Schizophrenia Research 236 (2021) 29–37

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

# The effects of antipsychotics on interactions of dynamic functional connectivity in the triple-network in first episode schizophrenia

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ARTICLE INFO

*Keywords:*
Schizophrenia
Resting-state functional magnetic resonance imaging
Triple-network
Dynamics
Machine learning

ABSTRACT

*Background:* Brain dynamics abnormalities in the triple-network, which involves the salience network (SN), the default mode network (DMN) and the central executive network (CEN), have been reported in schizophrenia. However, it remains to be clarified how antipsychotics affect dynamic functional connectivity (DFC) within the triple-network and whether differences in clinical outcomes are associated with varying levels of network model dysfunction.

*Methods:* Resting-state functional magnetic resonance imaging scans were obtained from 64 first-episode schizophrenia patients (SZ) and 67 healthy controls (HC). All patients were scanned before and after 12-week antipsychotic treatment and the HC were scanned only at baseline.

*Results:* At baseline, SZ participants showed significantly reduced dynamic functional interactions across the triple-network compared to HC. The SZ group displayed a pattern of reduction in resting-state DFC among the triple-network compared with HC. After medication, the mean dynamic network interaction index (dNII) value was improved. A significant quadratic relation was observed between longitudinal change of mean dNII and the reduction ratio of PANSS total score within the SZ group. The DFC within inter-network (between DMN and SN, and between DMN and CEN) and intra-network connections of DMN were significantly higher relative to baseline. Intra-SN DFC, intra-DMN DFC and DFC between SN and DMN were found to be predictive of clinical features at baseline. Intra-CEN DFC and DFC between DMN and CEN were predictive of treatment response.

*Conclusions:* Aberrant brain dynamics in the triple-network could be regulated with medication. DFC organization in the triple network was found to predict the clinical outcome.

## 1. Introduction

Schizophrenia is a complex mental illness that manifests in multiple symptom dimensions including psychotic symptoms, cognitive impairments and emotional dysregulation with a lifetime prevalence of approximately 1% (Dixon, 2017; van der Meer et al., 2010). The disease

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https://doi.org/10.1016/j.schres.2021.07.038
Received 17 November 2020; Received in revised form 8 May 2021; Accepted 28 July 2021
Available online 5 August 2021

is characterized by a typical onset in late adolescence or early adulthood, poor recovery outcomes and a significantly reduced life expectancy (Charlson et al., 2018; Jaaskelainen et al., 2013; Laursen et al., 2014). With the rapid development of neuroimaging technology, researchers have turned to the exploration of large-scale brain networks. There is growing consensus that the neurobiology of psychosis involves aberrations of various cognitive functions and associated brain network systems (Dong et al., 2017; Jiang et al., 2018; Menon, 2011). However, many studies lack a theoretical framework specifying how functional abnormalities in neural networks that underlie human cognition leading to the psychotic symptoms.

Recently, a unifying triple-network model (Bressler and Menon, 2010; Menon, 2011) has been proposed as a common framework for understanding dysfunctional brain dynamics across neuropsychiatric disorders. The model involves three core networks: the default mode network (DMN), the central executive network (CEN) and the salience network (SN). The DMN is thought to play an important part in internal self-referential processes and is characterized by being activated in a resting (task-free) state and deactivated when cognitive tasks need to be performed (Andrewshanna, 2012). The main components of the DMN include the posterior cingulate cortex (PCC), the medial prefrontal cortex (MPFC), the angular gyrus (AG) and the medial temporal gyrus (MTG). The CEN, represented by the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC), is most active in tasks that require attention and executive functions (Menon and Uddin, 2010). In general, cognitive states that activate the CEN usually inactivate the DMN, and vice versa. Finally, the SN is thought to be crucial in 'switching' between the CEN and DMN. A study comparing 193 studies in more than 7000 patients across 6 diagnostic groups including schizophrenia showed a feature of gray matter reduction in the medial frontal regions, insula, thalamus, hippocampus and amygdala and an increase in gray matter in the striatum (Goodkind et al., 2015). A transdiagnostic pattern of gray matter loss in the anterior insula (AI) and dorsal anterior cingulate cortex (dACC) was identified across psychiatric patients, which are core parts of the salience network involved in the detection and identification of external saliency and internal mental events, reallocating brain resources for information processing (Menon, 2019; Menon and Uddin, 2010; Seeley et al., 2007; Sridharan et al., 2008; Supekar et al., 2019; Young et al., 2017). Abnormal integration of information among these three networks may help us understand the relationship between impaired cognition and psychiatric symptoms across multiple brain disorders.

Many imaging studies have shown aberrant functional connectivity among the DMN, CEN and SN in patients with psychiatric disorders (Jiang et al., 2019; Liu et al., 2017; Wang et al., 2017). However, most studies focus on static measurements of functional connectivity (FC), while emerging evidence suggests that network connectivity manifests time-varying properties (Di and Biswal, 2013; Liu and Duyn, 2013; Luo et al., 2019). Dynamic functional connectivity (DFC) analysis may capture these time-varying properties of brain network interactions (Calhoun et al., 2014), which are ignored in static FC analyses. Zhang et al. (2016) proposed that temporal variability reflects the dynamic reconfiguration of a brain region into distinct functional modules at different times. Their work indicated opposing temporal variability patterns in schizophrenia and autism, compared with respective controls (Zhang et al., 2016). DFC analysis of functional interactions across the DMN, SN and CEN may provide a more comprehensive framework to improve our understanding of the neural mechanisms of mental illness (Damaraju et al., 2014; Supekar et al., 2019).

Several studies utilizing DFC approaches have reported abnormalities in brain dynamics among the DMN, CEN and SN and their relationship to psychosis in schizophrenia patients (Lancaster and Hall, 2016; Supekar et al., 2019; Wang et al., 2016). A recent study using resting state fMRI found that compared to healthy subjects, schizophrenia patients showed significantly reduced, less persistent, and more variable dynamic functional interactions across these three networks. In both of two independent cohorts, dynamic measures of functional interactions were correlated with positive symptoms, while there was no correlation with negative symptoms (Supekar et al., 2019). These findings suggest a role for dysregulated triple-network brain dynamics in schizophrenia. All the same, researchers have yet to determine whether levels of triple-network dysfunction relate to differences in outcome and if so, how triple-network dynamics change after antipsychotic treatment.

To clarify abnormalities in triple-network brain dynamics and their relation to psychosis and clinical outcomes in schizophrenia, we employed a DFC analysis of task-free fMRI data of 64 schizophrenia patients at baseline and after 12-week follow-up. We hypothesised that triple-network DFC organization at baseline may be predictive of clinical outcome and that impairments in the dynamic balance among the DMN, CEN, and SN may be restored to a certain extent following antipsychotic treatment.

## 2. Materials and methods

### 2.1. Participants

This study included 64 drug-naive, first-episode schizophrenia patients (SZ), aged 16 to 40 years and 67 healthy controls (HC). The patients were recruited from the inpatient ward and outpatient department at the Shanghai Mental Health Center (SMHC). Diagnosis of schizophrenia was verified using Diagnostic and Statistical Manual of Mental Disorders, 4th edition, (DSM-IV) criteria. Exclusion criteria included the following: 1) major medical conditions including neurological disorders; 2) a history of head trauma; 3) current drug or alcohol abuse or dependence; 4) current pregnancy or breastfeeding; 5) an unstable clinical state including aggressive behavior; 6) meeting other mental disorder criteria according to the DSM-IV; 7) electroconvulsive therapy or transcranial magnetic stimulation within the last six months; or 8) contraindications to MRI scanning. Following the baseline MRI scan, all patients were treated with second generation antipsychotics (SGAs). The choice of drug and dose were managed by their clinical psychiatrists. The Positive and Negative Syndrome Scale (PANSS) was used to assess symptoms (Kay et al., 1986) by the same researcher at baseline and at 12-week follow-up. Treatment response, measured as the reduction ratio in PANSS total score, was defined as follows (Howes et al., 2017; Obermeier et al., 2010):

$$\Delta PANSS = \frac{PANSS_{t1} - PANSS_{t2}}{PANSS_{t1} - 30} \times 100\%$$

67 HC matched on age, gender, education and handedness were recruited from the Shanghai Mental Health Center through online advertisement. They were screened by the Mini-International Neuropsychiatric Interview (M.I.N.I.) plus v 5.0 (Sheehan et al., 1998). The same exclusion criteria used for patients were also applied to HC. In addition, HC with any mental illness history or a family history in a first- or second-degree relative were also excluded.

The SZ patients underwent MRI at both baseline and the follow up while the controls only underwent MRI scans at baseline. All patients finished MRI scan and the clinical assessment. All participants contributed voluntarily to the study and signed written informed consents. The study was approved by the Institutional Review Board of Shanghai Mental Health Center.

### 2.2. Imaging data acquisition and preprocessing

The fMRI data were acquired in a Siemens Verio 3.0 T MRI scanner at the Shanghai Mental Health Center. Resting-state fMRI images were obtained using a gradient-echo (GRE) echo-planar imaging (EPI) sequence with the parameters as follows: TR = 2 s, TE = 30 ms, matrix = 74 × 74, flip angle = 77°, field of view = 220 mm, voxel size = 2.97 × 2.97 × 3 $mm^3$, slice thickness = 3 mm, and 50 slices without slice gap.

Totally, 240 volumes were obtained in 480 s. Data preprocessing steps were consistent with our previous studies (Jiang et al., 2017) and details are provided in the Supplement.

### 2.3. Definition of the triple-network of DMN, CEN and SN

Consistent with our previous study (Jiang et al., 2017), the triple-network was identified using seed-based FC analysis. The coordinates of seeds were from previous literature. The seed coordinates (−5, −49, 40) for the DMN were selected from a meta-analysis of anticorrelations during task performance (Fox et al., 2005). The seed for the CEN used the peak voxel coordinates (48, 18, 17) from an area with significant group differences between controls and schizophrenia patients (Whitfield-Gabrieli et al., 2009). The seed coordinates (38, 22, −10) for the SN is based on a previous study (Wotruba et al., 2014) The 8-mm spheres of the three coordinates were used as the seed regions for the DMN, CEN and SN separately. Voxel-wise functional connectivity (FC) analyses were performed to define the mask of the triple-network. Pearson's correlation coefficients were calculated between the time series of each seed and that of whole brain voxels, and then transformed into Fisher z scores. This yielded a FC z map of each seed and each subject. Finally, one sample *t*-tests were performed on the FC z maps to identify the regions exhibiting significantly positive connectivity with the seed. After multiple comparisons correction ($p < 0.05$, FDR correction), the peaks of clusters were considered as nodes of the triple-network. A total of thirteen nodes were included in this study (see Supplementary materials: Table S1).

### 2.4. Functional interactions across the triple-network

Dynamic cross-network interactions were estimated using dynamic FC analysis. Our dynamic FC approach was similar to prior studies (Supekar et al., 2019) and is briefly described here (see Supplement for details). First, functional interactions across the DMN, CEN and SN were estimated using a sliding window strategy. Second, group-specific brain functional states exhibiting distinct dynamic triple-network interactions were identified using a group-wise k-means clustering approach. Third, similar to previous studies (Supekar et al., 2019), we calculated the mean lifetime of each brain state to reveal the dwelling time of dynamic brain states for each subject. Fourth, we assessed the brain network interaction index (NII), which reflects functional interactions across the three networks (Menon, 2019; Menon and Uddin, 2010). The NII is calculated as the difference between the $FC_{(SN,\ CEN)}$ and $FC_{(SN,\ DMN)}$, thus capturing the degree to which the SN transiently connected with the CEN and separated from the DMN (Greicius et al., 2003; Supekar et al., 2019). As the SN and the CEN are typically co-activated during cognitive tasks, while the SN and the DMN are typically anti-correlated, the NII is defined as following equation:

$$NII = FC_{(SN,CEN)} - FC_{(SN,DMN)}$$

The $FC_{(SN,\ CEN)}$ is the functional connectivity, measured by the Fisher z-transform of Pearson's correlation coefficient between the time series of the SN and the CEN. The $FC_{(SN,\ DMN)}$ is the functional connectivity, measured by the Fisher z-transform of Pearson's correlation coefficient between the time series of the SN and the DMN. A larger NII reveals more segregation of functional interactions in the CEN-SN-DMN triple network. Here, we used the brain state–specific dynamic network interaction index (dNII) to further represent interactions across the networks in each dynamic brain state (Supekar et al., 2019). Specifically, the NII of each sliding window was calculated to yield time-varying NIIs. Subsequently, the averaged NIIs for the windows in corresponding brain state were computed as dNII. Next, we computed the mean value and variability (measured by standard deviations) of dNIIs of each subject across all dynamic brain states. Two sample *t*-tests were used to examine the difference between pre-treatment schizophrenia and HC and paired *t*-tests were used to investigate longitudinal changes after treatment.

### 2.5. Dynamic functional connectivity analysis

In addition to the dynamic functional interactions among the DMN, CEN and SN, we also investigated the sliding window dynamic FC (DFC) between any two nodes within the triple-network. Specifically, the FC between any two nodes was calculated for each sliding window. This yielded a series of time-varying FCs across all windows. The DFC was computed based on the standard deviations of time-varying FCs.

### 2.6. Statistical analysis

Two sample *t*-tests were performed to compare the differences in mean lifetime of dynamic brain states, dNII, and DFC between pre-treatment schizophrenia patients and controls. Paired t-tests were used to assess changes in the mean lifetime of brain states, dNII, and DFC between post-treatment and pre-treatment schizophrenia groups. The *t*-tests were conducted after controlling for the influence of age, sex, education and frame displacement of head motion.

Some priori studies suggest that there may be a nonlinear relationship between brain imaging indicators and clinical symptoms , such as the relation of the maturation of striatal connectivity with core deficits in motor and inhibitory control, impulsivity, and inattention, and dynamic associations between frontostriatal white matter integrity and delay of gratification skills (Achterberg et al., 2016; Barber et al., 2019). Therefore, an exploratory analysis was performed to investigate dynamic FC measures for potential associations with clinical symptoms, using a both linear and quadratic curve estimation model to assess mean values and variability of dNII for relevance with PANSS scores.

### 2.7. Predicting clinical features and treatment outcomes via machine learning

To examine whether DFCs within the triple-network could predict individual symptoms (PANSS scores at baseline) and clinical outcomes following antipsychotic treatment (PANSS reduction at follow-up), baseline DFCs were selected as features entered into a support vector machine (SVM) supervised multivariate regression model (https://www.csie.ntu.edu.tw/~cjlin/libsvm). A feature-selection procedure was further conducted using a stepwise linear regression during SVM training. Leave-one-out cross-validation (LOOCV) was used to validate the robustness and reliability of the model (Li et al., 2018; Shen et al., 2017). Specifically, in each cross-validation iteration, one subject's data was selected as a test set, using the remaining subjects' data as a training set to build the SVM regression model. The data of the subject who was left out was then used as input into the trained SVM regression model, yielding a prediction value. Repeating this procedure, the LOOCV produced a prediction for each subject. Finally, we used Pearson's correlation analysis to assess the association between the predicted values and observed true values. Statistically significant ($p < 0.05$) correlations would suggest that triple-network DFCs were predictive of clinical response following medication.

## 3. Results

### 3.1. Demographics

Table 1 lists the participant's demographic and clinical features. All subjects were right-handed. No significant difference was observed between the SZ and HC groups in age, sex, or education level. There was a significant difference in PANSS total and subscale scores between pre- and post- antipsychotic treatment (Table 2).

**Table 1**
Characteristics for the schizophrenia and health controls.

| | Schizophrenia (Mean ± SD) | Health controls (Mean ± SD) | Statistics | p value |
|---|---|---|---|---|
| Number | 64 | 67 | | |
| Gender (M/F) | 31/33 | 32/35 | $\chi^2$ = 0.006 | 0.938 |
| Age (years) | 24.69 ± 6.82 | 24.16 ± 6.07 | $t$ = 0.588 | 0.558 |
| Education (years) | 13.00 ± 3.02 | 13.64 ± 2.89 | $t$ = −1.244 | 0.216 |
| Handness (left/right) | 0/64 | 0/67 | | |
| DUP (months) | 16.25 ± 14.20 | | | |
| CPZ eq (mg/d) | 442.11 ± 195.64 | | | |
| PANSS-reduction (%) | 54.61 ± 22.86 | | | |

Notes: PANSS, Positive and Negative Syndrome Scale; DUP, Duration of untreated psychosis; CPZ eq, Chlorpromazine equivalent doses. Two-sample *t*-tests were used to compare age and education between the two groups, and $\chi^2$ test was used to compare gender distribution.

**Table 2**
Characteristics for the schizophrenia patients at baseline and after 12-week follow-up.

| | SZt1 (baseline) (Mean ± SD) | SZt2 (follow-up) (Mean ± SD) | Change (Mean ± SD) | Statistics | p value |
|---|---|---|---|---|---|
| PANSS Total scores | 88.22 ± 15.86 | 56.64 ± 14.86 | 32.09 ± 16.86 | $t$ = 15.227 | <0.001* |
| PANSS Positive scores | 24.05 ± 5.36 | 12.31 ± 4.45 | 11.73 ± 6.31 | $t$ = 14.883 | <0.001* |
| PANSS Negative scores | 19.77 ± 7.85 | 14.70 ± 6.15 | 6.29 ± 5.06 | $t$ = 6.440 | <0.001* |
| PANSS General scores | 44.39 ± 6.93 | 29.64 ± 6.81 | 14.75 ± 8.53 | $t$ = 13.836 | <0.001* |

Notes: PANSS, Positive and Negative Syndrome Scale. p values were obtained by using paired *t*-tests.
* $p < 0.05$.

### 3.2. Antipsychotic treatment

All the patients were treated with atypical antipsychotics. Forty patients(62.5%) received monotherapy: olanzapine (n = 15), risperidone (n = 7), amisulpride (n = 7), paliperidone (n = 6), aripiprazole (n = 4), and quetiapine (n = 1); and twenty-four patients (37.5%) received combined medication: aripiprazole and olanzapine (n = 8), risperidone and olanzapine (n = 4), amisulpride and olanzapine (n = 3), aripiprazole and paliperidone (n = 2), quetiapine and paliperidone (n = 2), risperidone and quetiapine (n = 1), aripiprazole and quetiapine (n = 1), ziprasidone and olanzapine (n = 1), ziprasidone and aripiprazole (n = 1) and olanzapine and quetiapine (n = 1) (see Supplement for details). The average dose in chlorpromazine equivalence (CPZ eq) was 442.11 ± 195.64 mg/day (Leucht et al., 2016).

### 3.3. Dynamic functional interactions across the triple-network

Dynamic functional interactions among the triple-network were measured using a DFC approach. There were eight states (temporal clusters) in the SZ group (Fig. 1A) at baseline (SZt1), four states at follow-up (SZt2) (Fig. 1B) and two states in the HC group (Fig. 1C). We compared the mean lifetime of dynamic brain states between the SZt1, SZt2 and HC groups (Fig. 1D). At baseline, the mean lifetime of state 1 and state 2 in the HC group was significantly longer than that of the eight states in the SZt1 group ($p < 0.0001$). After medication, the mean lifetime of corresponding brain states was significantly extended (SZt2-SZt1, $p < 0.0001$).

We next compared the mean value (Fig. 1E) of dNIIs in all dynamic brain states between SZt1, SZt2, and HC. At baseline, the mean value of dNIIs across dynamic brain states was significantly lower in the SZt1 group than in the HC ($p = 0.016$). After treatment, the mean value of dNIIs in the SZt2 group was significantly higher than in the SZt1 group ($p = 0.022$). We also compared variability in dynamic functional interactions in the triple-network between the SZt1, SZt2, and HC groups (Fig. 1F). Compared with HC, SZt1 showed greater variability in dNIIs across brain states, indicating that functional interactions are more variable in SZ than healthy controls ($p < 0.0001$). However, the increased variability of dNIIs in the SZ patients did not significantly change after treatment ($p = 0.594$).

### 3.4. Relationship between dynamic functional interactions and clinical outcomes

We found a significant quadratic relation between longitudinal change in mean dNII and the reduction ratio in PANSS total score after treatment ($F = 7.49$, $p < 0.001$) (Fig. 2). There was no significant linear or quadratic correlation between dynamic functional interactions and positive or negative symptoms either at baseline or at follow-up (all p values >0.05).

### 3.5. Changes in DFC within the triple-network

This study identified thirteen triple-network nodes, including six DMN nodes of the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), bilateral angular gyrus (AG) and bilateral middle temporal gyrus (MTG); four CEN nodes of the bilateral dorsolateral prefrontal cortex (DLPFC) and inferior parietal lobule (IPL); and three SN nodes of the anterior cingulate cortex (ACC) and bilateral insula (INS) (Table S1, Fig. 3A). Baseline comparisons between the SZt1 and HC groups indicated that the SZt1 group displayed a pattern of reduction in DFCs of some connections of the triple-network ($p < 0.05$, uncorrected) (Fig. 3B). Specifically, the DFCs between the DMN and SN (AG.L-ACC), between the CEN and SN (IPL.R-ACC), and intra-DMN (MPFC-MTG.L, and MPFC-AG.R) were lower in the SZt1 group compared to the HC group. No increased DFC was found in the SZt1 group. Longitudinal comparison between SZt1 and SZt2 showed that after 12 weeks of antipsychotic medication, the DFCs between the DMN and CEN (MTG.R - IPL.L), between the DMN and SN (AG.L- INS.R), and intra-DMN (MPFC-AG.L) were significantly higher at SZt2 relative to SZt1 ($p < 0.05$, uncorrected) (Fig. 3C). No decreased DFC was found in patients at follow-up compared with baseline.

### 3.6. Prediction of individual symptoms and medication outcomes using baseline DFC within triple-network via machine learning

We found that intra-SN DFC (INS.R-ACC), intra-DMN DFC (MTG.L-AG.L) and DFCs between the SN and the DMN (ACC-MTG.L, INS.L-AG.R, INS.L-AG.L, INS.R-PCC) were predictive of PANSS total scores ($r = 0.611$, $p < 0.001$) at baseline (Fig. 3D). In addition, intra-CEN DFC (DLPFC.L-IPL.L) and DFCs between the DMN and the CEN (MPFC-IPL.R, MTG.L-DLPFC.R, AG.R-IPL.L, AG.R-IPL.R, MTG.R-IPL.R) were predictive of PANSS reduction ($r = 0.539$, $p < 0.001$) after medication (Fig. 3E).

## 4. Discussion

This study investigated dynamic functional interactions among the triple-network in schizophrenia patients pre- and post- 12 weeks of antipsychotic treatment, and developed a model using dynamic FC

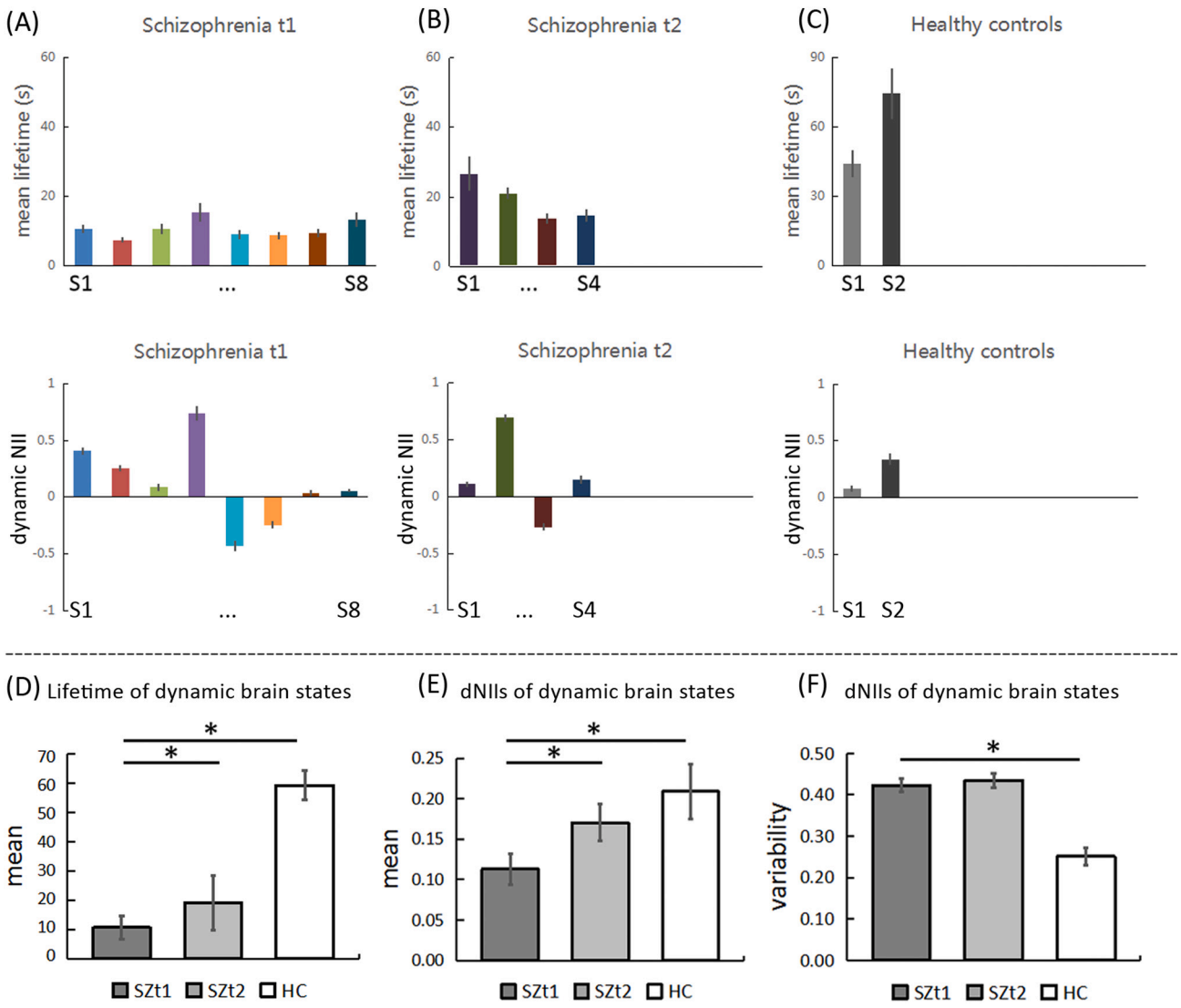


**Fig. 1.** Dynamic functional interactions among the triple network. (A) The schizophrenia group at baseline (SZt1) showed eight dynamic brain states (S1 to S8). (B) The schizophrenia group at follow-up (SZt2) showed four states (S1 to S4), and (C) The healthy control group (HC) showed two states (S1 to S2). In each brain state, the mean lifetime and dynamic network interaction index (dNII) were computed. (D) The mean lifetime of dynamic brain states was significantly shorter in the schizophrenia group compared with the HC. After treatment, the mean lifetime of states in the SZt2 group was significantly increased than that in the SZt1 group. (E) The temporal mean of dynamic cross-network interaction, assessed using the mean of the dNIIs across brain states, was significantly lower in the schizophrenia group compared with the HC group. After treatment, the mean of dNIIs in the SZt2 group was significantly increased than that in the SZt1 group. (F) The temporal variability of dynamic cross-network interaction, assessed using the standard deviation of the dNIIs across brain states, was significantly higher in the schizophrenia group compared with the HC group.

metrics and machine learning techniques to predict symptomatic response after treatment.

### 4.1. *Dynamic functional interactions across the triple-network*

We examined mean lifetime of dynamic brain states and found eight states in the schizophrenia group and two in the control group. The mean lifetime of state 1 and state 2 in the HC group was significantly longer than that of the eight states in the SZ group at baseline. After antipsychotic treatment, the mean lifetime of corresponding brain states was significantly extended in SZt2. These results are similar to previous studies (Lottman et al., 2017; Supekar et al., 2019), indicating that compared with healthy controls, patients show less persistent and more unstable brain states, which normalize to some extent after antipsychotic treatment. In this study, dynamic functional interactions across the triple-network were found to be altered in first-episode schizophrenia patients as compared to healthy controls at baseline. The patients showed significantly shorter and more unstable SN-centered functional interactions among the three networks. These abnormalities were found to normalize to some extent after antipsychotic treatment, with significant increases in mean dNII values, but no significant change in the variability of dNII. These results are consistent with a previous study (Supekar et al., 2019), suggesting an impairment of integration of the SN with the CEN and a de-linked dysfunction of the SN with the DMN in schizophrenia which improved after antipsychotics treatment. Reduced SN-centered cross-network interactions imply poor integration between the SN and the CEN, and decreased separation of the SN with the DMN, representing an impaired ability to flexibly and dynamically allocate cognition-related processing resources in schizophrenia (Menon, 2011; Menon and Uddin, 2010; Sridharan et al., 2008; Supekar et al., 2019). Failure to shift attention from the internal self-world to an objective external environment properly may hinder the ability to filter irrelevant neutral information, thus may lead to core symptoms of schizophrenia such as delusion of reference and autistic thinking.

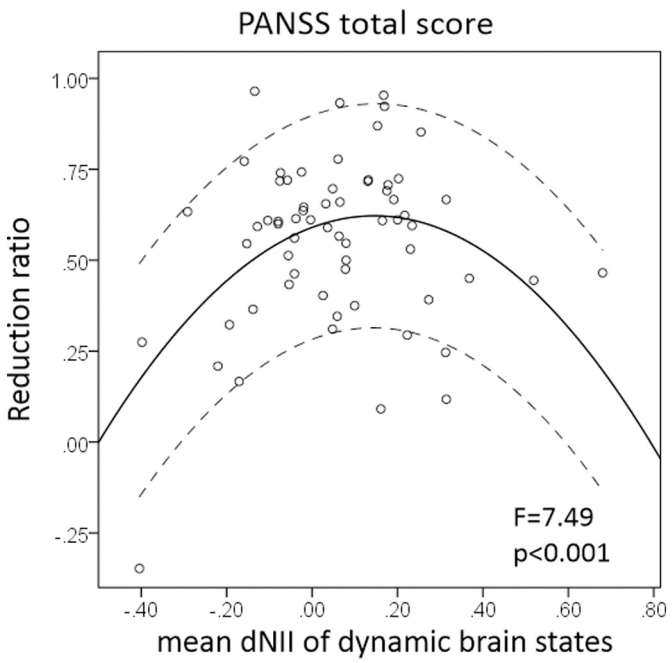


**Fig. 2.** A significant quadratic relation between longitudinal change in mean dNII of dynamic brain states and the reduction ratio in PANSS total score in patients with schizophrenia after medication.

In the current study, we found a significant quadratic relation between longitudinal change in mean NII and the reduction ratio in PANSS total score, indicating an inverted U-shaped pattern in the relationship between the dynamic functional interactions across the networks and the degree of symptom improvement. The inverted U curve is an important concept in developmental economics and psychology (Wiese, 2017; Xu et al., 2019). It is widely found in the study of relationship between motive and effect, pressure and efficiency. The inverted-U model is also used to describe a nonlinear relation between brain activation and cognitive capacity especially working memory load in schizophrenia (Eryilmaz, 2016; Snellenberg et al., 2016). The result of this study suggests that symptoms improvement is associated with dynamic functional interactions across the networks in a specific range, and when the difference between NII mean time at baseline and follow up reaches the most appropriate value, the best treatment effect is achieved. Future researches may further explore the significance of the network interaction index (NII) in evaluating treatment outcomes.

### 4.2. Dynamic functional connectivity in triple-network

We examined the dynamic functional connectivity between key nodes of the triple-network in schizophrenia patients' pre- and post-treatment utilizing resting state fMRI. By applying sliding window and functional connectivity methods, we investigated group differences between SZt1 and HC, and between SZt1 and SZt2. At baseline, patients showed decreased (less variable) DFC between the nodes involving inter-network (between DMN and SN and between CEN and SN) and intra-network connections of the DMN compared with healthy controls. Subsequently, an increased DFC pattern among the triple-network was observed at follow up. It is interesting that the longitudinal increases in DFC do not involve the same edge connections for which SZ showed reductions relative to HC. We infer that perhaps this is not strictly network function normalization, but more of a compensatory effect.

Recently, dynamic functional connectivity approaches have shown great promise for exploring the pathogenesis and investigating disease biomarkers of schizophrenia (Calhoun et al., 2014; Damaraju et al., 2014). A small number of longitudinal studies were conducted to assess brain network DFC changes after antipsychotic treatment. Similar to previous studies (Dong et al., 2019; Duan et al., 2020), our findings of decreased FC variability between the nodes in SZ compared with HC showed an abnormal dynamic interaction among the triple network and suggested a attenuated (less flexible) interaction of core brain networks in schizophrenia. After 12-week treatment, we found increased between-node DFC, especially for the DMN intra-network DFC. This finding suggests that schizophrenia symptom improvement may be associated with improved integration in the triple-network, especially the intra-network DFC in DMN post-treatment.

This study points out that triple-network DFC may predict clinical features and antipsychotic treatment response in drug-naïve first-episode schizophrenia patients. Using machine learning techniques, we identified triple-network DFC features that successfully predicted clinical features and response to antipsychotic medications. According to our findings, DFC features of different nodes in the triple-network are predictive of clinical symptoms as evaluated by the PANSS and reductions in clinical symptoms following treatment. The SVR model that significantly predicted PANSS total scores included intra-SN and intra-DMN DFC, and DFC between the SN and the DMN. Prediction of the PANSS total score reduction involved intra-CEN DFC and DFC between the DMN and the CEN. These findings suggest that intra-SN DFC, intra-DMN DFC and interactions between the SN and the DMN may play a more important role in clinical features while intra-CEN DFC and the relationship between CEN and DMN may mainly take effect in clinical outcomes. Ours is an exploratory result. Further research is needed to clarify the value of analyzing network interactions and dynamics to predict clinical characteristics and outcomes in patients with schizophrenia.

## 5. Limitations

Some limitations of the current study should be taken into account. First, patients were scanned pre- and post- treatment while the healthy controls participating in this study were scanned only at baseline, so we cannot completely exclude other causes of changes in brain imaging. Though changes over time were generally considered to be negligible in healthy subjects, some alteration such as normal neurodevelopment may have occurred. Therefore, a design of scanning at 2 time points in health controls is needed in future studies. Second, patients were treated with different types of antipsychotic medications in a naturalistic treatment and we did not perform analyses to separate drug specific effects. Third, the present study did not include neuropsychological assessments so we can only conclude that the altered network interactions are associated with patients' general psychopathology. As a next step, we plan to study the three core networks by combining resting-state fMRI with assessments of social cognition and neurocognitive functioning. Indeed, this is an exploratory study without prior hypothesis and the reliability of the findings still needs further confirmation. Future studies could utilize larger samples to examine effects of sex, antipsychotic agents, duration of untreated psychosis, and other factors that may influence SN and triple-network dysfunction. Longitudinal studies of longer-term follow-up for more accurate information about the clinical outcomes are also warranted.

## 6. Conclusions

Using DFC and machine learning analyses, we found that abnormalities in dynamic functional interactions among the triple-network are prominently featured in first episode schizophrenia. Abnormal dynamic functional interactions among the triple-network were found to be regulated with symptomatic improvement after medication and DFC organization in the triple-network model may predict symptom severity and outcome of schizophrenia. The current study supports the hypothesis of an aberrant salience triple-network model of psychosis and explores its potential role in predicting treatment outcomes.

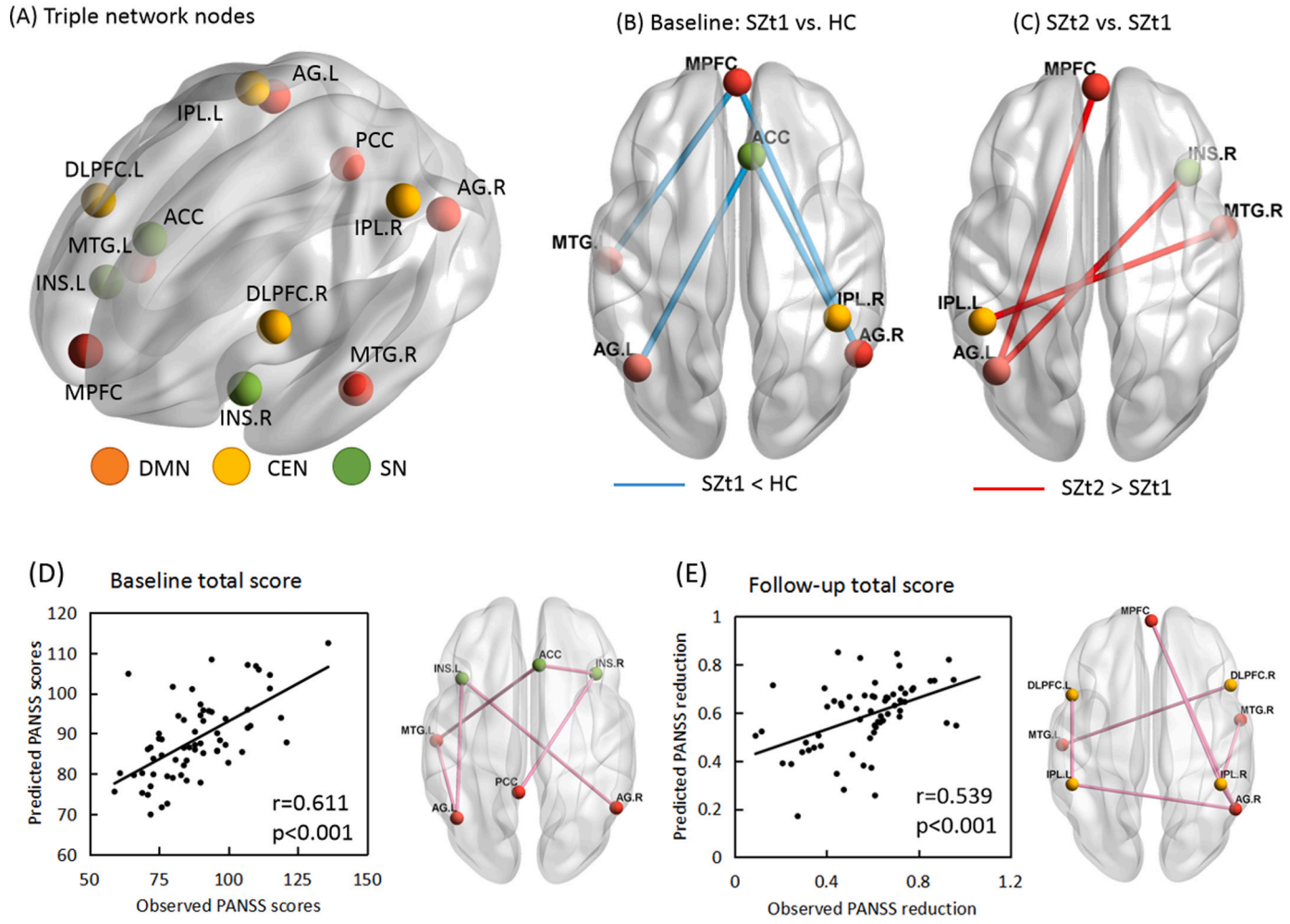


**Fig. 3.** Dynamic functional connectivity within the triple-network. (A) A total of thirteen nodes were identified in the triple network, including six DMN nodes of medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), bilateral angular gyrus (AG) and bilateral middle temporal gyrus (MTG); four CEN nodes of bilateral dorsolateral prefrontal cortex (DLPFC), inferior parietal lobule (IPL); and three SN nodes of anterior cingulate cortex (ACC) and bilateral insula (INS). (B) Baseline comparison between the SZt1 and HC groups indicated that the SZt1 group displayed a pattern of reduction in the dFC between the key nodes of the triple-network. (C) After the 12-week medication, the dFCs were significantly increased in the SZt2 group relative to the SZt1 group. (D) The connectome of intra-SN dFC, the intra-DMN dFC and the dFCs between the SN and the DMN could significantly predict the PANSS total scores for schizophrenia patients at baseline. (E) The connectome of the intra-CEN dFC and the dFCs between the DMN and CEN could significantly predict the PANSS reduction for schizophrenia patients after medication.

Comprehension of dynamic variation in the triple-network connectivity may advance our understanding of the neurobiological mechanisms and biomarkers that underlie psychopathology in schizophrenia.

## Role of funding sources

These funding agents had no role in the study design, collection, analysis and interpretation of the data, writing of the manuscript, or decision to submit the paper for publication.

## CRediT authorship contribution statement

Yingchan Wang and Yuchao Jiang conceived of the study, participated in the clinical treatment and helped to draft the manuscript. Wenjun Su, Lihua Xu, Yanyan Wei, Yingying Tang and Tianhong Zhang collected the data. Jianye Zhang, Xiaochen Tang and Yegang Hu carried out the MRI assessment and imaging data acquisition. Huiru Cui, Jinhong Wang, Dengtang Liu and Dezhong Yao contributed toward data analysis. Guusje Collin helped to revise the manuscript. Jijun Wang and Cheng Luo are the guarantors of integrity of the entire study. All authors read and approved the final manuscript.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

This work was supported by Ministry of Science and Technology of China, National Key R&D Program of China (2016YFC1306800); National Natural Science Foundation of China grants (81671332, 81971251, 81671329, and 81871050); Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and ZJLab; Shanghai Science and Technology Committee Foundations (16ZR1430500, 19411969100, 19410710800); Clinical Research Center at Shanghai Mental Health Center grants CRC2018ZD01, CRC2018ZD04, and CRC2018YB01; Clinical Research Center at Shanghai Jiaotong University School of Medicine (DLY201817).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.07.038.

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