



## Abnormal patterns of regional homogeneity and functional connectivity across the adolescent first-episode, adult first-episode and adult chronic schizophrenia

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### ABSTRACT

Functional deficits in schizophrenia (SZ) are observed prior to the onset of psychosis and differ at different stages of SZ. However, there is a paucity of studies focused on adolescent first-episode SZ (AOS), adult first-episode SZ (AFES), and adult chronic SZ (CHSZ). In this study, we investigated regional activity and corresponding functional connectivity alterations that have aimed to compare the three disease stages simultaneously. The subjects comprised 49 patients with AOS, 57 patients with AFES, 51 patients with CHSZ, 41 adolescent healthy controls, and 138 adult healthy controls. We compared regional homogeneity (ReHo) between patients at each disease stage with matched healthy controls. We focused on the shared brain regions that showed significant differences between SZ patients at the three different disease stages and healthy controls. Further analysis was conducted to explore whether the patterns of the whole brain functional connectivity alterations were similar. The putamen and medial frontal gyrus (MFG) showed consistently abnormal patterns in AOS, AFES, and CHSZ. Commonly decreased ReHo values in the MFG and increased ReHo values in the bilateral putamen were found in AOS, AFES, and CHSZ. Functional connectivity of MFG remained common abnormality in different SZ stage. In conclusion, ReHo abnormalities in the MFG and the putamen may be common abnormal patterns of brain function in the three different stages of SZ. The vmPFC-dlPFC FC abnormality common occurs in adolescence and adulthood. This study may provide a more comprehensive understanding of the neurodevelopmental abnormality across the AOS, AFES, and CHSZ.

### 1. Introduction

Schizophrenia (SZ) is a devastating mental disorder characterized by psychotic symptoms, neurocognitive impairment, and abnormal social behavior, affecting nearly 1 % of the human population (Marder & Cannon, 2019). The neurodevelopmental abnormality hypothesis is one

of the main hypotheses regarding the pathogenesis of SZ. Therefore, it is important to explore the pathogenesis of SZ at different developmental stages. Abnormal brain activities have been found in patients with SZ by analyzing resting-state functional magnetic resonance imaging (rs-fMRI), and they are associated with clinical symptoms in SZ (Liu et al., 2006; Whitfield-Gabrieli et al., 2009). Therefore, exploring local neural

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activities and functional connectivity (FC) in brain regions are of great importance for understanding the neurodevelopmental abnormalities pathogenesis of SZ.

Regional homogeneity (ReHo) enables the evaluation of regional neural activities on the rs-fMRI (Zang, et al., 2004). It measures the similarity of the time series of a given voxel and its neighboring voxels. A large ReHo value reflects high coordination of neural activity, while a low ReHo value indicates disconnection in brain regions. Comparing with the FC analysis, ReHo is unsusceptible to phase changes across measurement time series and phase differences across brain regions (Liu et al., 2018). Because of these advantages, ReHo has been widely applied in SZ to detect local abnormalities (Gao et al., 2018; Liu et al., 2019; Liu et al., 2018; Wang et al., 2018).

SZ can roughly be divided into adolescent SZ and adult SZ based on age at onset. In addition, according to the duration of illness, SZ can be further divided into first-episode and chronic SZ. Patients with adolescent-onset SZ (AOS) have the same diagnostic criteria as those with adult-onset SZ, but they have more severe symptoms and a worse response to antipsychotic treatment than patients with adult-onset SZ. Therefore, a lot of rs-fMRI studies aimed to identify the brain abnormalities of different stages of SZ (Pantelis et al., 2005; Zhao et al., 2018). However, most previous studies actually involved patients at only one or two stages of SZ (Y. Liu et al., 2018; Zhao et al., 2018; Gong et al., 2020). Studies on patients with first-episode SZ (FES) are particularly instrumental to the understanding of the pathophysiology of SZ because of the reduced impact of potential confounders, such as large amounts of antipsychotic medication or social deprecation (Q. Gong, Lui, & Swee-ney, 2016). Therefore, a large number of longitudinal imaging studies have focused on patients with FES (Chen et al., 2013; Cui et al., 2016). Meanwhile, some studies focused on chronic SZ to explore whether ongoing pathophysiological processes may underlie brain structural and functional changes (Liao et al., 2012; Liu et al., 2016; Liu et al., 2006). Default-mode network (DMN) is a well-known brain network that including the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, and parietal regions (PTL). FES and chronic SZ also had common abnormal DMN homogeneity. Meanwhile, FES patients had the specific abnormal of function activity in putamen, middle occipital gyrus, left mPFC, inferior parietal gyrus, and right precuneus (Gong et al., 2020). Chronic SZ patients had the specific abnormal of function activity in amygdala, inferior frontal gyrus (IFG), left inferior temporal gyrus, right ACC, left insula and superior frontal gyrus (SFG), left precuneus, and postcentral gyrus (Gong et al., 2020). AOS had the abnormal neural activity in right inferior parietal lobule (IPL) and bilateral precuneus (Liu et al., 2018). Moreover, our previous studies showed the abnormal DMN homogeneity in AOS patients (Peng et al., 2021; Zhang et al., 2020).

Studies between adolescent and adult SZ may be helpful to improve our understanding of the pathophysiology of SZ and developing new treatment strategies. However, there is a lack of study on the different stages including adolescent SZ, adult SZ and chronic SZ; it remains unclear at which stage the structural and functional deficits occur. Considering the commonality and specificity in clinical characteristics of the three stages of SZ, we hypothesized that there are also similarities and differences in their abnormal brain activity. In this study, we used rs-fMRI to explore the functional characteristics between adolescent and adult SZ and expect to provide a systematic understanding of the patterns of change in brain functions of SZ patients.

## 2. Methods and materials

### 2.1. Subjects

The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University, Xinxiang, China. Written informed consent was obtained from all participants and/or their legal guardians.

The present study recruited SZ patients and healthy controls (HCs) from the Second Affiliated Hospital of Xinxiang Medical University. A consensus diagnosis of SZ was made by two experienced senior psychiatrists according to Diagnosis and Statistic Manual and Mental Disorders, 4th Edition (DSM-IV) criteria for SZ using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I, patient edition). AOS was defined as being between 13 and 18 years old (Fraguas et al., 2016), with an illness duration less than 1 year. Adult chronic SZ (CHSZ) was defined as patients over the age of 18, with an illness duration less than 2 years (Hollis, 2000). Adult chronic SZ (CHSZ) was defined as patients over the age of 18, with an illness duration over 2 years (Velakoulis et al., 1999). The symptoms were assessed by trained and experienced psychiatrists using the positive and negative syndrome scale (PANSS) (Kay et al., 1987). Inclusion criteria were: diagnosed with SZ according to DSM-IV, age range from 13 to 55 years old, more than 60 on the total PANSS score, right-handed, and Han ethnicity. Exclusion criteria were: diagnosed with other mental disorders; severe, unstable physical diseases (such as diabetes, thyroid diseases, hypertension, and cardiac diseases); a well-documented history of epilepsy; treated with electroconvulsive therapy within the last 6 months; pregnant or breastfeeding; previously attempted suicide; or had experienced the symptoms of severe excitement and agitation within one week before MRI scanning.

HC individuals, including adolescent HCs (Ado-HC) who were under the age of 18 and adult HCs (Adu-HC) who were over 18, were recruited from the same site and screened using the SCID-I (non-patient edition). Inclusion criteria were: age range from 13 to 55 years old, right-handed, and Han ethnicity. Exclusion criteria: diagnosed with any mental disorders; severe, unstable physical diseases (such as hypertension, diabetes, thyroid diseases, and cardiac diseases); a well-documented history of epilepsy; pregnant or breastfeeding; any history of mental disorders, or first- or second-degree relatives with any history of mental disorders; or had experienced the symptoms of severe excitement and agitation within one week before MRI scanning.

### 2.2. MRI data acquisition and preprocessing

MRI data were acquired using 3.0-T MR scanners (Siemens, Verio, Germany). fMRI data were acquired using an echo planar imaging (EPI) sequence sensitive to BOLD contrast: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, matrix size = 64 × 64, resolution of axial slice 3.4 × 3.4 mm<sup>2</sup>, slice thickness = 4 mm, gap between slices = 0.6 mm. Resting-state data were acquired for a period of 8 min (240 time points). Acquisition parameters for T1-weighted scans were: repetition time = 2,530 ms, echo time = 2.43 ms, inversion time = 1,100 ms, flip angle = 7°, matrix size = 256 × 256 × 192, and voxel size = 1 × 1 × 1 mm.

Data quality was ensured by screening artifacts, head motion (translation > 3 mm or degree > 3°), registration, and normalization quality as well as by excluding left- and mixed-handed subjects and by matching age and sex. The first 10 time points of the EPI images were discarded to account for equilibration effects. The preprocessing pipeline included the following steps: slice timing correction, within subject EPI image realignment, rigid-body registration of each subject's T1 image to the EPI mean image, and normalization of the EPI images to the Montreal Neurological Institute (MNI) standard space using the T1 image. After spatial normalization, the EPI images were resampled to 3 × 3 × 3 mm<sup>3</sup>, followed by a noise removal process including a multiple regression model and band-pass filtering. Regressors of the regression model included linear trends, averaged white matter (WM), cerebrospinal fluid, and whole brain (global signal) voxels, the first derivatives of WM, and the Friston's 24 parameters' head motion model (Friston, Williams, Howard, Frackowiak, & Turner, 1996). After removing potential noisy signals using averaged brain tissue time series and estimated head motion signals in the multiple regression model, the residuals were band-pass filtered (0.01–0.08 Hz) to further suppress low-frequency drifts and psychological noises such as breathing and

heartbeat. All of the above processes were performed using BRANT version 3.36 (Xu, et al., 2018), a MATLAB toolbox built on SPM (Eickhoff et al., 2005) for batch preprocessing fMRI data.

### 2.3. ReHo calculation

After preprocessing, voxel-wise ReHo for each participant was computed using the BRANT toolbox (<https://sphinx-doc-brant.readthedocs.io/en/latest/>). ReHo was calculated to measure the similarity of each voxel's time series with its 26 nearest neighbor voxels using Kendall's coefficient of concordance (KCC), which ranged from 0 (the lowest regional synchronization) to 1 (the highest regional synchronization). Then, the images were spatially smoothed with a Gaussian filter with a full width at half maximum (FWHM) of 6 mm.

### 2.4. Functional connectivity calculation

Given a region of interest (ROI), we calculated the average fMRI signals of voxels within it. For functional connectivity (FC), we computed the Pearson's correlation coefficients of time series between the ROI and each voxel in the whole brain. Then, Fisher's z-transform was calculated to convert the correlation coefficients to z-values to improve the normality at an individual level.

### 2.5. Statistical analysis

Group differences in demographic characteristics and clinical data were assessed using single-factor analysis of variance (ANOVA), adjusted for covariates (sex and age) when appropriate. To determine the voxel-wise ReHo differences between patients with different stages of SZ and their corresponding HCs, we used two-sample t-test or Welch's t-test, adjusted for sex and age. All analyses were corrected for multiple comparisons using the Alphasim method in the RESTplus toolkit (Jia et al., 2019), which applied Monte Carlo simulation and taken into account both individual voxel probability and cluster size to calculate the probability of false positive detection. The voxels that exhibited significant ( $P_{\text{Alphasim}} < 0.05$  and the single voxel level  $p < 0.01$ , and a maximum cluster size threshold) and consistent (increased or decreased) ReHo abnormalities at all stages of the SZ were extracted and the corresponding clusters of these voxels were defined as ROIs in subsequent FC analyses. To examine the FC differences of ROIs between patients with different stages of SZ and the corresponding HCs, we also used two-sample t-test or Welch's t-test with Alphasim correction ( $P_{\text{Alphasim}} < 0.05$  and the single voxel level  $p < 0.01$ , and a maximum cluster size threshold), while controlling for sex and age.

## 3. Results

### 3.1. Demographic and clinical data

A total of 336 subjects were enrolled in this study, including 157 SZ patients and 179 HCs. The SZ patients were further divided into three subgroups, including 49 patients with AOS, 57 with AFES, and 51 with CHSZ. The HCs were divided into two groups, including 41 in the Ado-HC group and 138 in the Adu-HC group. As shown in Table 1, the groups

**Table 1**  
Demographic data in SZ patients and healthy controls.

Group	AOS	Ado-HC	P values	AFES	Adu-HC	P values	CHSZ	Adu-HC	P values
No.	49	41		57	138		51	138	
Age (year)	15.16 ± 1.44 (13–18)	15.57 ± 1.54 (13–18)	0.19	25.93 ± 6.56 (18–53)	31.04 ± 8.89 (18–55)	<0.05	27.16 ± 5.39 (18–44)	31.04 ± 8.89 (18–55)	<0.05
Gender (M/F)	19/30	15/26	0.83	23/34	63/75	0.50	27/24	63/75	0.38

AOS, adolescent first-episode schizophrenia; AFES, adult first-episode schizophrenia; CHSZ, adult chronic schizophrenia; Ado-HC, adolescent healthy controls; Adu-HC, adult healthy controls; M, male; F, female.

were matched for sex. As shown in Table 2, the AOS subjects had higher negative scores and total scores than AFES and CHSZ patients ( $P < 0.05$ ).

### 3.2. ReHo abnormalities in patients at different stages of SZ

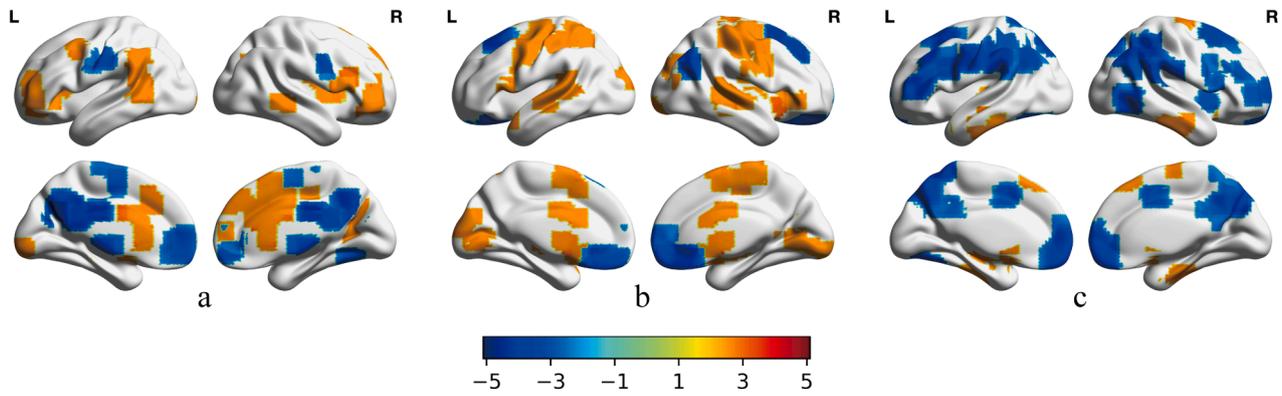
We determined the ReHo differences between patients with different stages of SZ and their corresponding HC ( $P_{\text{Alphasim}} < 0.05$  and cluster size  $> 39$ ). Decreased ReHo values were observed in the AOS group compared with the Ado-HC group in the medial frontal gyrus (MFG), left precentral gyrus, and precuneus. Increased ReHo values were found mainly in the bilateral middle frontal gyrus, putamen, left middle temporal gyrus (MTG), right SFG, and anterior cingulate (ACC). When comparing the AFES group with the Adu-HC group, decreased ReHo values were found in the MFG, right IPL, and left SFG. Increased ReHo values were found in the bilateral putamen, bilateral superior temporal gyrus (STG), left precentral gyrus, bilateral postcentral gyrus and right middle frontal gyrus. When comparing the CHSZ group with the Adu-HC group, decreased ReHo values were found in the MFG, IPL, SFG, right middle frontal gyrus, bilateral IFG, and precuneus. Increased ReHo values were found in the bilateral inferior temporal gyrus and putamen (Fig. 1 and Supplementary Table 1). The increased and decreased ReHo values suggest that the aberrant regional synchronization and neuron activity in patients at different stages of SZ. In this study, abnormal brain regions in different stages of SZ belong to DMN, such as MFG, MTG, precuneus, and IPL. Therefore, those results show that DMN network abnormalities occur in different stages of SZ.

Patients with the three different stages of SZ showed commonly decreased ReHo values in the MFG and increased ReHo values in the bilateral putamen when compared with matched HCs (Fig. 2 and Supplementary Table 1). In addition, we also applied a strict Bonferroni correction to correct the three group comparisons and had consistent findings (Supplementary Figs. 1–2 and Supplementary Table 2). These consistent regions (bilateral putamen and MFG) across different stages of SZ were extracted as ROIs for subsequently FC analyses.

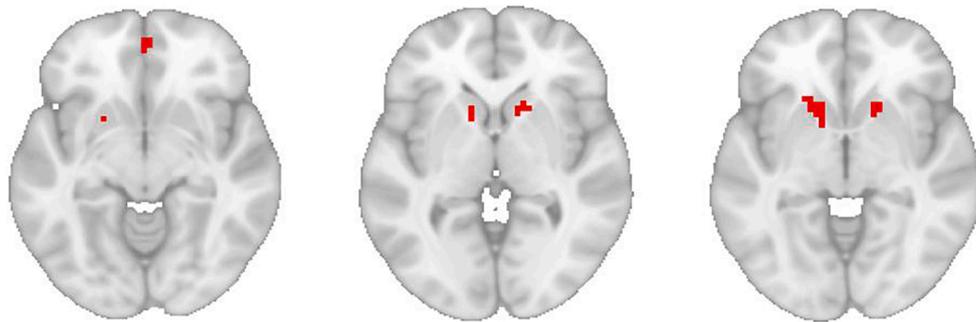
**Table 2**  
Clinical information in SZ patients.

	AOS	AFES	CHSZ	p values
	n = 49	n = 57	n = 51	
Onset (year)	14.64 ± 1.49	25.37 ± 6.49	20.88 ± 4.07	–
PANSS Total	87.15 ± 14.34 (61–116)	81.48 ± 7.74 (63–103)	82.68 ± 8.43 (66–106)	<0.05
Positive	23.36 ± 6.33 (7–32)	22.98 ± 3.48 (14–33)	23.44 ± 3.38 (17–34)	0.87
Negative	22.90 ± 5.53 (12–36)	18.54 ± 3.67 (10–34)	19.41 ± 5.23 (7–32)	<0.05
General	38.05 ± 6.31 (28–58)	39.59 ± 5.27 (24–53)	39.67 ± 4.25 (31–51)	0.86

AOS, adolescent first-episode schizophrenia; AFES, adult first-episode schizophrenia; CHSZ, adult chronic schizophrenia; PANSS, Positive and Negative Syndrome Scale.



**Fig. 1. Abnormal ReHo patterns at different stages of schizophrenia.** a, ReHo abnormalities in the AOS group compared with the Adu-HC group; b, ReHo abnormalities in the AFES group compared with the Adu-HC group; c, ReHo abnormalities in the CHSZ group compared with the Adu-HC group. Warm color indicates that ReHo was higher in patients than in healthy controls, and vice versa. AOS: adolescent first-episode schizophrenia; AFES: adult first-episode schizophrenia; CHSZ: adult chronic schizophrenia.

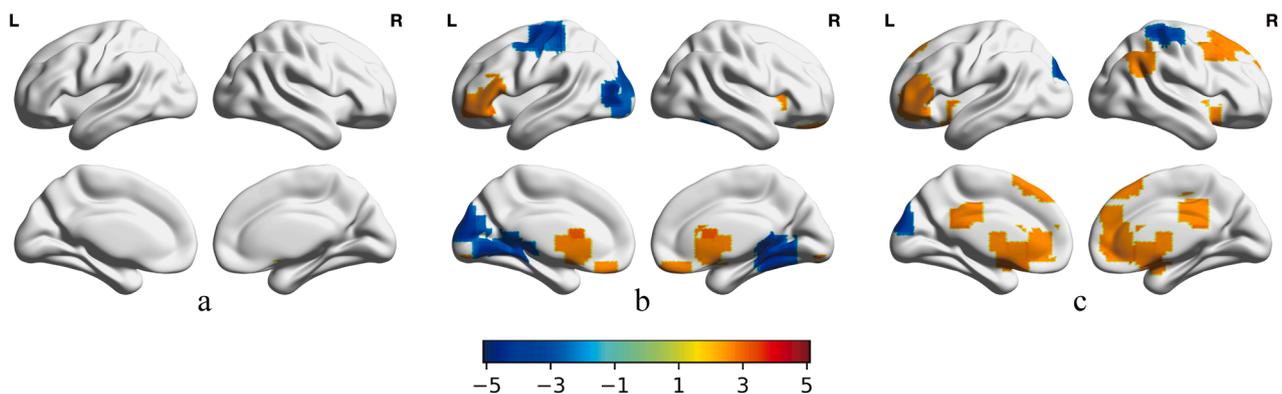


**Fig. 2. Shared regions at different stages of schizophrenia.** Red color of brain regions indicate that commonly decreased ReHo values in the MFG and increased ReHo values in the bilateral putamen at three different stages of SZ. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**3.3. Abnormal FC patterns in the putamen at different stages of SZ**

We conducted FC analyses based on the right putamen. The basic pattern of whole brain FC of the putamen is widespread positive connections, especially with the striatum, ACC, and the frontal lobe (Supplementary Fig. 3). We further determined the right putamen-seeded FC differences between patients with different stages of SZ and their corresponding HC ( $P_{\text{Alphasim}} < 0.05$  and cluster size  $> 39$ ). When compared with HCs, AOS patients showed significantly increased

connectomes only in the right putamen (Supplementary Table 3). Since the voxel is relatively small, it cannot be displayed when mapped to the cortex (Fig. 3a). AFES patients showed increased connectomes in the right putamen, left IFG, and left putamen (Fig. 3b and Supplementary Table 3). Additionally, CHSZ patients showed increased functional connectomes in the left IFG, ACC, right IPL, right middle frontal gyrus, and SFG, as well as decreased connectomes in the left cuneus and right postcentral gyrus compared with the HCs (Fig. 3c and Supplementary Table 3). A similar pattern was also found in the left putamen



**Fig. 3. Abnormal FC patterns of the putamen at different stages of schizophrenia.** a, FC abnormalities of the putamen in the AOS group compared with the Adu-HC group; b, FC abnormalities of the putamen in the AFES group compared with the Adu-HC group; c, FC abnormalities of the putamen in the CHSZ group compared with the Adu-HC group. Warm color indicates that functional connectomes were higher in patients than in healthy controls, and vice versa. AOS: adolescent first-episode schizophrenia; AFES: adult first-episode schizophrenia; CHSZ: adult chronic schizophrenia.

(Supplementary Fig. 4).

### 3.4. Abnormal FC patterns in the MFG at different stages of SZ

Next, we conducted FC analyses based on the MFG. The basic pattern of the FC from the MFG to the whole brain includes positive connections mainly with the MTG, IPL, and precuneus, as well as negative connections mainly with the IFG and IPL (Supplementary Fig. 5). We further determined the MFG-seeded FC differences between patients with different stages of SZ and their corresponding HC ( $P_{\text{Alphasim}} < 0.05$  and cluster size  $> 39$ ). In the AOS group, decreased FC values were observed in the precuneus, middle occipital gyrus, SFG, and right postcentral gyrus. Increased FC values were found in the middle frontal gyrus, left IFG, and right IPL (Fig. 4a and Supplementary Table 4). When comparing the AFES group with the Adu-HC group, decreased FC values were found in the lingual gyrus, left parahippocampal gyrus, left MTG, MFG, left STG, left IPL, left precuneus, precentral gyrus, bilateral middle frontal gyrus, and right postcentral gyrus. Increased FC values were found in the bilateral middle frontal gyrus and left IFG (Fig. 4b and Supplementary Table 4). In contrast, in the CHSZ group, decreased FC values connected with the MFG were found in the precentral gyrus and right postcentral gyrus besides the ROI. Increased FC values were found in the left ITG, bilateral middle frontal gyrus, right putamen, IPL, and left IFG besides the ROI (Fig. 4c and Supplementary Table 4).

While the abnormalities of the FC from the MFG differed at the three SZ stages, there were also some stable abnormalities identified across the different stages (Supplementary Table 4). Therefore, further analyses were conducted to explore the connections with the same abnormal pattern in a voxel-based manner. The main finding was that the connections between the ventromedial prefrontal cortex (vmPFC) and dorsolateral prefrontal cortex (dlPFC) showed consistently increased values at all three SZ stages. (Supplementary Figs. 5–6). In addition, we also applied a strict Bonferroni correction to correct the three group comparisons and had consistent results (Supplementary Figs. 7–8 and Supplementary Table 5).

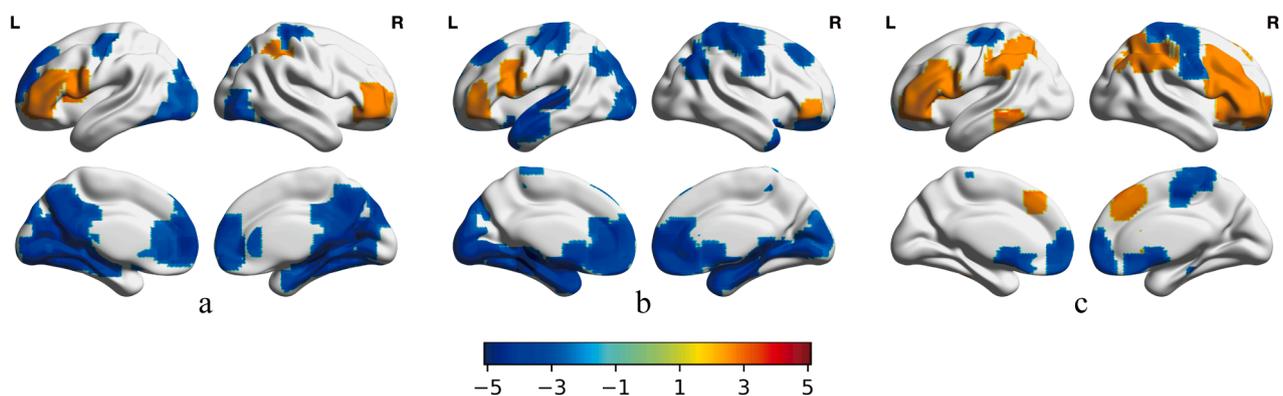
## 4. Discussion

This study explored abnormal brain activities via ReHo and FC in patients with AOS, AFES, and CHSZ. We found widespread ReHo abnormalities in the whole brain of SZ patients and the putamen, and MFG showed consistent ReHo abnormalities across the three different stages of SZ. Moreover, the FC between the vmPFC and dlPFC increased across the three SZ stages. Overall, our findings demonstrated the specificity and similarities of aberrant neural activities in the brain in adolescent and adulthood SZ.

Most brain regions which showed significant ReHo abnormalities in the three different SZ stages belong to the DMN (Whitfield-Gabrieli et al., 2009), including the MFG, MTG, precuneus, and IPL. DMN is associated with the construction of internal self-reference and has been widely explored abnormal in SZ (Frascarelli et al., 2015; Peng et al., 2021). Moreover, abnormal DMN homogeneity in AOS patients was confirmed in our previous studies (Peng et al., 2021; Zhang et al., 2020). A meta-analysis showed that the FES and chronic SZ also have common abnormal DMN homogeneity (Gong et al., 2020). Therefore, our finding is consistent with previous studies that found that the abnormalities of the DMN were present at different stages of SZ and even at an early stage of the illness (C. Liu et al., 2016; H. Liu et al., 2006; Watsky et al., 2018; Zhao et al., 2018; Gong et al., 2020). Especially, we provided more information of regional homogeneity of DMN in different stages of SZ than our previous studies only focused on AOS patients (Peng et al., 2021; Zhang et al., 2020).

We found ReHo abnormalities in the bilateral putamen and MFG in patients with AOS, AFES, and CHSZ, indicating abnormal brain regional activities of these regions in SZ. The putamen is a key part of the striatum, which has been found to play a central role in the pathophysiology of SZ (Simpson, Kellendonk, & Kandel, 2010). A recent study found that striatal dysfunction is a new neuroimaging biomarker in SZ, and the dorsolateral putamen of the striatum has also been shown to be dysfunctional (Li et al., 2020). We found increased ReHo values in the putamen in different stages of SZ, suggesting the enhanced neural activity coordination in the putamen. This finding is consistent with previous ReHo studies in adult SZ (Cui et al., 2016; S. Liu et al., 2019) and provides new evidence for the central role of the putamen in SZ. MFG is associated with cognitive processes such as decision-making, discrimination, motor planning, reasoning and computation (Talati & Hirsch, 2005), which are vulnerable to impairment in SZ (Del Missier et al., 2020). We found decreased ReHo values in MFG, suggesting the uncoordinated movement and disconnection within local neurons. The result is in agreement with previous reports of decreased ReHo values in MFG in AFES, and CHSZ (Zhao et al., 2018). However, some studies have found increased ReHo values in MFG in SZ (Cui et al., 2016; Yan et al., 2020). The discrepant results may partially be due to the illness stages and their matched HCs and we applied strict criteria to define subgroups of patients with regard to the stages of illness and their corresponding Adu-HC and Adu-HC. Overall, our findings indicated that the putamen and MFG may play key roles in the pathogenesis of different stages of SZ and may be the targets for antipsychotic medication.

Previous studies provide little evidence to abnormal FC in childhood and adulthood in patients with SZ (Gong et al., 2020; Zhang et al., 2020). In our study, we further add novel evidence. Firstly, for putamen-seeded FC, same abnormal FC connectivity were observed in AFES and



**Fig. 4. Abnormal FC patterns of the vmPFC at different stages of schizophrenia.** a, FC abnormalities of the vmPFC in the AOS group compared with the Adu-HC group; b, FC abnormalities of the vmPFC in the AFES group compared with the Adu-HC group; c, FC abnormalities of the vmPFC in the CHSZ group compared with the Adu-HC group. Warm color indicates that functional connectomes were higher in patients than in healthy controls, and vice versa. AOS: adolescent first-episode schizophrenia; AFES: adult first-episode schizophrenia; CHSZ: adult chronic schizophrenia.

CHSZ, including the increased FC with left IFG and decreased FC with left cuneus. However, such pattern in the AOS was not found. Secondly, for MFG-seeded FC, similar abnormal FC patterns were observed in AOS and AFES. Importantly, we found that vmPFC-dlPFC connectivity was significantly increased in the three SZ groups. The connection between vmPFC and dlPFC is associated with working memory performance (Potkin et al., 2009) and the disturbance of intrinsic brain activity may be associated with the consistent cognitive deficits in different stages of SZ. This finding may indicate a crucial role for the interaction between vmPFC and dlPFC in the psychopathology of SZ. Therefore, those findings indicate that abnormal brain function appears in adolescent SZ and adult SZ, with more brain abnormalities becoming apparent as the illness progresses.

## 5. Limitation

This study had several limitations. First, the sample size of the current study was relatively small. Independent replication with larger samples is desirable in future studies. Second, we did not explore the impact of antipsychotic drugs. Thus, there is a need for dynamic evaluation of longitudinal samples and for the impact of antipsychotic drugs to be explored.

## 6. Conclusion

In conclusion, ReHo abnormalities in the MFG and the putamen may be common abnormal brain function patterns across the different stages of SZ. The vmPFC-dlPFC FC abnormality common occurs in adolescence and adulthood. This study may provide a more comprehensive understanding of the neurodevelopmental abnormality across the AOS, AFES, and CHSZ. Focusing on the shared brain regions and FC with consistent abnormal patterns may help us to better understand the core pathology of SZ.

## Author contributions

Authors LL, and BL designed the study protocol. Authors YY, XJ, ZL, YZ, MD, and HS conducted sample selection. Authors QL, LZ, XS, MiS, MS, and WL managed the literature searches and data management. Authors YY, YS, and YuZ undertook the statistical analysis, and authors YY, YS, WY and BL wrote the first draft of the manuscript. All authors contributed to and have 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.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

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