Alterations in Spontaneous Brain Activity in Drug-Naïve First-Episode Schizophrenia: An Anatomical/Activation Likelihood Estimation Meta-Analysis

Xiaolei Qiu^{1*}, Rongrong Zhang^{2*}, Lu Wen¹, Fuli Jiang², Hongjun Mao¹, Wei Yan², Shiping Xie², and Xinming Pan¹

¹Department of Psychiatry, Jiangning District Second People's Hospital, Nanjing, China ²Department of Psychiatry, the Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China

Objective The etiology of schizophrenia is unknown and is associated with abnormal spontaneous brain activity. There are no consistent results regarding the change in spontaneous brain activity of people with schizophrenia. In this study, we determined the specific changes in the amplitude of low-frequency fluctuation/fractional amplitude of low-frequency fluctuation (ALFF/fALFF) and regional homogeneity (ReHo) in patients with drug-naïve first-episode schizophrenia (Dn-FES).

Methods A comprehensive search of databases such as PubMed, Web of Science, and Embase was conducted to find articles on resting-state functional magnetic resonance imaging using ALFF/fALFF and ReHo in schizophrenia patients compared to healthy controls (HCs) and then, anatomical/activation likelihood estimation was performed.

Results Eighteen eligible studies were included in this meta-analysis. Compared to the spontaneous brain activity of HCs, we found changes in spontaneous brain activity in Dn-FES based on these two methods, mainly including the frontal lobe, putamen, lateral globus pallidus, insula, cerebellum, and posterior cingulate cortex.

Conclusion We found that widespread abnormalities of spontaneous brain activity occur in the early stages of the onset of schizophrenia and may provide a reference for the early intervention of schizophrenia. **Psychiatry Investig 2022;19(8):606-613**

Keywords Schizophrenia; Resting-state; Regional homogeneity; Amplitude of low-frequency fluctuation; Fractional amplitude of low-frequency fluctuation; Meta-analysis.

INTRODUCTION

Schizophrenia is a severe mental disorder with multiple symptoms and dysfunctions.¹ Epidemiological surveys have shown that the global prevalence of schizophrenia is about 1% and causes huge economic losses and tremendous pressure on families and society.^{2,3} Resting-state functional magnetic

resonance imaging (rs-fMRI) studies have suggested that functional abnormalities may contribute to the development and progression of schizophrenia.

rs-fMRI is a magnetic resonance technique that reflects the functional activity of a specific brain region through changes in the magnetic resonance signal produced by altered blood oxygen levels, and it is commonly used to study local brain functional changes using the amplitude of low-frequency fluctuation (ALFF) or fractional amplitude of low-frequency fluctuation (fALFF) and regional homogeneity (ReHo).³⁻⁵ These two methods have satisfactory stability and can be easily duplicated and does not need a priori hypothesis. ALFF uses the power of low-frequency signals to determine strong and weak neuronal activity in different brain regions, and is often used to measure blood oxygen level dependent signals in the frequency range of 0.01–0.1 Hz,⁶ while fALFF is a standardized ALFF method that can effectively suppress the effects of noise and has higher sensitivity and specificity in de-

Received: March 10, 2022 **Revised:** May 19, 2022 **Accepted:** June 21, 2022

Correspondence: Shiping Xie, MD, PhD

Department of Psychiatry, the Affiliated Brain Hospital of Nanjing Medical University, No.264, Guangzhou Road, Gulou District, Nanjing 210029, China **Tel**: +86-13851588810, **Fax**: +86-025-82296224, **E-mail**: xieshiping6365@126.com

Correspondence: Xinming Pan, MD, PhD

Department of Psychiatry, Jiangning District Second People's Hospital, No.50, Chenling Road, Nanjing 211103, China

Tel: +86-13952097370, Fax: +86-025-52702705, E-mail: xinming.pan@163.com *These authors contributed equally to this work.

[©] This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/bync/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

tecting spontaneous neural activity signals.⁷ ReHo reflects the synchronization degree of neuronal activity in local brain area indirectly by calculating the consistency of time series between each voxel and adjacent voxels.⁸⁹ Therefore, the above methods have their own advantages in studying the functional changes of schizophrenia. They are commonly used to identify the local neural activity abnormalities in patients with schizophrenia and are considered to be a reliable imaging marker, but the results may be influenced by medication and duration of illness, thus leading to inconsistent results.^{8,10-13} For instance, current cross-sectional studies found increased ALFF/fALFF and ReHo in putamen in first-episode schizophrenia,^{14,15} while others failed to replicate the above results in chronic patients.^{16,17}

To the best of our knowledge, a simultaneous meta-analysis of the two measures of spontaneous brain activity based on resting-state fMRI has not been performed. Gong et al.¹⁸ conducted a meta-analysis to compare the differences in ALFF between first-episode schizophrenia and chronic schizophrenia. Xu et al.¹⁹ included six studies on ALFF/fALFF and used the ALE method to compare the differences brain activity between schizophrenia patients and the control group. Additionally, Qiu et al.³ conducted a meta-analysis comparing differences in ReHo among all schizophrenia patient groups, chronic schizophrenia groups, and healthy controls (HCs). However, studies have not fully elucidated the abnormalities in spontaneous brain activity in patients with drug-naïve firstepisode schizophrenia (Dn-FES) using ALFF/fALFF and ReHo, which might be due to the unavailability of data.

Anatomical/activation likelihood estimation (ALE) is a highly reliable coordinate-based meta-analysis method, which was developed by Turkeltaub et al.²⁰ A random-effects model is constructed to fit each activation point into a probability distribution to obtain the ALE map.²⁰ Previous studies mostly focused on a single resting-state function index, and no researcher used the ALE software to study the specific changes in the brain function in patients with schizophrenia.²¹ Therefore, it is crucial to use the ALE meta-analysis method to conduct a quantitative meta-analysis on neuroimaging studies at rest using ALFF/fALFF and ReHo to find specific markers in patients with Dn-FES.

To address the abovementioned issues, in this study, we used the accurate ALE algorithm to evaluate the two indices (ALFF/ fALFF and ReHo) and determine specific alterations in Dn-FES. We hypothesized that both ALFF/fALFF and ReHo would elucidate abnormal changes in brain function.

METHODS

Literature selection

The meta-analysis of the studies that performed resting-state function imaging was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement and recorded using the suggested checklist.

Search strategy

We obtained the studies published between the date of the first available date and January 2022 through a systematic and comprehensive search in the PubMed, Web of Science, and Embase databases. The retrieval strategy involved selecting studies with 1) "Schizophrenia" [Mesh] and (amplitude of low-frequency fluctuation [Title/Abstract] or ALFF [Title/Abstract] or fractional amplitude of low frequency fluctuation [Title/Abstract] or fALFF [Title/Abstract]) and ("resting state" or "functional magnetic resonance imaging" or "fMRI"); 2) "Schizophrenia" [Mesh] and (ReHo [Title/Abstract]) or Regional homogeneity [Title/Abstract]) and (resting-state [Title/ Abstract] or functional magnetic resonance imaging [Title/ Abstract]) or (fMRI [Title/Abstract]) (Supplementary Table 1 in the online-only Data Supplement).

Inclusion and exclusion criteria

In this meta-analysis, the inclusion criteria were listed as below: patients diagnosed with schizophrenia using the Diagnostic and Statistical Manual of Mental Disorders international standardized diagnostic criteria, who had first psychotic episode and not administered antipsychotic medication; studies that focused on rs-fMRI, with ALFF/fALFF or ReHo application; studies that were peer-reviewed original studies published in English language journals; studies that compared the two resting-state function indices between the Dn-FES group and the HC group.

In this meta-analysis, the exclusion criteria were listed as below: studies without the full text or those that did not improve the coordinates of the human brain and studies that were unavailable even after communicating with the author over the telephone or mail; studies involving subjects with psychiatric disorders besides schizophrenia (comorbidity); studies that were not based on ALFF/fALFF or ReHo.

Data extraction and quality assessment

Literature search, screening, and data extraction were conducted by two psychiatrists (X.L.Q. and R.R.Z.) who had received consistent training. Any differences in opinions and doubts were resolved by two senior psychiatrists (L.W. and H.J.M). Data were extracted for the name of the author, sample size, sex, age, course of the disease, positive and negative

| Table 1. Demographic a | and imaging | informati | on of elig | lible studies | | | | | | | | |
|---|---|--|--|---|---|---|--|---|---|--|---|---|
| Anthor | Sample | Sex (| M/F) | Diagnostic | Age | (yr) | Correction for | Llness | PANSS | FWHM | Coordinate | Quanlity |
| 101111117 | size | SZ | HC | criteria | ZS | HC | multiple comparisons | duration (mon) | total score | TATTIAN T | | score |
| ALFF | | | | | | | | | | | | |
| Lui et al., ²⁶ 2010 | 34/34 | 13/21 | 13/21 | DSM-IV | 24.6±8.5 | 25.0 ± 8.0 | FWE<0.05 | 7.8±12.4 | 104.2 ± 13.9 | 8 | Talairach | 10 |
| Cui et al. ¹⁴ 2016 | 32/19 | NA | NA | DSM-IV-TR | NA | NA | AlphaSim<0.01 | NA | NA | 4 | INM | 8 |
| Lei et al., ²⁷ 2015 | 124/102 | 61/63 | 50/52 | NI-MSD | 24.31±6.57, 24.62±6.82 | 24.80±6.74, 24.71±6.98 | AlphaSim<0.05 | $8.19\pm 8.97,$ 5.50 ± 8.03 | 87.59±17.07, 89.27±17.04 | 9 | INM | 10 |
| Huang et al. 28 2010 | 66/66 | 30/36 | 30/36 | DSM-IV | 24.2 ± 8.4 | 24.5±8.6 | Cluster level<0.05 | 8.8 ± 14.1 | 107.2 ± 15.1 | 8 | Talairach | 10 |
| Zheng et al., ²⁹ 2016 | 35/30 | 20/15 | 13/17 | DSM-IV-TR | 15.50 ± 1.76 | 15.43 ± 1.54 | AlphaSim<0.05 | 6.6±6.7 | 74.62±10.61 | 9 | INM | 10 |
| Li et al. ³⁰ 2017 | 83/42 | 48/35 | 24/18 | DSM-IV | 23.32±2.94, 22.86± 6.70 | 23.29±7.33 | voxel level p<0.005 | $20.15\pm 14.00,$ 19.83 ± 13.00 | 99.38±14.86, 86.22±15.72 | 9 | INM | 10 |
| Li et al., ³¹ 2016 | 20/16 | 6/14 | 6/2 | DSM-IV | 22.9±8.5 | 22.4±4.4 | AlphaSim<0.05 | 6.4±13.6 | 101.6 ± 12.3 | 8 | INM | 9.5 |
| Ren et al., ³² 2013 | 100/100 | 41/59 | 41/59 | DSM-IV | 24.3±7.5 | 24.4±7.6 | AlphaSim<0.05 | 6.25±11.00 | 97.9±17.8 | 8 | INM | 10 |
| fALFF | | | | | | | | | | | | |
| He et al., ³³ 2013 | 104/104 | 49/55 | 50/54 | DSM- IV | 25.36±8.26 | 26.61 ± 8.90 | FDR<0.05 | 39.54±31.88 | 92.14±17.48 | 9 | INM | 10 |
| Wu et al., ³⁴ 2019 | 32/32 | 16/16 | 21/11 | DSM-IV | 30.94 ± 8.25 | 31.37±7.84 | GRF<0.05 | 8.91 ± 6.39 | 77.38±5.17 | NA | INM | 9.5 |
| Guo et al., ³⁵ 2017 | 28/40 | 18/10 | 20/20 | DSM-IV | 22.93±3.92 | 23.28 ± 2.60 | GRF<0.005 | 24.14 ± 7.17 | 88.11±10.29 | 8 | INM | 10 |
| Hu et al. 36 2016 | 42/38 | 27/15 | 25/13 | DSM-IV-TR | 24.86±4.80 | 24.76±4.56 | AlphaSim<0.05 | 8.38±2.61 | 91.90±11.23 | 8 | INM | 10 |
| Guo et al. 37 2015 | 49/50 | 30/19 | 23/27 | DSM-IV | 22.69±4.62 | 23.48±2.49 | GRF<0.005 | 22.45 ± 6.71 | 91.31±10.98 | 8 | INM | 10 |
| ReHo | | | | | | | | | | | | |
| Cui et al., ¹⁴ 2016 | 32/19 | NA | NA | DSM-IV-TR | NA | NA | AlphaSim<0.05 | NA | NA | 4 | INM | 8 |
| Hu et al. 36 2016 | 42/38 | 27/15 | 25/13 | DSM-IV | 24.86 ± 4.80 | 24.76±4.56 | AlphaSim<0.05 | 8.38±2.61 | 91.90±11.23 | NA | INM | 9.5 |
| Wang et al., 10 2018 | 48/31 | 21/27 | 14/17 | DSM-IV-TR | 15.79 ± 1.64 | 15.42 ± 1.52 | GRF<0.005 | 5.35 ± 6.12 | 75.10±9.88 | 4 | INM | 10 |
| Yan et al., 8 2020 | 69/74 | 50/19 | 45/29 | DSM-IV | 24.22±7.08 | 26.27±6.97 | TFCE<0.05 | 13.74±11.76 | 84.19±8.25 | 4 | INM | 10 |
| Zhao et al., ¹⁵ 2019 | 44/26 | 31/13 | 17/9 | DSM-IV | 23.7±5.3 | 22.6±3.7 | TFCE<0.01 | 12.0±9.2 | 102.0 ± 16.7 | 4 | INM | 10 |
| Jin et al., ²⁵ 2021 | 23/24 | NA | NA | DSM-IV | 31.74 ± 6.71 | 30.92 ± 6.26 | FDR<0.05 | NA | NA | 9 | INM | 8.5 |
| Lyu et al., ²⁴ 2021 | 32/27 | 15/17 | 10/17 | DSM-IV | 16.75 ± 1.22 | 16.40 ± 2.12 | AlphaSim<0.05 | 9.19±12.73 | 79.44±15.95 | 9 | INM | 10 |
| Values are presented as ReHo, regional homoge DSM-IV-TR, Diagnostić wise error rate; FDR, fals | mean±star neity; SZ, s and Statist e discovery | ndard devi chizophre 'ical Manu ' rate; GRI | ation un nia; HC, ıal of Meı 3, Gaussia | less otherwise healty control ntal Disorders, un random fiel | : indicated. AI l; NA, not avai , Fourth Editic d; TFCE, three | JFF/fALFF, thu lable; M, male on, Text Rivisio shold free clus | e amplitude of low-freq ;; F, female; DSM-IV, Di m; FWHM, full width at ter enhancement | uency fluctuation/ lagnostic and Statis t half maximum; M | fractional ampli stical Manual of INI, Montreal N | ttude of lov Mental Di Jeurologica | <i>v</i> -frequency f isorders, Four il Institute; FW | uctuation; h Edition; ⁷ E, family- |

syndrome scale (PANSS) total score, full width at half maximum, and coordinate. The ten-point checklist was used to assess the quality of each study.³

Data analysis procedures

The ALE software (http://www.brainmap.org)22 was used



Figure 1. Flow-diagram of studies selection. rs-fMRI, resting-state functional magnetic resonance imaging; ROI, region of interest.

to perform a meta-analysis of the differences in ALFF/fALFF and ReHo between Dn-FES and HCs. According to the findings of the two different approaches (ALFF/fALFF, ReHo), we divide them into four groups: increased ALFF/fALFF, ReHo), we divide them into four groups: increased ALFF/fALFF group (number of foci=37, n=715), decreased ALFF/fALFF group (number of foci=29, n=630), decreased ReHo group (number of foci=11, n=166), and increased ReHo group (number of foci=17, n=272). First, we put the extracted peak coordinate information in independent text, imported it into the ALE software, and transformed Talairach coordinates into Montreal Neurological Institute coordinates. Then, we performed the false discovery rate multiple comparison correction, with the p-value set to 0.05,²³ and the ALE brain map was visualized using the BrainNet software (http://www.nitrc.org/projects/bnv/) running in the Dpabi environment.

RESULTS

Search results and sample features

A total of 549 studies were searched in three databases (PubMed, n=98; Embase, n=164; Web of Science, n=287). After deleting duplicate studies and screening titles and abstracts, we found 39 potentially eligible studies for inclusion. Then, after a detailed review of the full texts, 18 datasets of

| Table 2. | Specific b | orain alterations | compared of | drug naïve | first-episode | schizophrenia with HCs |
|----------|------------|-------------------|-------------|------------|---------------|------------------------|
| | | | | | | |

| Cluster | Volume (mm ³) | MNI (X, Y, Z) | Anatomical region | Maximum ALE value | Side | Brodmann |
|---|---------------------------|---------------|-------------------------|-------------------|------|----------|
| ALFF/fALFF | | | | | | |
| FES>HC | | | | | | |
| 1 | 50,080 | 24, 2, 10 | Putamen | 0.0033048263 | R | - |
| 1 | 50,080 | 36, 40, -18 | MFG | 0.0010549506 | R | 47 |
| 2 | 30,816 | -26, -4, 10 | Putamen | 0.0032242807 | L | - |
| 3 | 10,184 | -10, -44, 26 | PCC | 0.0017087442 | L | 31 |
| 3 | 10,184 | 12, -48, 18 | PCC | 0.0009695893 | R | 29 |
| 4 | 5,168 | 12, -36, -40 | Cerebellar | 0.0009920112 | R | - |
| 5 | 4,152 | -6, 48, 42 | SFG | 0.0009560061 | L | 8 |
| 5 | 4,152 | -10, 54, 26 | SFG | 0.0009415437 | L | 9 |
| ReHo | | | | | | |
| FES>HC | | | | | | |
| 1 | 70,016 | -18, 10, 0 | Putamen | 0.002040051 | L | - |
| 1 | 70,016 | 14, 10, -8 | Lateral globus pallidus | 0.001826505 | R | - |
| 1 | 70,016 | -42, 10, 42 | MFG | 0.000959284 | L | 6 |
| 1 | 70,016 | -42, -14, 18 | Insula | 0.000952498 | L | 13 |
| FES <hc< td=""><td></td><td></td><td></td><td></td><td></td><td></td></hc<> | | | | | | |
| 1 | 21,816 | -12, -24, 72 | PreCG | 0.0009670623 | L | 4 |
| 1 | 21,816 | 6, -38, 66 | Paracentral lobule | 0.0009625384 | R | 5 |
| 2 | 19,488 | 51, -3, 33 | PreCG | 0.0016285478 | R | 6 |

ALE, anatomical/activation likelihood estimation; MNI, Montreal Neurologic Institute; FES, first episode schizophrenia; HC, healthy control; ALFF/fALFF, the amplitude of low-frequency fluctuation/fractional amplitude of low-frequency fluctuation; ReHo, regional homogeneity; MFG, middle frontal gyrus; PCC, posterior cingulate cortex; SFG, superior frontal gyrus; PreCG, precentral gyrus; L, left; R, right; -, not available

rs-fMRI studies, 1,039 Dn-FES patients, and 1,425 HCs were included in our meta-analysis.^{8,10,14,15,24-37} The sample characteristics and imaging information of the included studies are shown in Table 1 and Figure 1.

The amplitude of low frequency fluctuation/ fractional amplitude of low-frequency fluctuation specific brain alterations in drug-naïve first-episode schizophrenia

We found higher ALFF/fALFF in the bilateral putamen and the posterior cingulate cortex (PCC), right cerebellum, right middle frontal gyrus (MFG), and left superior frontal gyrus (SFG) of Dn-FES patients compared to that of the HCs (Table 2, Figure 2). Significant abnormal reduction in the brain areas was not found in Dn-FES.



Figure 2. Increased the amplitude of low-frequency fluctuation/ fractional amplitude of low-frequency fluctuation in drug naïve first-episode schizophrenia compared with healthy controls. MFG, middle frontal gyrus; PCC, posterior cingulate cortex; SFG, superior frontal gyrus; L, left; R, right.

Regional homogeneity specific brain alterations in drug-naïve first-episode schizophrenia

We found higher ReHo in the left putamen, MFG, insula, and right lateral globus pallidus (Table 2, Figure 3), and lower ReHo in the right paracentral lobule and bilateral precentral gyrus (PreCG) in Dn-FES patients compared to those of the HCs (Table 2, Figure 3).

DISCUSSION

This was the first systematic meta-analysis investigating rsfMRI-specific alterations in ALFF/fALFF and ReHo in patients with Dn-FES. We found that both ALFF/fALFF and ReHo values were altered in Dn-FES. In Dn-FES, higher ALFF/ fALFF values were mainly in the putamen, MFG, PCC, SFG, and cerebellum; however, no brain region with lower ALFF/ fALFF was identified. Moreover, our study showed higher ReHo in the putamen, MFG, insula, and lateral globus pallidus, and lower ReHo in the right paracentral lobule and Pre-CG in Dn-FES. These results provided new insights into the neurophysiological mechanism of Dn-FES.

We found higher ALFF/fALFF in the bilateral putamen and higher ReHo in the left putamen and right lateral globus pallidus. The putamen and lateral globus pallidus are important components of the striatum. Several studies have demonstrated abnormalities in the striatum in schizophrenia.^{36,38,39} If destroyed, it may lead to dopamine release disorder in the striatum, resulting in mental symptoms. Sui et al.³⁹ found higher fALFF in the striatum and thalamus of patients with schizophrenia. Furthermore, higher spontaneous neural activity in the striatum was significantly associated with positive symptoms. The dysfunction of the striatum may be the basis of schizophrenia. Moreover, a longitudinal study showed high-



Figure 3. Brain regions with specific alterations in ReHo in Dn-FES compared to HCs. A: Increased ReHo in Dn-FES compared with HCs. B: Decreased ReHo in Dn-FES compared with HCs. ReHo, regional homogeneity; MFG, middle frontal gyrus; PreCG, precentral gyrus; L, left; R, right; Dn-FES, drug-naïve first-episode schizophrenia; HC, healty control.

er fALFF and ReHo in the putamen before treatment; after eight weeks of treatment, fALFF and ReHo in the putamen increased further.³⁶ These results suggested that the striatum might be a relatively stable imaging biomarker for schizophrenia, independent of the duration of illness and medication.

The default mode network (DMN) is a set of key brain regions, including the PCC, medial prefrontal cortex, angular gyrus, and other important nodes.40 It plays a significant role in stimulating independent thoughts and monitoring the external environment.5 Abnormal alterations in the spontaneous brain activity of the DMN occur in schizophrenia.⁴¹ By performing resting-state fMRI, a study found that the DMN connectivity increased in patients with schizophrenia; thus, these findings are in accordance with findings reported by our meta-analysis.42 A recent systematic literature review of rs-fMRI showed a decrease in the DMN activity in the schizophrenia group compared to that of the HC group.3 Another study found mixed results regarding the changes in the DMN of schizophrenia patients.⁴³ The differences in the results of the above studies may be due to the influence of confounding factors such as duration of the disease course, administration of antipsychotics, or sample size. Therefore, including data of more patients and using specific neuroimaging markers associated with the DMN are essential for understanding the pathophysiological mechanisms of schizophrenia.

In our meta-analysis, we also found an increase in ALFF/ fALFF in the left SFG and right MFG, an increase in ReHo in the left MFG, and a decrease in ReHo in the bilateral PreCG and the right paracentral lobule. These regions are components of the frontal lobe. Some researchers found that the frontal lobe, which is the most commonly affected region in schizophrenia, is the hub of high-level intellectual activities involving cognition, clinical syndrome and thought disorder.^{3,44} By performing functional MRI, a study showed that the spontaneous neural activity of the frontal cortex was increased in people with chronic schizophrenia.45 In the aspect of Dn-FES, another study showed increased regional functional abnormalities in the frontal lobe.8 Thus, abnormal spontaneous activity in the frontal lobe may be a reliable biomarker for schizophrenia, and the simultaneous increase and decrease in the spontaneous activity in the frontal lobe may be a compensatory mechanism in the early stages of psychiatric illness. Based on the nature of the study, the results need to be interpreted carefully.

We also found an increase in ReHo in the left insula of patients with Dn-FES. The insula is one of the major nodes of the Salience Network, which helps in adjusting the DMN and the central execution network.⁴⁶ These internal networks influence each other and play a common role in various activities.¹³ Abnormal functions in one of the resting networks in patients with schizophrenia may result in misprojection of internal and external information, presenting symptoms such as auditory hallucinations and cognitive disorder.^{43,44} By performing rs-fMRI, a study showed that functional activity of insula in schizophrenia group was abnormal compared with HCs group, consistent with our findings.⁴⁷ These results suggested that abnormalities in the insula might be the basis of schizophrenia. Other abnormal brain regions, such as the cerebellum, also play a major role in patients with schizophrenia.⁴⁸ Typical features of cerebellar impairment include deficits in working memory, emotion regulation, verbal and visuospatial learning.

Limitations

Although we found promising results, some limitations of this study need to be mentioned. First, although we tried to maintain homogeneity of the sample, it was not always possible to do so because the software could not account for the influence of the PANSS score, head motion and the duration of the disease on the results. Another limitation, publication bias must be mentioned, negative results cannot be published, and the quality of research can lead to it.49 Because ALE software is only suitable for the research that reported the peak coordinates, we cannot include the studies that did not report any cluster, but we conduct a perfect retrieval strategy to find out all the published literature, strictly evaluate the quality of all the included original research, and exclude low-quality research, so as to minimize the publication bias. Nevertheless, we need to interpret the results carefully. Moreover, this meta-analysis was based on whole-brain analysis, and no specific analysis of various networks in the brain was performed.

Conclusion

This was the first meta-analysis to systematically evaluate abnormal changes in the spontaneous neural activity of patients with Dn-FES by measuring different indices. We found varying degrees of increase and decrease in the spontaneous neural activity in Dn-FES patients, including activities in the frontal lobe, putamen, lateral globus pallidus, insula, cerebellum, and PCC. This study provided new insights into the pathophysiological mechanisms of Dn-FES from different perspectives.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.30773/pi.2022.0074.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Shiping Xie, Xinming Pan. Data curation: Xiaolei Qiu, Rongrong Zhang. Formal analysis: Xiaolei Qiu. Funding acquisition: Shiping Xie, Xiaolei Qiu. Investigation: all authors. Methodology: Xiaolei Qiu, Rongrong Zhang, Lu Wen. Project administration: Shiping Xie, Xinming Pan. Resources: Rongrong Zhang, Wei Yan. Software: Xiaolei Qiu, Lu Wen. Supervision: Shiping Xie. Validation: Shiping Xie, Xiaolei Qiu, Lu Wen. Visualization: Xiaolei Qiu, Hongjun Mao, Fuli Jiang. Writing—original draft: Xiaolei Qiu. Writing—review & editing: Xiaolei Qiu, Rongrong Zhang, Hongjun Mao, Wei Yan, Shiping Xie, Xinming Pan.

ORCID iDs

| Xiaolei Qiu | https://orcid.org/0000-0002-3881-2616 |
|--|---|
| Rongrong Zhang | https://orcid.org/0000-0002-3117-4869 |
| Lu Wen | https://orcid.org/0000-0002-4111-2821 |
| Fuli Jiang | https://orcid.org/0000-0001-6999-4523 |
| Hongjun Mao | https://orcid.org/0000-0002-1949-9388 |
| Wei Yan | https://orcid.org/0000-0002-7596-4192 |
| Shiping Xie | https://orcid.org/0000-0002-9947-2440 |
| Xinming Pan | https://orcid.org/0000-0002-9286-2075 |
| Fuli Jiang Hongjun Mao Wei Yan Shiping Xie Xinming Pan | https://orcid.org/0000-0001-6999-4523 https://orcid.org/0000-0002-1949-9388 https://orcid.org/0000-0002-7596-4192 https://orcid.org/0000-0002-9947-2440 https://orcid.org/0000-0002-9286-2075 |

Funding Statement

This study was supported by the Project of science and technology benefits the people program of Jiangning (20212021NJNQKJHMJHXM0077) and the Key Project of Nanjing Municipal Bureau of Health 303 Commission (ZKX15033).

Acknowledgments

The authors express their deepest thanks to Mr. Jie Bai for helping to polish the manuscript.

REFERENCES

- 1. Schultz SK, Andreasen NC. Schizophrenia. Lancet 1999;353:1425-1430.
- Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. Schizophr Bull 2018;44: 1195-1203.
- Qiu X, Xu W, Zhang R, Yan W, Ma W, Xie S, et al. Regional homogeneity brain alterations in schizophrenia: an activation likelihood estimation meta-analysis. Psychiatry Investig 2021;18:709-717.
- Liu C, Xue Z, Palaniyappan L, Zhou L, Liu H, Qi C, et al. Abnormally increased and incoherent resting-state activity is shared between patients with schizophrenia and their unaffected siblings. Schizophr Res 2016;171:158-165.
- Yang ZY, Zhang RT, Li Y, Wang Y, Wang YM, Wang SK, et al. Functional connectivity of the default mode network is associated with prospection in schizophrenia patients and individuals with social anhedonia. Prog Neuropsychopharmacol Biol Psychiatry 2019;92:412-420.
- Zang YF, He Y, Zhu CZ, Cao QJ, Sui MQ, Liang M, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev 2007;29:83-91.
- Song Y, Xu W, Chen S, Hu G, Ge H, Xue C, et al. Functional MRI-specific alterations in salience network in mild cognitive impairment: an ALE meta-analysis. Front Aging Neurosci 2021;13:695210.
- Yan W, Zhang R, Zhou M, Lu S, Li W, Xie S, et al. Relationships between abnormal neural activities and cognitive impairments in patients with drug-naïve first-episode schizophrenia. BMC Psychiatry 2020;20:283.
- 9. Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to

fMRI data analysis. Neuroimage 2004;22:394-400.

- Wang S, Zhang Y, Lv L, Wu R, Fan X, Zhao J, et al. Abnormal regional homogeneity as a potential imaging biomarker for adolescent-onset schizophrenia: a resting-state fMRI study and support vector machine analysis. Schizophr Res 2018;192:179-184.
- Fan J, Gan J, Liu W, Zhong M, Liao H, Zhang H, et al. Resting-state default mode network related functional connectivity is associated with sustained attention deficits in schizophrenia and obsessive-compulsive disorder. Front Behav Neurosci 2018;12:319.
- Mothersill O, Tangney N, Morris DW, McCarthy H, Frodl T, Gill M, et al. Further evidence of alerted default network connectivity and association with theory of mind ability in schizophrenia. Schizophr Res 2017;184:52-58.
- Zhou C, Tang X, You W, Wang X, Zhang X, Zhang X, et al. Altered patterns of the fractional amplitude of low-frequency fluctuation and functional connectivity between deficit and non-deficit schizophrenia. Front Psychiatry 2019;10:680.
- Cui LB, Liu K, Li C, Wang LX, Guo F, Tian P, et al. Putamen-related regional and network functional deficits in first-episode schizophrenia with auditory verbal hallucinations. Schizophr Res 2016;173:13-22.
- Zhao X, Yao J, Lv Y, Zhang X, Han C, Chen L, et al. Abnormalities of regional homogeneity and its correlation with clinical symptoms in Naïve patients with first-episode schizophrenia. Brain Imaging Behav 2019;13:503-513.
- Gao B, Wang Y, Liu W, Chen Z, Zhou H, Yang J, et al. Spontaneous activity associated with delusions of schizophrenia in the left medial superior frontal gyrus: a resting-state fMRI study. PLoS One 2015;10: e0133766.
- Hoptman MJ, Zuo XN, Butler PD, Javitt DC, D'Angelo D, Mauro CJ, et al. Amplitude of low-frequency oscillations in schizophrenia: a resting state fMRI study. Schizophr Res 2010;117:13-20.
- Gong J, Wang J, Luo X, Chen G, Huang H, Huang R, et al. Abnormalities of intrinsic regional brain activity in first-episode and chronic schizophrenia: a meta-analysis of resting-state functional MRI. J Psychiatry Neurosci 2020;45:55-68.
- Xu Y, Zhuo C, Qin W, Zhu J, Yu C. Altered spontaneous brain activity in schizophrenia: a meta-analysis and a large-sample study. Biomed Res Int 2015;2015:204628.
- Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox P. Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. Hum Brain Mapp 2012;33:1-13.
- 21. Xiao B, Wang S, Liu J, Meng T, He Y, Luo X. Abnormalities of localized connectivity in schizophrenia patients and their unaffected relatives: a meta-analysis of resting-state functional magnetic resonance imaging studies. Neuropsychiatr Dis Treat 2017;13:467-475.
- Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage 2002;16(3 Pt 1):765-780.
- 23. Zhang X, Xue C, Cao X, Yuan Q, Qi W, Xu W, et al. Altered patterns of amplitude of low-frequency fluctuations and fractional amplitude of low-frequency fluctuations between amnestic and vascular mild cognitive impairment: an ALE-based comparative meta-analysis. Front Aging Neurosci 2021;13:711023.
- 24. Lyu H, Jiao J, Feng G, Wang X, Sun B, Zhao Z, et al. Abnormal causal connectivity of left superior temporal gyrus in drug-naïve first- episode adolescent-onset schizophrenia: a resting-state fMRI study. Psychiatry Res Neuroimaging 2021;315:111330.
- 25. Jin K, Xu D, Shen Z, Feng G, Zhao Z, Lu J, et al. Distinguishing hypochondriasis and schizophrenia using regional homogeneity: a restingstate fMRI study and support vector machine analysis. Acta Neuropsychiatr 2021;33:182-190.
- 26. Lui S, Li T, Deng W, Jiang L, Wu Q, Tang H, et al. Short-term effects of antipsychotic treatment on cerebral function in drug-naive first-episode schizophrenia revealed by "resting state" functional magnetic resonance imaging. Arch Gen Psychiatry 2010;67:783-792.

- 27. Lei W, Li M, Deng W, Zhou Y, Ma X, Wang Q, et al. Sex-specific patterns of aberrant brain function in first-episode treatment-naive patients with schizophrenia. Int J Mol Sci 2015;16:16125-16143.
- Huang XQ, Lui S, Deng W, Chan RC, Wu QZ, Jiang LJ, et al. Localization of cerebral functional deficits in treatment-naive, first-episode schizophrenia using resting-state fMRI. Neuroimage 2010;49:2901-2906.
- Zheng J, Zhang Y, Guo X, Duan X, Zhang J, Zhao J, et al. Disrupted amplitude of low-frequency fluctuations in antipsychotic-naïve adolescents with early-onset schizophrenia. Psychiatry Res Neuroimaging 2016;249:20-26.
- 30. Li Z, Lei W, Deng W, Zheng Z, Li M, Ma X, et al. Aberrant spontaneous neural activity and correlation with evoked-brain potentials in first-episode, treatment-naïve patients with deficit and non-deficit schizophrenia. Psychiatry Res Neuroimaging 2017;261:9-19.
- 31. Li F, Lui S, Yao L, Hu J, Lv P, Huang X, et al. Longitudinal changes in resting-state cerebral activity in patients with first-episode schizophrenia: a 1-year follow-up functional MR imaging study. Radiology 2016; 279:867-875.
- Ren W, Lui S, Deng W, Li F, Li M, Huang X, et al. Anatomical and functional brain abnormalities in drug-naive first-episode schizophrenia. Am J Psychiatry 2013;170:1308-1316.
- 33. He Z, Deng W, Li M, Chen Z, Jiang L, Wang Q, et al. Aberrant intrinsic brain activity and cognitive deficit in first-episode treatment-naive patients with schizophrenia. Psychol Med 2013;43:769-780.
- 34. Wu R, Ou Y, Liu F, Chen J, Li H, Zhao J, et al. Reduced brain activity in the right putamen as an early predictor for treatment response in drugnaive, first-episode schizophrenia. Front Psychiatry 2019;10:741.
- 35. Guo W, Liu F, Chen J, Wu R, Li L, Zhang Z, et al. Hyperactivity of the default-mode network in first-episode, drug-naive schizophrenia at rest revealed by family-based case-control and traditional case-control designs. Medicine (Baltimore) 2017;96:e6223.
- 36. Hu ML, Zong XF, Zheng JJ, Pantazatos SP, Miller JM, Li ZC, et al. Short-term effects of risperidone monotherapy on spontaneous brain activity in first-episode treatment-naïve schizophrenia patients: a longitudinal fMRI study. Sci Rep 2016;6:34287.
- Guo W, Liu F, Xiao C, Zhang Z, Yu M, Liu J, et al. Dissociation of anatomical and functional alterations of the default-mode network in firstepisode, drug-naive schizophrenia. Clin Neurophysiol 2015;126:2276-2281.

- Karcher NR, Rogers BP, Woodward ND. Functional connectivity of the striatum in schizophrenia and psychotic bipolar disorder. Biol Psychiatry Cogn Neurosci Neuroimaging 2019;4:956-965.
- Sui J, Pearlson GD, Du Y, Yu Q, Jones TR, Chen J, et al. In search of multimodal neuroimaging biomarkers of cognitive deficits in schizophrenia. Biol Psychiatry 2015;78:794-804.
- Raichle ME. The brain's default mode network. Annu Rev Neurosci 2015;38:433-447.
- 41. Du Y, Pearlson GD, Yu Q, He H, Lin D, Sui J, et al. Interaction among subsystems within default mode network diminished in schizophrenia patients: a dynamic connectivity approach. Schizophr Res 2016;170: 55-65.
- 42. Jiang Y, Duan M, Chen X, Chang X, He H, Li Y, et al. Common and distinct dysfunctional patterns contribute to triple network model in schizophrenia and depression: a preliminary study. Prog Neuropsychopharmacol Biol Psychiatry 2017;79(Pt B):302-310.
- 43. Wang S, Zhan Y, Zhang Y, Lyu L, Lyu H, Wang G, et al. Abnormal longand short-range functional connectivity in adolescent-onset schizophrenia patients: a resting-state fMRI study. Prog Neuropsychopharmacol Biol Psychiatry 2018;81:445-451.
- Mubarik A, Tohid H. Frontal lobe alterations in schizophrenia: a review. Trends Psychiatry Psychother 2016;38:198-206.
- 45. Yu L, Guo L, Fang X, Yang F, Chen Y, Wang Y, et al. Altered brain activity in the bilateral frontal cortices and neural correlation with cognitive impairment in schizophrenia. Brain Imaging Behav 2022;16:415-423.
- 46. Qiu X, Lu S, Zhou M, Yan W, Du J, Zhang A, et al. The relationship between abnormal resting-state functional connectivity of the left superior frontal gyrus and cognitive impairments in youth-onset drug-naïve schizophrenia. Front Psychiatry 2021;12:679642.
- 47. Yu R, Hsieh MH, Wang HL, Liu CM, Liu CC, Hwang TJ, et al. Frequency dependent alterations in regional homogeneity of baseline brain activity in schizophrenia. PLoS One 2013;8:e57516.
- Brady RO Jr, Gonsalvez I, Lee I, Öngür D, Seidman LJ, Schmahmann JD, et al. Cerebellar-prefrontal network connectivity and negative symptoms in schizophrenia. Am J Psychiatry 2019;176:512-520.
- Müller VI, Cieslik EC, Laird AR, Fox PT, Radua J, Mataix-Cols D, et al. Ten simple rules for neuroimaging meta-analysis. Neurosci Biobehav Rev 2018;84:151-161.

| Database | Search term |
|----------------|--|
| PubMed | 1) "Schizophrenia" [Mesh] AND (amplitude of low-frequency fluctuation [Title/Abstract] OR ALFF [Title/Abstract] OR fractional Amplitude of low frequency fluctuation [Title/Abstract] OR fALFF [Title/Abstract]) AND ("resting state" OR "functional magnetic resonance imaging" OR "fMRI"); 2) "Schizophrenia" [Mesh] AND (ReHo [Title/Abstract]) OR Regional homogeneity [Title/Abstract]) AND (resting state [Title/Abstract] OR functional magnetic resonance imaging [Title/Abstract]) OR functional magnetic resonance imaging [Title/Abstract]] OR functional functional magnetic resonance imaging [Title/Abstract]] OR functional functional functional functional functional functional functional func |
| Web of Science | Same as PubMed |
| Embase | Same as PubMed |

Supplementary Table 1. Search terms for the literature search