameters of high-resolution T1-weighted structural image and rs-fMRI were as follows: (i) structural image: repetition time = 8.2 ms, echo time = 3.2 ms, flip angle = 12°, field of view = 256 × 256 mm, matrix = 256 × 256, slice thickness = 1 mm, number of slices = 196; (ii) rs-fMRI: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, field of view = 240 × 240 mm, matrix = 64 × 64, slice thickness = 3.5 mm, number of slices = 45.

### 2.3. Data preprocessing

Data preprocessing was carried out using the Statistical Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging, University College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm), implemented in MATLAB. After discarding the first 10 time points, rs-fMRI data were further corrected for the acquisition delay between slices and then realigned to the first volume. Motion scrubbing was applied to fMRI data to avoid possible confounding effect of head motion on the measures of functional connectivity. We removed the volumes that showed higher frame-wise displacement than 0.2 mm. The one volume before and two volumes after the volume that had been removed were also discarded. Individual T1-weighted images were co-registered to the mean of the realigned functional images. The Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) tool was used to compute the transformation from individual space to Montreal Neurological Institute (MNI) space (Ashburner, 2007). The fMRI images were normalized at a resolution of $3 \times 3 \times 3$ mm$^3$ using the same transformation information as the T1 images. Finally, following the smoothing procedure, all data were temporally bandpass filtered (0.01–0.08 Hz).

### 2.4. Brain network construction and analysis

A prior atlas introduced by Craddock et al. was adopted in this study to define regions of interest by dividing the whole brain into 200 nodes of the network (Craddock et al., 2012). The functional connectivity (i.e. edges of the network) among all possible pairs of brain regions were evaluated by calculating Pearson's correlation coefficient of regional residual mean time series, resulting in a $200 \times 200$ matrix for each subject. Then we applied a pre-defined range of sparsity threshold S to all correlation matrices, thus converting all correlation matrix to binarized matrix. The pre-defined range of S assured that the small-worldness scaler $\sigma$ for all subjects was larger than 1.1, which could guarantee that the binarized networks were estimable for small-worldness. The subsequent network analysis was performed within the small-worldness regime of 0.08–0.48 with an interval of 0.01. For each subject's graph thresholded by this predefined range, we assessed the global network metrics, which comprise: (i) small-world properties: clustering coefficient ($C_p$), characteristic path length ($L_p$), normalized clustering coefficient ($\gamma$), normalized characteristic path length ($\lambda$), and small-worldness ($\sigma$); (ii) network efficiency: global network efficiency ($E_g$) and local network efficiency ($E_{loc}$). We calculated the area under curve (AUC) of each global network efficiency for statistical comparisons between patients and control groups. All network construction and analysis were carried out by GRETNA (v2.0) (Wang et al., 2015).

### 2.5. Statistical analysis

#### 2.5.1. Network statistical analysis

Since the years of education was significantly higher in HC, we compared the network properties between SZ patients at baseline (SZ-pre) and HC, SZ patients after treatment (SZ-post) and HC using general linear model, with the education years as a covariance. Specifically, paired *t*-test was used between SZ-pre and SZ-post. The statistical analyses were performed in the Statistical Product and Service Solutions (SPSS, version 22.0). Additionally, to detect whether the strength of functional connections between brain regions changed after treatment or not, we utilized FDR (false discovery rate) correction within GRETNA, with the inter-scan interval set as a covariance. The significant level was 0.05.

#### 2.5.2. Clinical correlation

The correlation between the relative reduction of network metrics that showed significant differences in SZ (i.e. $C_p$) with the relative reduction of PANSS scores after treatment was evaluated using the partial correlation test. We also examined the correlation between network

metrics at baseline and the relative reduction of PANSS scores using the same method. The inter-scan interval, cumulative dose of drugs prior to baseline and cumulative dose during follow-up were used as covariance. In addition, to determine whether the connections between brain regions that showed significant change after treatment were related with PANSS scores or not, the same method was utilized. One patient in this cohort received iloperidone prior to baseline, which could not be converted to olanzapine equivalence according to the method by Leucht et al. (2016), was discarded in the analysis of clinical correlations. The relative reduction was calculated as (baseline − follow-up) / baseline. The clinical correlations were assessed by the SPSS. There were 4 times correlations concerning the analysis between *Cp* and PANSS scores, and 12 times correlations between the three edges and PANSS scores. Such multiple correlations were corrected using FDR within R (version 3.5.2). The significant level was set as 0.05.

## 3. Results

### 3.1. Demographic characteristics and clinical improvement

We observed non-significant differences between SZ and HC concerning age and sex, but HC showed higher level of education (Table 1). After treatment, the PANSS positive, negative, general and total scores decreased significantly (positive score, $t = 11.68$, $p < 0.001$; negative score, $t = 4.97$, $p < 0.001$; general score, $t = 10.32$, $p < 0.001$; total score, $t = 9.01$, $p < 0.001$), so as the HAMA and HAMD scores (HAMA, $t = 3.65$, $p = 0.003$; HAMD, $t = 4.26$, $p = 0.001$).

### 3.2. Topological metrics

As displayed by Fig. 1 and Table 2, the $C_p$ and $E_{loc}$ of SZ were significantly lower than HC at baseline but returned to normal after treatment. Pearson's correlation coefficients (edges) were calculated between each pair of preprocessed node time series, resulting in 40,000 (200 × 200) edges for each participant, Edges which showed significant difference after treatment were determined by comparing each pair of Pearson's correlation coefficient (baseline and follow-up) using paired *t*-test which is embedded in the analysis toolbox. Results are shown in Fig. 2. The connection strength was significantly increased between right frontal pole and superior parietal lobule (edge 1), left inferior frontal gyrus and temporal pole (edge 2), as well as right middle temporal gyrus and left cuneal cortex (edge 3) after treatment ($t = -5.47$, $p = 3.56 \times 10^{-6}$; $t = -5.53$, $p = 2.92 \times 10^{-6}$; $t = -5.23$, $p = 7.34 \times 10^{-6}$, respectively).

### 3.3. Clinical correlation

Since only $C_p$ showed significant difference after treatment in SZ patients, we mainly calculated the correlation between $C_p$ and the clinical improvement after treatment. We observed significant association between $C_p$ and negative symptom ($r = 0.45$, FDR $p = 0.04$), displayed in Fig. 3A. When assessing the correlation between $C_p$ at baseline and the relative reduction of clinical scores, no significant association survived after multiple correction ($r = 0.38$, FDR $p = 0.12$). All clinical correlations between $C_p$ and PANSS scores were shown in Supplementary materials 1 and 2. In addition, the correlation between changes of edge 1 and PANSS general scores showed a strong tendency towards

**Table 1**
Demographic characteristics and clinical measurements of patients with first-episode schizophrenia and healthy controls.

| | Patients ($n = 36$) | Healthy controls (n = 36) | t/$\chi^2$ | *p*-value |
|---|---|---|---|---|
| *Demographic characteristics* | | | | |
| Age (years) | 16–59 (24.4 ± 8.8) | 17–58 (24.7 ± 8.4) | −0.1 | 0.91[a] |
| Gender (male/female) | 20/16 | 20/16 | 0 | 1[b] |
| Education (years) | 4–19 (12.4 ± 3.0) | 7–20 (14.4 ± 3.1) | −2.4 | 0.02[a] |
| *Clinical measurements* | | | | |
| Family history (y/n) | 5/31 | 0/36 | – | – |
| Duration of illness (m) | 0.2–84 (9.5 ± 16.6) | NA | – | – |
| Prior treatment before baseline scanning (days) | 0–13 (4.7 ± 3.8) | NA | – | – |
| Inter-scan interval (months) | 1–12 (4.4 ± 2.0) | NA | – | – |
| HAMA scores[c] (baseline) | 7–19 (11.86 ± 3.11) | NA | – | – |
| HAMA scores[c] (follow-up) | 3–11 (7.0 ± 2.3) | NA | – | – |
| HAMD scores[c] (baseline) | 12–22 (14.8 ± 2.8) | NA | – | – |
| HAMD scores[c] (follow-up) | 4–18 (8.6 ± 3.9) | NA | – | – |
| Medication dose at baseline[d] (mg/d) | 0–26.3 (7.8 ± 5.3) | NA | – | – |
| Cumulative dose before first scan[d] (mg) | 0–183.8 (46.1 ± 48.8) | NA | – | – |
| Medication dose during follow-up[d] (mg/d) | 1.2–25 (12.0 ± 5.9) | NA | – | – |
| Cumulative dose during follow-up[d] (g) | 0.2–7.2 (1.6 ± 1.3) | NA | – | – |
| *PANSS baseline* | | | | |
| Positive scores | 7–31 (22.6 ± 4.7) | NA | – | – |
| Negative scores | 7–34 (21.1 ± 6.8) | NA | – | – |
| General scores | 30–64 (44.4 ± 8.4) | NA | – | – |
| Total scores | 63–124 (88.4 ± 13.7) | NA | – | – |
| *PANSS follow-up* | | | | |
| Positive scores | 7–21 (10.3 ± 3.8) | NA | – | – |
| Negative scores | 7–28 (15.0 ± 4.7) | NA | – | – |
| General scores | 11–42 (26.8 ± 6.5) | NA | – | – |
| Total scores | 33–131 (55.4 ± 14.3) | NA | – | – |

Data were presented as mean ± SD.
PANSS, the positive and negative syndrome scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale.
[a] p: Paired *t*-test.
[b] p: Pearson chi-square.
[c] Data for HAMA/HAMD were available in 14 patients.
[d] Dose of antipsychotic medication was converted according to Defined Daily Dose (DDD) as olanzapine equivalence (Leucht et al., 2016).

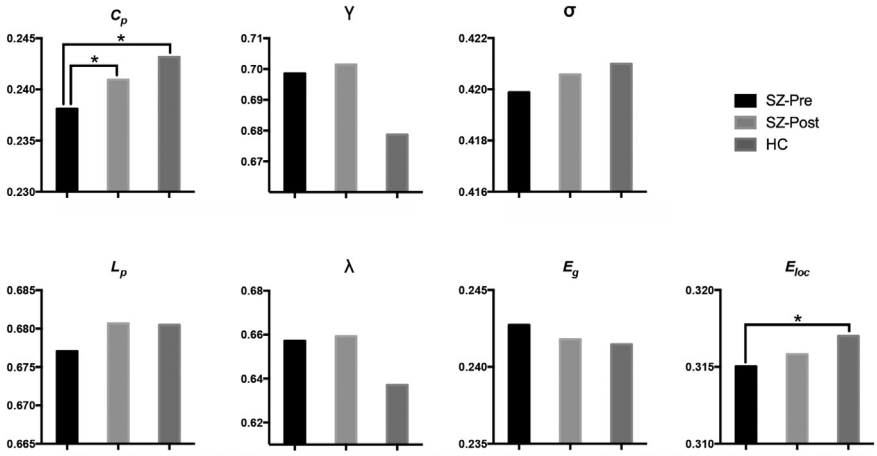


**Fig. 1.** Brain network topology in healthy controls and patients with schizophrenia. Results for $C_p$, $L_p$, γ, λ, σ, $E_g$ and $E_{loc}$. $C_p$: clustering coefficient, $L_p$: characteristic path length, γ: normalized clustering coefficient, λ: normalized characteristic path length, σ: small-worldness, $E_g$: global network efficiency, $E_{loc}$: local network efficiency.

statistical significance ($r = 0.42$, FDR $p = 0.052$) (Fig. 3B). Correlation analyses indicated that edge 3 was positively correlated with PANSS general and total scores ($r = 0.56$, FDR $p = 0.005$; $r = 0.54$, FDR $p = 0.005$, respectively) (Fig. 3C and D).

## 4. Discussion

Compared with HC, SZ patients showed lower local clustering (i.e. $C_p$) and local network efficiency (i.e. $E_{loc}$) at baseline, and such abnormalities were modulated to normal status after 4 months treatment with second-generation antipsychotic drugs. Correlation analyses revealed that $C_p$ was associated with the improvement of clinical symptoms. Moreover, two functional connections between brain regions were identified to be related with the amelioration of SZ symptoms after treatment.

At baseline, SZ showed lower $C_p$ and $E_{loc}$, suggesting disrupted local specialization, while the $L_p$ and $E_g$ were normal in patients compared with HC. Since the small-world organization of brain is characterized by highly clustered nodes and short path length that facilitate efficient signal propagation, such faulty network we found implied a trend towards random network in SZ. Compared with small-world networks, random network has less modular information processing and is more vulnerable to pathological attack (Achard et al., 2006; Liu et al., 2008). This "subtle randomization" process of SZ revealed in our study was consistent with previous studies (Liu et al., 2008; Lo et al., 2015; Lynall et al., 2010; Wang et al., 2010b). However, a recent study by Hadley et al. found greater global clustering coefficient and lower efficiency in SZ and attributed such discrepancies to different inclusion criteria that previous studies only included medicated subjects (Hadley et al., 2016).

To be more specific, in a network, $C_p$ measures local clustering, while $E_{loc}$ measures the ability a network transmits information locally (Wang et al., 2010a). Brain networks with high clustering and local efficiency are robust in local information processing, while lower $C_p$ and $E_{loc}$ of SZ suggest that the network is less efficient for local information transfer. Together with former viewpoints, our study adds evidence to the assumption that SZ is featured by aberrant topological architecture, especially at the local level.

Longitudinally, after the treatment of antipsychotic drugs for 4 months, the abnormal $C_p$ and $E_{loc}$ were normalized. Our results are consistent with Hadley et al.'s concerning the "normalizing influence" of drugs on brain topological organization in individuals in reaction to treatment, especially the local information processing (Hadley et al., 2016), which implies that the functional segregation reflected by $C_p$ and $E_{loc}$ is more sensitive to the normalizing influence of antipsychotic drugs.

Based on previous evidence, we hypothesize such normalizing effect of antipsychotic drugs might reflect the improvement of clinical symptoms. In this study, we found that the change of $C_p$ was positively correlated with the improvement of negative symptom. A former study that focused on the electroencephalography in SZ patients also found that $C_p$ was significantly associated with symptom severity of SZ (Shim et al., 2014). Our results suggest that $C_p$, the metric reflecting the strength of local information transfer, could possibly serve as a biomarker to quantitatively assess the improvement of patients' negative symptom and monitor the effects of treatment.

Although the abnormal local clustering in SZ patients was normalized after treatment, were there any particular functional connections responsible for such normalization? Different from the former study by Hadley et al., our study also analyzed how functional connections changed after treatment (Hadley et al., 2016). We identified three connections that susceptible to treatment, whose functional connectivity strength increased at follow-up and might be responsible for the improvement of local clustering, including the functional connection between the right frontal pole and superior parietal lobule (edge 1), the left inferior frontal gyrus and temporal pole (edge 2), and the right middle temporal gyrus and the left cuneal cortex (edge 3).

The superior parietal lobule is one of the most developmentally delayed regions in the brain, thus the connections around it are considered to be vulnerable to developmental changes during a long time, consistent with the onset of SZ (Guo et al., 2014). Physiologically, the superior parietal lobule mainly receives visual and sensory input. It has been reported that this area also participates in the process of information

**Table 2**
Brain network topology in patients with schizophrenia and healthy controls.

| | SZ-pre - SZ-post | | SZ-pre - HC | | SZ-post - HC | |
|---|---|---|---|---|---|---|
| | t[a] | p | F[b] | p | F[b] | p |
| Small-world properties | | | | | | |
| $C_p$ | −9.11 | <0.001* | 5.07 | 0.03* | 1.11 | 0.30 |
| $L_p$ | −1.80 | 0.08 | 1.36 | 0.25 | 0.003 | 0.95 |
| γ | −0.17 | 0.86 | 1.36 | 0.25 | 0.89 | 0.35 |
| λ | −0.91 | 0.37 | 1.09 | 0.30 | 0.34 | 0.56 |
| σ | −0.13 | 0.90 | 1.50 | 0.23 | 0.97 | 0.33 |
| Network efficiency | | | | | | |
| $E_g$ | 1.81 | 0.08 | 2.32 | 0.13 | 0.26 | 0.61 |
| $E_{loc}$ | −1.64 | 0.11 | 4.45 | 0.04* | 2.03 | 0.16 |

Group SZ-pre, SZ-post and HC each included 36 participants.
[a] *t* value was calculated using paired *t*-test.
[b] F value was calculated using general linear model, with the education years as a covariance.

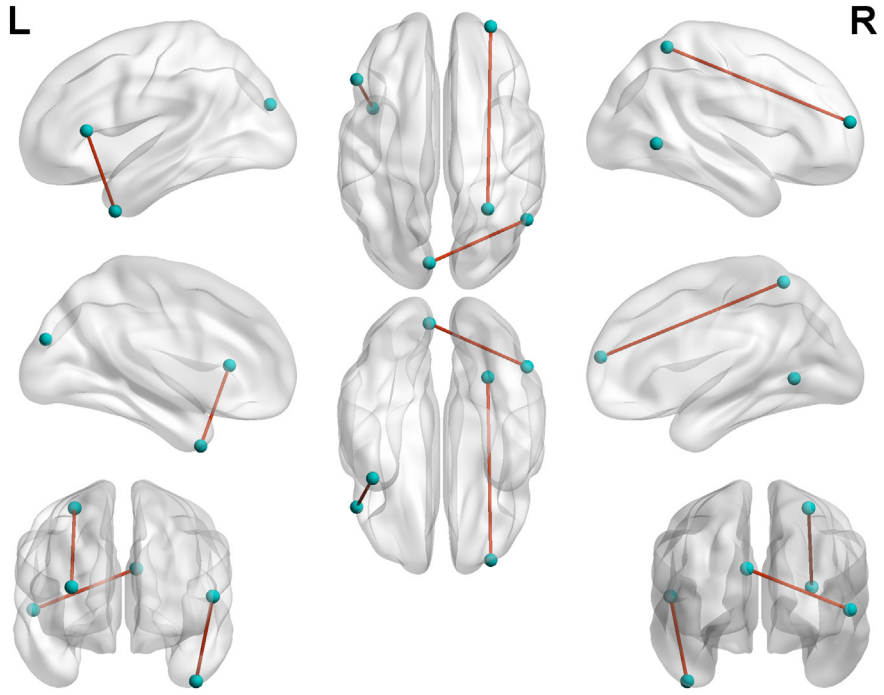


**Fig. 2.** The change of brain functional connections in patients with schizophrenia after the treatment with antipsychotic drugs.

about working memory (Koenigs et al., 2009). With regard to the frontal pole, there is a clear consensus that this area participates in higher-order cognition (Burgess et al., 2007). In addition, Orr et al. reported that the functional connections between the frontal pole and other areas also played a role in action plans, motivate behaviors, emotion and behavior (Orr et al., 2015). The increased functional connection between the superior parietal lobule and frontal cortex after treatment might indicate that the abnormal coupling of fronto-parietal network was normalized by antipsychotic drugs, and the higher the coupling of this network increased, the lower the PANSS general score was (although there was just marginally significant correlation).

Similar significant correlation between functional connection of the right middle temporal gyrus and left cuneal gyrus and clinical symptom was also observed. The middle temporal gyrus was found to be related with several cognitive functions of brain, such as contemplating distance or recognition of faces (Acheson and Hagoort, 2013). Winkelbeiner et al. also reported that the disorganization syndrome of SZ was correlated with decreased cerebral blood flow of the right middle temporal gyrus (Winkelbeiner et al., 2018). Additionally, the cuneal cortex, a part of the occipital lobe, undertakes the function of receiving visual information and involves in basic visual processing, but also could be modulated by higher-level brain function. The increased

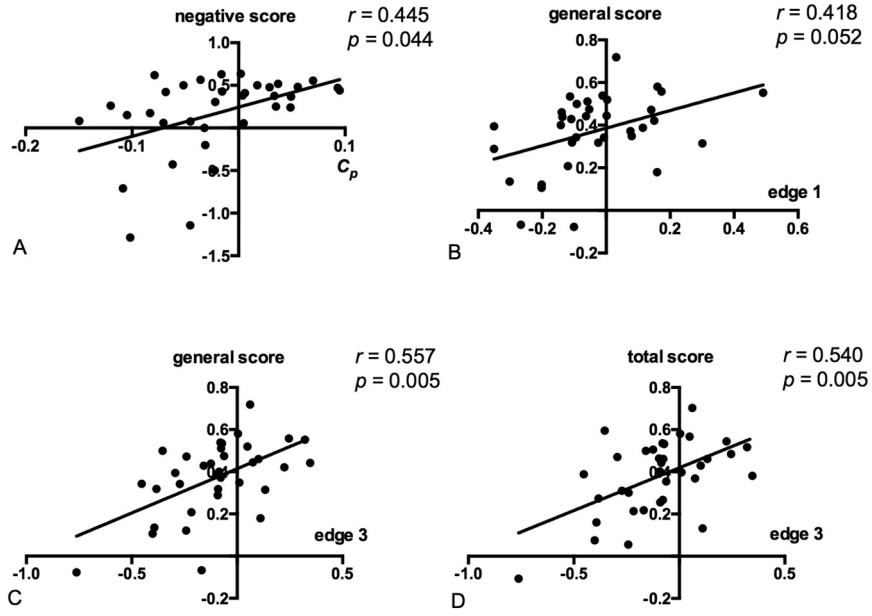


**Fig. 3.** Significant correlations between PANSS scores and $C_p$/specific functional connections in SZ patients. A: the scatter plot between the relative reduction of $C_p$ and the relative reduction of negative score; B: edge 1 and general score (strong tendency towards statistical significance); C: edge 3 and general score; D: edge 3 and total score. Edge 1: functional connection between right frontal pole and superior parietal lobule; edge 3: functional connection between right middle temporal gyrus and left cuneal cortex.

functional connectivity between these two areas might hint at a possible increased coupling of temporal lobe and occipital lobe, and the increased coupling might be associated with the improvement of cognitive function of SZ and clinical symptoms after treatment.

In general, antipsychotic drugs include first-generation and second-generation antipsychotics. Different from the first generation, the second generation antipsychotic drugs not only block the dopamine D2 receptor, but also exert effect on the serotonin 5-$HT_{1A}$, 5-$HT_{2A}$, 5-$HT_{2C}$ and other receptors as antagonists (Miyamoto et al., 2005). With regard to SZ, the decreased dopamine release in the frontal cortex has been reported, as well as the enhancement of prefrontal dopamine release induced by serotonin antagonists after treatment (Ichikawa et al., 2001; Liemburg et al., 2012). In addition, it has been reported that higher concentrations of 5-$HT_{2A}$ receptors in cortical and subcortical areas could be found in SZ (McDonald and Murphy, 2003). In this study, all patients received second-generation antipsychotic drugs that could exert an effect on both dopamine D2 and serotine receptors, possibly leading to the increased release of dopamine in frontal cortex and decreased concentration of serotine receptors in cortical and subcortical areas, thus might be related with the increased local clustering ($C_p$, $E_{loc}$) and strength of functional connections between specified regions from a topological view. However, since patients in this cohort received multi-drug therapy, the possible mechanism underlying topological changes should be considered as a general one but not specific. The individual effect of each single antipsychotic drug might be covered up.

Our results should be considered in the text of several limitations. At baseline, the patient population were treated with antipsychotic drugs prior to scan. Although the patients exposed to antipsychotic drugs within 2 weeks (Fleischhacker et al., 2005), potential influence of medication contributing to the findings might not be ignored. Another obvious limitation of this study was the various antipsychotic medication that patients received during follow-up and various inter-scan intervals. Although all patients in this study were treated with second-generation antipsychotic drugs, each specific affinity to various receptors and pharmacological properties might bring confound to the results. Such heterogeneity was inevitable in studies in which patients received multi-drug therapy. However, regarding the former two limitations, in the statistical analysis of clinical correlation, we set the inter-scan interval, cumulative dose prior the first scan and the cumulative dose during follow-up as covariance, so as to reduce the influence of confounding factors as much as possible. The sample size in this cohort was relatively small. With 36 patients with SZ and 36 controls, the statistical significance power might be limited, thus it was possible that some significant changes concerning topological parameters had not been detected. It was impossible to exactly attribute the changes of topological architecture to antipsychotic drugs or natural progress of SZ, because antipsychotic treatment for patients with SZ could not be withheld.

In conclusion, the current study suggested that $C_p$ could serve as a tool to monitor the improvement of clinical symptoms. Moreover, the functional connection between frontal pole and superior parietal lobule, and between middle temporal gyrus and cuneal cortex might be responsible for the change of topological parameters after treatment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.03.015.

#### Conflict of interest

All authors declared no conflict of interest.

#### Contributors

Author Yi-Bin Xi, Hong Yin and Hua-Ning Wang designed the study and wrote the protocol. Author Xing-Rui Wang and Wen-Ming Liu managed the literature searches and analyses. Author Yuan-Qiang Zhu and Chen Li analyzed the data of MRI. Author Liu-Xian Wang, Fan Guo and Yuan-Qiang Zhu undertook the statistical analysis. Author Liu-Xian Wang wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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