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Longitudinal Network Analysis Reveals Interactive Change of Schizophrenia Symptoms During Acute Antipsychotic Treatment

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***Background and Hypothesis*: Complex schizophrenia symptoms were recently conceptualized as interactive symptoms within a network system. However, it remains unknown how a schizophrenia network changed during acute antipsychotic treatment. The present study aimed to evaluate the interactive change of schizophrenia symptoms under seven antipsychotics from individual time series. *Study Design*: Data on 3030 schizophrenia patients were taken from a multicenter randomized clinical trial and used to estimate the partial correlation cross-sectional networks and longitudinal random slope networks based on multivariate multilevel model. Thirty symptoms assessed by The Positive and Negative Syndrome Scale clustered the networks. *Study Results*: Five stable communities were detected in cross-sectional networks and random slope networks that describe symptoms change over time. Delusions, emotional withdrawal, and lack of spontaneity and flow of conversation featured as central symptoms, and conceptual disorganization, hostility, uncooperativeness, and difficulty in abstract thinking featured as bridge symptoms, all showing high centrality in the random slope network. Acute antipsychotic treatment changed the network structure (M-test = 0.116, $P < .001$) compared to baseline, and responsive subjects showed lower global strength after treatment (11.68 vs 14.18, S-test = 2.503, $P < .001$) compared to resistant subjects. Central symptoms and bridge symptoms kept higher centrality across random slope networks of different antipsychotics. Quetiapine treatment network showed improvement in excitement symptoms, the one featured as both central and bridge symptom. *Conclusion*: Our findings revealed the central symptoms, bridge symptoms, cochanging features, and individualized features under different antipsychotics of schizophrenia. This brings implications for future targeted drug development and search for pathophysiological mechanisms.**

Key words: network analysis/schizophrenia/antipsychotic agents/PANSS

Introduction

Schizophrenia is a disorder of complex psychopathology characterized by a range of psychological, behavioral, and cognitive symptoms. Diagnosis of schizophrenia from the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) contained psychotic symptoms of hallucinations, delusions, and disorganized speech, negative symptoms involving diminished emotional expression or avolition, and cognitive deficits such as impaired executive functions and speed of mental processing.[1] The complexity of schizophrenia symptoms has indicated the heterogeneous clinical manifestation, illness trajectories, and treatment response.

Recently, the multiple connected symptoms of psychiatric disorders (ie, schizophrenia,[2] major depressive disorders,[3] social anxiety disorder,[4] post-traumatic stress disorder (PTSD),[5] etc.) [AU: Please provide the expansion for the abbreviation "PTSD."] were conceptualized as interactive symptoms within a network rather than individual pathological symptoms.[2,6] In a network, *nodes*

represent symptoms while *edges* represent correlations between 2 nodes. The network theory suggests that the occurrence or elimination of one symptom produces a spreading effect to its interrelated symptoms, and even to the global symptoms in a strongly connected network.[7] Network perspectives seem to be an anticipated way to understand the complex schizophrenia symptoms structure and the interactive relationship within this system.

Studies on schizophrenia networks have provided encouraging implications. Focusing on negative symptoms, Strauss, and his colleague identified 6 domains through network analysis to capture the nature of the negative symptom construct in schizophrenia,[8] and revealed the feature of less densely connected negative symptom network in schizophrenia than that in bipolar disorder.[9] Identifying highly influential symptoms has been a central argument for the clinical application of networks.[10,11] Several central symptoms like alogia, avolition and depression, and bridge symptoms that play important roles in mediating exacerbated or treatment effects across the network, like conceptual disorganization, hallucinations, and suspiciousness, have been identified in previous schizophrenia studies and recommended as future treatment targets.[9,12,13] A network that contained multidimensional structure including schizophrenia-related variables, personal resources, context-related factors, and real-life functioning strongly suggested that tightly coupled symptoms tend to maintain each other's activation and contribute to poor outcomes in schizophrenia.[2]

Network analysis sheds new light on understanding psychopathological characteristics and potential treatment targets of schizophrenia. However, whether and how cross-sectional relationships in a complex network system relate to the longitudinal course of schizophrenia is still a matter of debate.[14] One way to deal with this question is to estimate within-subject relationships from individual time series.[4] Network comparison analysis using longitudinal measurements has been conducted as the network methods improve. Macroscopic, mesoscopic, and microscopic network characteristics were compared between baseline network and follow-up network, and network structure, network dense, and stability of central symptoms were found to change over time, even though not always consistent across previous studies.[2,12,15] Following this argument, network of direct change within the subject can clearly serve for the representation of the longitudinal network course.

One clinical fact that needs to be stressed in schizophrenia is the mainstay of antipsychotic agents.[16] But it is unclear how the schizophrenia symptom network changed during antipsychotic treatment. Strauss and his colleague[17] recently explored the network features of successful treatment using Roluperidone for negative symptoms and found Roluperidone reduced the centrality of avolition. We can therefore make inferences of discrepancy networks, especially networks of symptom change, to different antipsychotic drugs on the basis of the different pharmacological mechanisms.

Therefore, in a large antipsychotic treatment cohort that randomly assigned 7 antipsychotic drugs, the current study aims to estimate within-subject networks from individual time series so that to clarify the interactive change in schizophrenia symptoms during acute antipsychotic treatment, and to estimate the distinct networks for different antipsychotic drugs, thereby revealing potential therapeutic effect.

Methods

Sample

Patients with schizophrenia were recruited from 5 research centers in China between July 6, 2010 and November 30, 2011. The inclusion criterion was mainly a diagnosis of schizophrenia based on the Structured Clinical Interview of the DSM-IV, aged 18–45 years, were of Han Chinese ancestry, scored more than 60 on the Positive and Negative Syndrome Scale (PANSS; and scored more than 4 on at least 3 positive items), had a condition to be treated with oral antipsychotic medications, and were able to provide informed consent. Well-organized inclusion and exclusion criteria can be found in the Supplementary File.

Procedure

This is a large randomized controlled trial with 7 different antipsychotic drugs from the Chinese Antipsychotics Pharmacogenomics Consortium.[18] Patients were consecutively randomly assigned (1:1:1:1:1:1:1) to 6 groups (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, or one of the first-generation antipsychotics [haloperidol or perphenazine]) according to entry order. All patients were screened and assessed at baseline (T1), and then followed up at weeks 2 (T2), 4 (T3), and 6 (T4) by a psychiatrist. The PANSS scores were recorded at each time point. Study protocol was approved by the institutional ethics review boards at each site, and written informed consent was obtained. All participants appointed a family member or close friend to participate in the informed consent discussion and help with decision-making.

Assessment

Structured Clinical Interview for PANSS (SCI-PANSS) was used to assess schizophrenia severity. SCI-PANSS is an interval scale ranging from 1 (= "absent") to 7 (= "extreme").[19] It contains of 30 items measuring the severity of positive, negative, and general symptoms.[20] For the present study, scores for all the 30 items were included in network analyses.

The indicators for the side effects were recorded before and after treatment. Genomic DNA was extracted[18]

and polygenetic risk scores (PRS) of schizophrenia were calculated using Psychiatric Genomics Consortium East Asian autosome summary data as base data.[21]

Statistical Analyses

Descriptive data analysis and network estimations were carried out using R 4.1.0.

Missing Data. Item level data for PANSS were missing for no more than 0.3% of the sample across each time point and were imputed using mean value of specific PANSS items.

Network Estimation. Networks were estimated using the *bootnet* package[22] which implements the "*EBICglasso*" algorithm, where nodes represent single PANSS item and edges between nodes represent partial correlations. Given the ordinal nature of the data, *Spearman*'s correlations were applied to create covariance matrix and estimate network structure. The Least Absolute Shrinkage and Selection Operator regularization technique[23,24] was employed to retrieve sparse networks. On the basis of the estimated networks, the strength centrality of nodes was calculated by summing the absolute edge weights connected to a particular node. *EGAnet* package[25] using a weighted network community detection algorithm was applied to identify distinct communities within a network. And bootEGA function was used to evaluate community stability.[26] The bridge centrality that was defined as important in communication between communities were estimated using *networktool*s package.[27] In addition, comparison between network analysis and factor analysis method was compared according to KJ Kan's tutorial.[28]

The networks were visualized using *qgraph* package. Blue edges represent positive partial correlation while red edges represent negative partial correlation. Nodes within a network were placed on the basis of modified Fruchterman-Reingold algorithm. To facilitate visual comparison of the edges at 4-time points, the 4 networks were constrained to be the same using the "*averageLayout*" function. Maximum edge value was set to 0.6 (no less than the strongest edge identified in any network) and minimum edge value was set to 0.08, indicating compared edge thickness across graphs.

$$\text{PANSSpercentage change} = \frac{\text{PANSS endpoint score} - \text{PANSS baseline score}}{\text{PANSS baselinescore} - 30} \times 100$$

Cross-sectional networks in the overall study population across 4-time points and responsive and resistant networks at 6-week follow-up were estimated to compare the pattern of relationships among PANSS items. Patients were classified as responsive or resistant according to PANSS percentage change (formula see below). PANSS percentage change ≥50 is considered as responsive while PANSS percentage change <50 is considered as resistant.

Network Comparison Test. R package network comparison test was utilized to test the differences in global network structure and global strength (overall connectivity level by average strength of all edge weights) across 2 networks, using the permutation-based M-test and S-test.[29]

Random Slope Network Estimation. During antipsychotic treatment, the change of symptoms reveals how the medications work. Random slope networks in the overall sample and subgroups across different antipsychotic drugs (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, and first-generation antipsychotics) were estimated.

$$(Y_{1ij}|d_{j=}1,\ q_j = 0) = (\beta_{10} + \beta_{11}Time_{ij}) + (u_{1j} + v_{1j}Time_{ij} + e_{1ij}) \quad (1)$$

$$(Y_{2ij}|d_{j=}0,\ q_j = 1) = (\beta_{20} + \beta_{21}Time_{ij}) + (u_{2j} + v_{2j}Time_{ij} + e_{2ij}) \quad (2)$$

Change in PANSS items from baseline to after treatment was first modeled using multivariate multilevel linear regressions. This model can accommodate hierarchical data (repeated measurements of individuals are nested within cases) by distinguishing fixed effects and random effects. In addition, the multivariate technique of this model extends one single outcome into 2 outcomes, allowing to directly estimate the correlations between individual item trajectories (random slopes) in a pair of variables. Details related to the multivariate multilevel linear regressions can see in Baldwin et al.[30] and Klipstein et al.[31] In brief, we performed separate models for each PANSS item. Each model contained 2 dependent variables: The PANSS item and the rest-score (total PANSS score excluding the specific PANSS item). The models estimated fixed and random effects in intercepts and slopes for time. The model equations are as follows:

$$Y_{hij} = (\beta_{10}d_j + \beta_{20}q_j + \beta_{11}Time_{ij}d_j + \beta_{21}Time_{ij}q_j) + (u_{1j}d_j + u_{2j}q_j + v_{1j}Time_{ij}d_j + v_{2j}Time_{ij}q_j + e_{1ij}d_j + e_{2ij}q_j) \quad (3)$$

We created indicators to represent 2 dependent variables: d_j and q_j, where $d_j = 1$ for the PANSS item and $q_j = 1$ for the rest-score. Y_{1ij} and Y_{2ij} refer to the response on dependent variable d_j and q_j, at time point *i*, in individual *j*. β_{10} and β_{20} represent the fixed intercept at baseline; β_{11} and β_{21} represent the fixed slope for time; u_{1j} and u_{2j} represent the random intercept varying between individuals; v_{1j} and v_{2j} represent the random slope for time-varying between individuals; and e_{1ij} and e_{2ij} represent the residuals. Equations (1) and (2) can be combined into (3).

Bayesian statistics and Markov chain Monte Carlo (MCMC) methods implemented in *MCMCglmm* package were applied to estimate the model parameters. And random slopes for each PANSS item were extracted from the above models to estimate random slope networks. In addition, the correlation between random slopes of PANSS item and random slopes of rest-score [cor(v_{1j}, v_{2j})] is able to indicate the centrality of the PANSS item within the random slope network.

Network Accuracy and Stability Assessment. The accuracy of edge weights was measured by the 95% confidence intervals obtained from 1000 bootstrap samples drawn from the study population using *bootnet* package.[32] The stability of the centrality indices was evaluated by the case-dropping bootstrap, which can be summarized as CS coefficients. CS-coefficients measured the maximum drop proportions to retain a correlation of 0.7 with at least 95% certainty. The CS-coefficient should be ideally above 0.5 but at least above 0.25.[33]

Results

Descriptive Statistics of PANSS Symptoms

For the full sample (N = 3030), there were 3029 complete cases at baseline, 2755 complete cases at T2, 2630 complete cases at T3, and 2489 complete cases at T4. A total of 2334 patients (77.0%) completed all follow-ups and were analyzed in the sensitivity analysis. The mean age of the full sample is 30.74 (SD: 7.98) years and 51.3% are male. Sample characteristics can be found in Table 1. PANSS scores for 30 items included in the network analysis at 4-time points can be found in Supplementary Figure S1 and the total scores is reported in Supplementary Table S1.

Cross-Sectional Network Analysis Across Different Time Points

Figure 1A shows 4 cross-sectional networks at 4-time points and Table 2 lists the representations of nodes. Five stable communities were detected across the 4 networks: positive symptoms community, negative symptoms community, anxiety/depression community, hostility/excitement community, and disorganized thought community (community stability shown in Supplementary Table S2 and Supplementary Figure S2). Strongest edges emerge in nodes of the same community. Even though fluctuating, P1 (Delusions), P4 (Excitement), N2 (Emotional withdrawal), and N6 (Lack of spontaneity and flow of conversation) remained in top 20% of strength centrality across 4 cross-sectional networks (Figure 1B), and P2 (Conceptual disorganization), P4 (Excitement), P7 (Hostility), G8 (Uncooperativeness), and N5 (Difficulty in abstract thinking) were stable top bridge symptoms across 4 networks (Figure 1C).

Aftertreatment network (T4) showed significant difference on global structure (M = 0.116, P < .001) compared to the baseline network (T1), suggesting that links among variables were changed after antipsychotic drugs

Table 1. Demographic Data at Baseline

	Original Data	Data All Complete	Response	Resistance	*T*/Chi-Square[a]	*P*
Sample size	3030	2334	1486 (59.7%)	1003 (40.3%)		
Age	30.74 ± 7.98	31.26 ± 7.89	31.01 ± 7.92	31.27 ± 7.85	0.83	.41
Sex					0.69	.41
Male	1553 (51.3%)	1207 (51.7%)	779 (52.4%)	508 (50.7%)		
Female	1477 (48.7%)	1127 (48.3%)	707 (47.6%)	495 (49.3%)		
First episode					2.31	.129
Yes	876 (28.9%)	615 (26.3%)	417 (28.1%)	253 (25.2%)		
No	2154 (71.1%)	1719 (73.7%)	1069 (71.9%)	750 (74.8%)		
First age	25.26 ± 6.98	25.45 ± 7.03	25.79 ± 7.17	24.82 ± 6.75	−3.46	<.001
Course/month	76.70 ± 70.89	80.37 ± 71.44	73.48 ± 70.4	88.12 ± 70.9	5.07	<.001
Family history of psychiatric disorders					0.16	.69
No	2372 (78.6%)	1807 (77.8%)	1166 (78.7%)	776 (77.9%)		
Yes	646 (21.41%)	516 (22.2%)	316 (21.3%)	220 (22.1%)		
Drugs					40.60	<.001
Aripiprazole	503 (16.6%)	383 (16.4%)	227 (15.3%)	191 (19.0%)		
Olanzapine	510 (16.8%)	412 (17.7%)	294 (19.8%)	139 (13.9%)		
Risperidone	517 (17.1%)	407 (17.4%)	289 (19.4%)	137 (13.7%)		
Quetiapine	497 (16.4%)	389 (16.7%)	227 (15.3%)	175 (17.4%)		
Ziprasidone	507 (16.7%)	375 (16.1%)	216 (14.5%)	197 (19.6%)		
Haloperidol	242 (8.0%)	176 (7.5%)	114 (7.7%)	75 (7.4%)		
Perphenazine	254 (8.4%)	192 (8.2%)	119 (8.0%)	89 (8.9%)		

[a]Comparison between response subjects and resistance subjects.

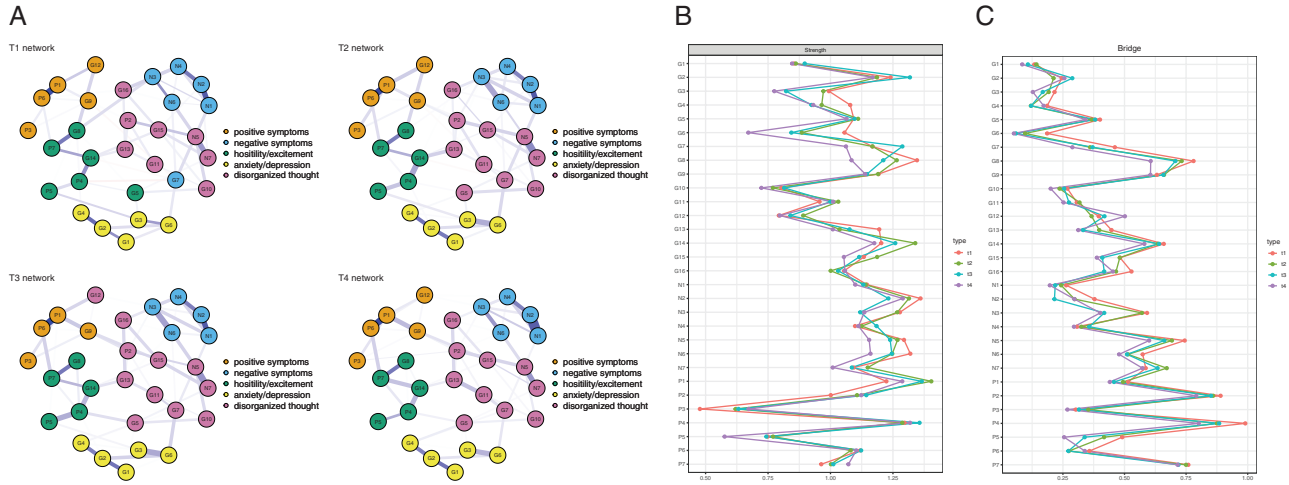

Fig. 1. Cross-sectional networks at 4-time points. (A) represents networks at T1, T2, T3, and T4; (B) represents strength centrality for 4 networks; (C) represents bridge strength for 4 networks; node names can be found in Table 2.

treatment. The global strength was lower after treatment but the difference between T1 and T4 was not significant (16.29 vs 15.34, S = 0.950, P = .25). The edge invariance comparison test and visual inspection provided intuitively different edges between the 2 networks. Some cross-community edges like G8–N3, G8–G12, and P5–G3 significantly weakened or disappeared, while edges within community, like P1–G9 and N2–N3 significantly strengthened after treatment.

Sensitivity analysis identified the same results as the main analysis, but G2 (Anxiety) and G14 (Poor impulse control) also showed higher strength centrality in subjects who completed all follow-ups (see Supplementary Files). Edge accuracy of the networks at each time point was estimated and showed narrow confidence intervals (see Supplementary Figure S3). The CS-coefficients of strength centrality remained 0.75 at each network, suggesting the relationships between variables kept stable (see Supplementary Table S3).

Network Analysis of Responsive and Resistant Patients

At the 6-week follow-up, 1486 patients met the criteria for treatment response (59.7%) and 1003 (40.3%) were resistant (see Table 1).

Figure 2A shows the after-treatment (T4) network structure of patients who are resistant and those who responded. The network structure and global strength of resistant patients were similar to those found in the overall sample (M = 0.068, P = 1; S = 1.158, P = .83), but remarkably different from those observed in responsive patients. The strength of connections was significantly lower in responsive than in resistant patients (11.68 vs 14.18, S = 2.503, P < .001), and the network structure was marginally different between the 2 subgroups (M = 0.137, P = .05) but reached statistical significance in the sensitivity analysis (M = 0.1607, P = .01). The visualized network and the edge invariance comparison showed that, in the responsive network, G2–G4, G8–P7, G14–P4, G4–G5, and P1–G12 were weakened or disappeared, but P4–G5 emerged. Regarding to the node centrality (see Figure 2B), the top symptoms that had high strength centrality (P1, P4, N2, and N6) and high bridge strength (P2, P4, P7, G8, and N5) were identified in the overall sample remained the high centrality values.

Random Slope Network During Acute Antipsychotic Treatment

Figure 3A shows the random slope network, illustrating the interplay of symptom change trajectory during acute antipsychotic treatment. The same communities as the cross-sectional networks were detected in the random slope network and the dimension stabilities were 1.00, 0.83, 1.00, 0.99, and 0.80 for positive symptoms community, negative symptoms community, anxiety/depression community, hostility/excitement community, and disorganized thought community separately, indicating the nodes within a community were cochanging during antipsychotic treatment. Another outcome of interest was the degree to which change in a given node correlated with change in the remainder of the PANSS items (rest-score), defined as the centrality of random slope network. Results showed that P1 (Delusions), P6 (Suspiciousness/persecution), N3 (Poor rapport), and G12 (Lack of judgment and insight) had higher centrality (Figure 3B). The central symptoms (P1, N2, and N6) and bridge symptoms (P2, P7, G8, and N5) identified in cross-sectional networks also showed high centrality in the random slope network except for P4 (Excitement).

Random slope networks in different medications were established (shown in Figure 3 and Supplementary

Table 2. Nodes of PANSS Network

PANSS Item	Node Name	Schizophrenia Symptom
PANSS: positive scale		
Item 1	P1	Delusions
Item 2	P2	Conceptual disorganization
Item 3	P3	Hallucinatory behavior
Item 4	P4	Excitement
Item 5	P5	Grandiosity
Item 6	P6	Suspiciousness/persecution
Item 7	P7	Hostility
PANSS: negative scale		
Item 8	N1	Blunted affect
Item 9	N2	Emotional withdrawal
Item 10	N3	Poor rapport
Item 11	N4	Passive/apathetic social withdrawal
Item 12	N5	Difficulty in abstract thinking
Item 13	N6	Lack of spontaneity and flow of conversation
Item 14	N7	Stereotyped thinking
PANSS: general psychopathology scale		
Item 15	G1	Somatic concern
Item 16	G2	Anxiety
Item 17	G3	Guilt feelings
Item 18	G4	Tension
Item 19	G5	Mannerisms and posturing
Item 20	G6	Depression
Item 21	G7	Motor retardation
Item 22	G8	Uncooperativeness
Item 23	G9	Unusual thought content
Item 24	G10	Disorientation
Item 25	G11	Poor attention
Item 26	G12	Lack of judgment and insight
Item 27	G13	Disturbance of volition
Item 28	G14	Poor impulse control
Item 29	G15	Preoccupation
Item 30	G16	Active social avoidance

Note: PANSS, The Positive and Negative Syndrome Scale.

Figure S4). Central symptoms and bridge symptoms kept the higher centrality across random slope networks of different antipsychotics. Notably, of the 6 antipsychotic groups, quetiapine had the highest N3 (Poor rapport) and G12 (Lack of judgment and insight) centrality, and especially higher P4 (Excitement, a central and bridge symptom) centrality than other drugs. Olanzapine slope network showed the lowest P1 (Delusions, a central symptom) centrality. The node centrality of the risperidone slope network was low at nodes N1 (Blunted affect), N2 (Emotional withdrawal), N3 (Poor rapport), N4 (Passive/apathetic social withdrawal), N5 (Difficulty in abstract thinking), G14 (Poor impulse control) and G15 (Preoccupation). Same results were also reported in the sensitivity analysis (shown in Supplementary Files).

PANSS Changing Network Containing Side Effects and PRS Score

The association between the schizophrenia network and the PRS of schizophrenia and the side effects were also explored, but no association was found between the change of PANSS items and the change of side effects, or between PANSS items and PRS of schizophrenia. Details can be found in the Supplementary Files (shown in Supplementary Figure S12).

Discussion

The current study established networks of schizophrenia symptoms on the basis of individual time series and evaluated the cochanging and individualized network features during acute antipsychotic treatment. Specifically, 3 central symptoms, bridge symptoms, and 5 stable PANSS communities were identified in both cross-sectional networks and random slope networks. Acute antipsychotic treatment changed the network structure and resulted in a weak-strength network. Olanzapine treatment network performed poor on the symptom of delusions; risperidone treatment network performed poor on negative symptoms, impulse control symptoms, and preoccupation symptoms; but quetiapine treatment network showed outstanding improvement on symptoms of poor rapport, lack of judgment and insight, and relatively improvement on excitement symptom. These findings strongly support the stability of key network features over time and may provide a new vision for the different mechanisms of antipsychotics.

One of the greatest controversies of network analysis is the transfer of results from cross-sectional networks to clinical practice, such as applying central symptoms to be treatment targets.[4,14] In the current study, 4 chronologically within-subject networks and a direct random slope network that delineates the change trajectory of schizophrenia symptoms over time reported similar network features (communities, central symptoms, and bridge symptoms), providing solid support for further clinical utility of network results. In fact, the 5 communities detected in the current study were consistent with the 5-factor structure of PANSS that was reported previously.[34,35] And the PANSS communities identified through change trajectory during acute antipsychotic treatment corresponded well with that in cross-sectional status networks.

Antipsychotic treatment changed the network structure and lowered the network strength, which is one of the major findings of the current study. An advanced integrated real-life functioning network of schizophrenia patients revealed that tightly connected symptoms made prominent contributions to maintaining the highly activating disease state.[2] Previous study has found a significant change of network structure in 12-month follow-up compared to baseline network in first episode psychosis patients.[12] Another study compared the remitters' and no-remitters' networks and reported that network structure and nodal strengths changed significantly

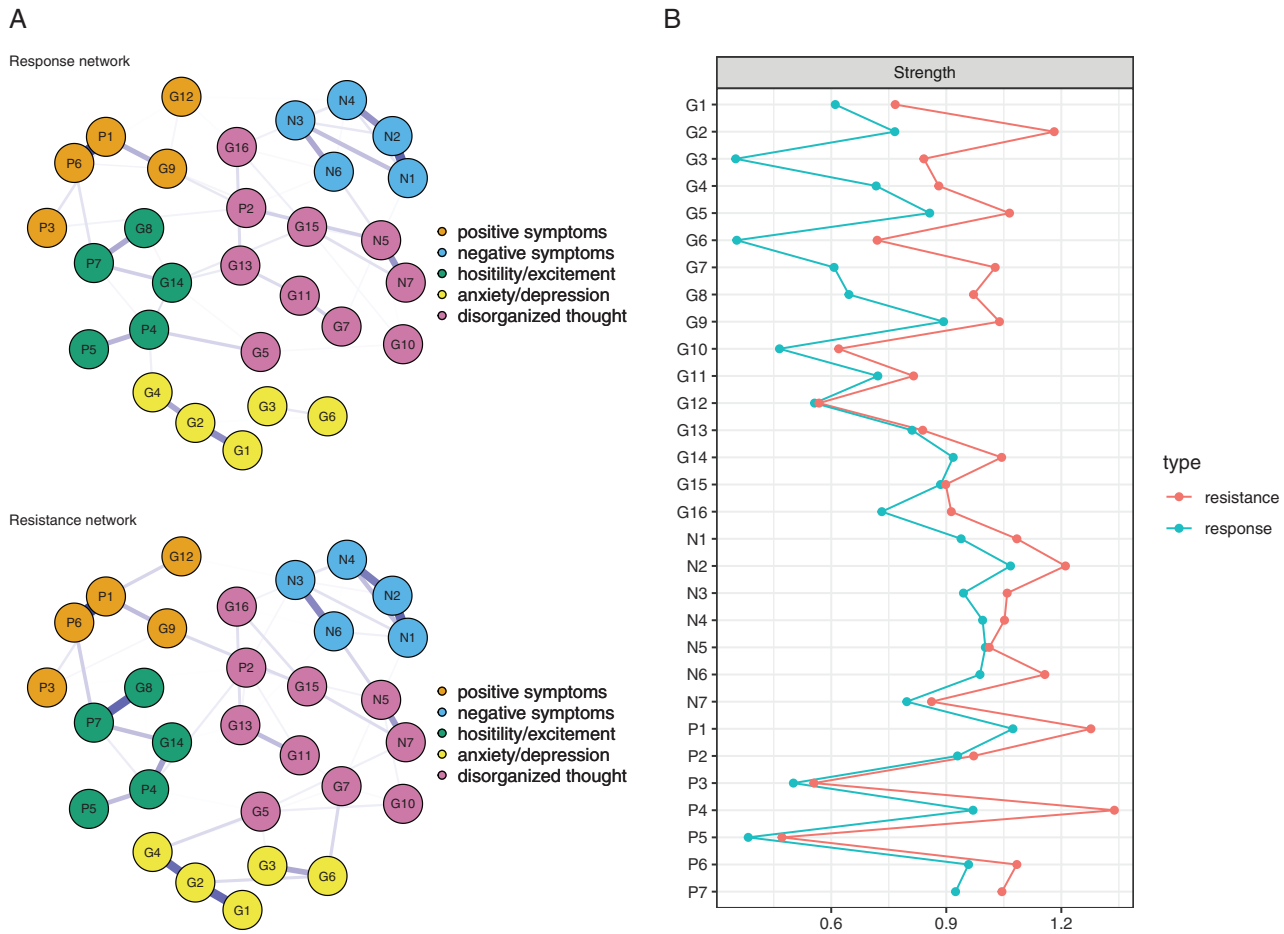

Fig. 2. Resistant network and responsive network (A) and the related strength centrality (B). Node names can be found in Table 2.

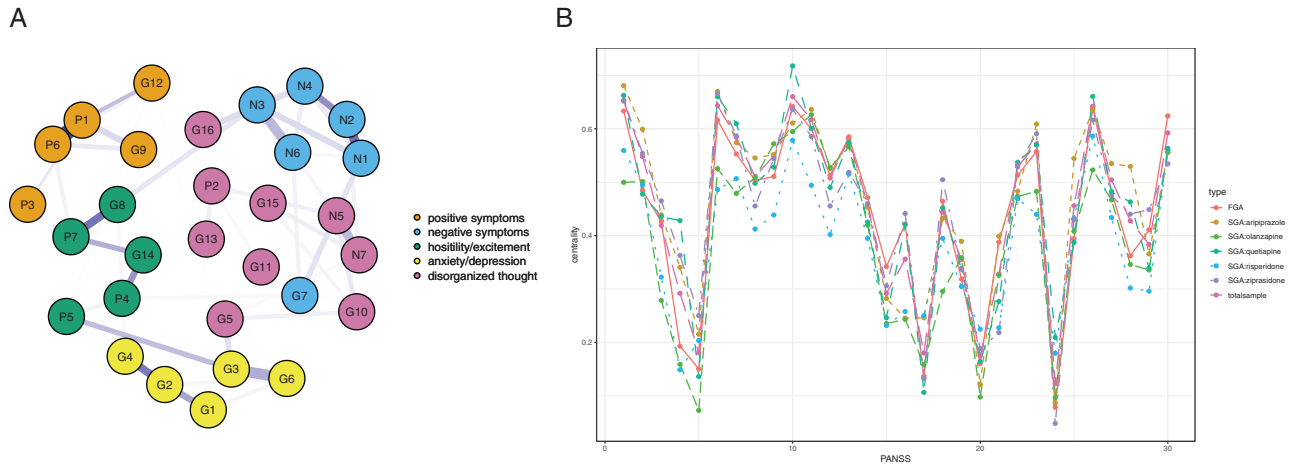

Fig. 3. Random slope networks across overall sample and centrality of random slope networks. A: Random slope network across the overall sample, B: Centrality of random slope network across total sample and samples with different antipsychotics; FGA, first-generation antipsychotics; SGA, second-generation antipsychotics; *x-axis* represents 30 PANSS symptoms, nodes name can be found in Table 2.

in the remitters over time.[36] In the current study, the after-treatment network, especially the response network, confirms that the direction of antipsychotic treatment is to decrease the strength: this will also be a new treatment goal or idea in addition to reducing the PANSS score in the future.

Furthermore, it may be difficult to treat a dense or strong network due to the great clustering of symptoms, but focusing on the central symptoms is a wise and practical way.[37,38] Central symptoms in a dense network connected with other symptoms strongly, and this also applied a spreading effect to the antipsychotic treatment. Delusions, emotional withdrawal, and lack of spontaneity and flow of conversation are such central symptoms. And it's not surprising because previous study has found alogia a most central symptom in negative symptoms of schizophrenia patients.[9] There is another group of symptoms that gathered our interest: the bridge symptoms, which also showed high centrality during antipsychotic treatment. This group of symptoms played important mediating roles across different communities. The bridging role of conceptual disorganization was previously reported in the psychopathology of psychosis.[12] But the present study was more concerned about their promising effect as treatment targets, because bridge symptoms can help to explain the continuity of clinical efficacy on different symptoms.[12,39] When bridge symptoms improved under treatment, the likelihood of other communities of improved symptoms increases. This may suggest potential targets for future antipsychotic treatment. In addition to the central symptoms and bridge symptoms, unusual thought content, lack of judgment and insight, and active social avoidance also had high centrality in the random slope network. The 3 symptoms were clustered in the positive symptom community and negative symptom community, which is still in line with the traditional opinion of the core of positive and negative symptoms of schizophrenia.[40]

Pharmacological mechanisms of antipsychotics have not been fully understood yet, but different performances on clinical efficacy were observed in clinical practice.[41,42] In the light of the objective of this trial on precision antipsychotic treatment, the longitudinal network analysis also illustrated the individualized way of antipsychotics to achieve their effects from network perspectives. Of the random slope networks, quetiapine showed higher centrality in excitement than other drugs, which was defined as both central symptom and bridge symptom. Excitement symptoms are connected with poor impulse control directly and with hostility and uncooperativeness indirectly. This result was consistent with previous studies that reported quetiapine treatment mediated an improvement in agitation assessed by PANSS score.[43,44] Network analysis seems one way to explain risperidone's very low effects on social functioning for the acute treatment of adults.[45] Centrality of overall PANSS symptoms was not so high in the risperidone slope network, especially on a series of negative symptoms. That is, risperidone treatment was not so superior from the network perspective. However, not all network features of antipsychotics met with the clinical performance assessed by PANSS scores. For example, centralities of all positive symptoms were weak in olanzapine slope network, especially on delusion, although olanzapine was reported higher effect sizes on positive symptoms in a meta-analysis.[45]

Other interesting results included that all PANSS negative scales showed high centrality in both cross-sectional network and random slope network, while positive scales were not (ie, hallucinatory behavior and grandiosity). This is an obvious difference with the PANSS scores method, where positive scales showed higher scores or larger mean differences change than negative scales. In line with the previous study,[12] hallucinatory behavior seems a rather separate symptom in addition to the connection with delusion. Additionally, polygenic risk score of schizophrenia did not predict the change of single psychotic symptoms. The comprehensive genetic effects from multiple minor genes may explain this result. The risk architecture of schizophrenia has been previously reported as multifinality and equifinality, where a number of separate genotypic networks were uncovered associating with several distinct clinical syndromes.[46] To identify candidate genes specific to distinct clinical symptoms could be more targeted in future network studies.

The present study has many strengths, in particular the large sample size, the randomized assignment of the first-line antipsychotics, and the random slope networks that showed interplay change of schizophrenia symptoms. However, certain limitations should be considered when interpreting these findings. The patients recruited in the current study were mostly those trapped in positive symptoms, resulting in selection bias to some extent. Considering the treatment purpose of this trial, such selection bias tends to identify positive communities and changing trajectories of positive symptoms, but would be not enough to identify features of negative symptoms in a network due to the flooring effect. The estimations on centrality of negative symptoms in random slope networks under different antipsychotics were also limited by the selection bias and absence of statistical tests and should be interpreted in caution. And also, the patients were in the acute-treatment phase, thus it is unclear whether these results generalize to chronic maintenance treatment phases. Network analysis provides new sights into the treatment course of antipsychotics, but the corresponding pharmacological mechanism was underexplored. Experimental research using animal models are needed in the future to reveal the pharmacological mechanisms so that to increase the reliability and interpretability. It is unclear how genetic, clinical, and demographic factors might influence the interplay change of schizophrenia symptoms during antipsychotic treatment. Future studies should replicate these findings in other datasets.

The current study has several important implications. First, the cochanging features of a community suggest that study on schizophrenia psychopathology should

focus on the commonality of symptoms within one community, which may reduce the complexity and heterogeneity of this illness thus pure the mechanism pathways. Second, targeted treatment development should focus on the central symptom: delusions, emotional withdrawal, and lack of spontaneity and flow of conversation, expecting that the entire symptom constellation can be improved if the 3 central symptoms are effectively treated. Third, the treatment effects on excitement symptom can be enhanced because excitement symptom was recognized as a central symptom and bridge symptom but does not reach the corresponding role during antipsychotic treatment except quetiapine. Finally, we need to reconsider the treatment objectives from the network perspective. Although the responsive pattern has not been completely identified yet, putting schizophrenia symptoms in a certain status, not just low severity may be also important.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Conflict of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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