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Original Article

Precentral gyrus abnormal connectivity in male and female patients with schizophrenia

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Abstract

Aim: Dysfunction of the precentral gyrus plays a role in the impairments of voluntary movement associated with schizophrenia and it has significantly reduced functional activity in patients with schizophrenia. The aim of this study was to demonstrate the precentral gyrus alteration and its abnormal connectivity in schizophrenia.

Methods: The region of interest-based analysis method was used to investigate the precentral gyrus connectivity alteration in schizophrenia. The resting-state functional magnetic resonance imaging data of healthy control subjects and patients with schizophrenia (Centers of Biomedical Research Excellence data set) was used to examine the aberrant functional brain connectome in schizophrenia. This data set contains raw anatomical and functional magnetic resonance data from 72 patients with schizophrenia and 75 healthy controls, ranging in age from 18 to 65 years old.

Results: Our results show precentral gyrus has abnormal communication with thalamus, hippocampus, parahippocampal gyrus, posterior division of supramarginal gyrus and medial prefrontal cortex (pFDR = 0.05). This information is expected to provide a better understanding of altered functional connectivity of the precentral gyrus in the male and female patients with schizophrenia.

Conclusion: Collectively, these findings support the hypothesis that precentral gyrus has an abnormal connectivity in schizophrenia and this alteration is not the same in the male and female patients with schizophrenia.

Keywords: Schizophrenia, functional magnetic resonance imaging, functional connectivity, resting-state, precentral gyrus

INTRODUCTION

Schizophrenia is a severe mental disorder, affecting ~1% of the population[1,2]. Recent studies have shown dysfunction of the precentral gyrus (PreCG) has long been thought to play a role in the impairments of voluntary movement associated with Schizophrenia and it has significantly reduced functional activity (FC) in patients with schizophrenia[3,4]. Also, schizophrenia is associated with volume deficits in PreCG[5]. Another research indicates the patients with schizophrenia showed lower activation in left PreCG than right PreCG[6] and a regional homogeneity (ReHo) study showed decreased ReHo in right precentral gyrus[7]. In this research, we examined the PreCG functional connectivity impairment in patients with schizophrenia using ROI based analysis[8]. We used the Center for Biomedical Research Excellence data set (COBRE)[9] to demonstrate how the functional connectivity of the PreCG with the rest of the brain regions changes in schizophrenia. In conjunction with previous studies[10-13], our results indicate the PreCG has abnormal connectivity with brain regions like Thalamus and Hippocampus, but these impairments are not similar in two hemispheres. We also analyzed the functional connectivity differences between male and female patients with schizophrenia and showed the regions like Thalamus are more affected in the female patients with schizophrenia.

METHODS

Data

Two groups of subjects from the COBRE data set are used to examine the aberrant functional brain connectome in schizophrenia. COBRE data set contains raw anatomical and functional MRI data from patients with schizophrenia and healthy controls. Some papers that by the COBRE group published on this data[14-16]. This data set is available on and contains raw anatomical and functional MR data from patients with Schizophrenia and healthy controls, ranging in age from 18 to 65 years old. Resting fMRI, anatomical MRI, phenotype data for every participant including gender, age, handedness and diagnostic information are released[17]. More details about the COBRE data set can be found in the Table 1.

Analysis

Different preprocessing methods like realignment[18], coregistering, normalization are applied to the structural and functional data. The functional volumes are coregistered with the region of interest and structural volumes[19,20]. Regions of interest and all the Brodmann areas defined by the Talairach daemon assigned to all subjects. By segmentation of structural image for each subject, grey matter, white matter and cerebrospinal fluid (CSF) mask generated. Here, the time series of interest are numbers of PCA components.
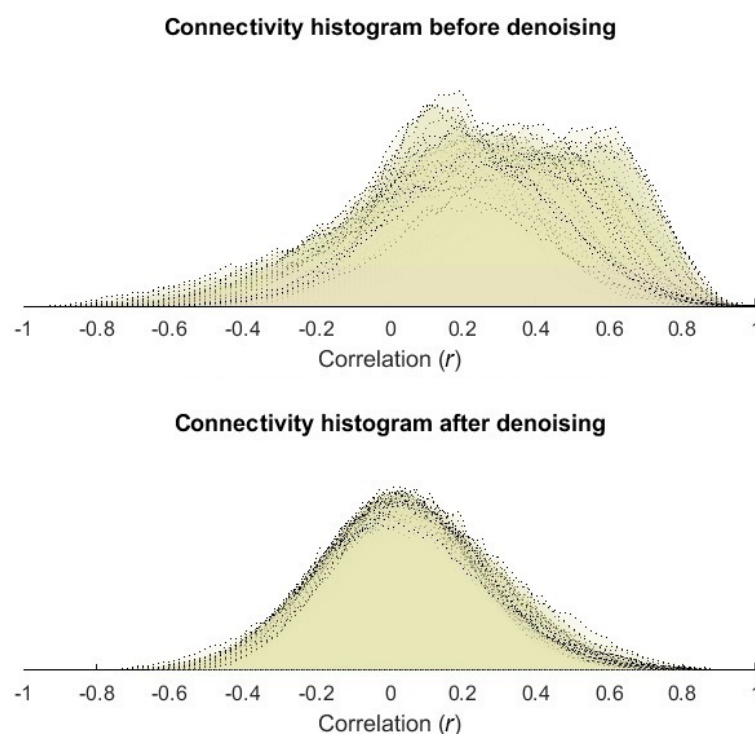
First and second level of covariates

In this step, the realignment parameters in Blood-Oxygen-Level-Dependent (BOLD) model is defined (the first level covariate), then in the second level covariate, the group level regressor is performed. We categorized the data input data into 4 groups: females and males healthy control, females and males patients with schizophrenia. After defining the experimental data, the functional data is imported, then the structural data segmented to define the grey matter, white matter, the cerebrospinal fluid region of interest. By performing principal component analysis (PCA) on within region of interests the ROIs time series is extracted.

Data preprocessing

Before analyzing the data, we need to explore and remove the confound. The different source of possible confounds like cerebrospinal fluid and white matter signal and within-subject covariate (realignment parameters) are considered. We chose the 5-dimension numbers of temporal components are being used. Similarly, numbers of dimension for the white matter was 5 and the derivative order was 0 and the histogram

Table 1. Demographic characteristics of subjects in COBRE data

	N	Age (SD)	Female (%)
Patients with schizrenia	72	38.16 (13.89)	0.19
Healthy control	74	35.82 (11.58)	0.31

Connectivity histogram before denoising

Connectivity histogram after denoising

Figure 1. Connectivity histogram before and after denoising

plot *r* value before and after confounds removal and the band-pass filter is set to (0.008, 0.09). Here the histograms *r*-square to identify outlier subject and the quality control is computed for every subject. Figure 1 shows the connectivity histogram before and after denoising.

The functional connectivity (CONN) and Statistical Parametric Mapping (SPM) toolboxes[21] used for spatially preprocessing (realignment, coregistering, normalization) of structural and functional data of functional data are done using SPM toolbox. The functional volumes are coregistered with the region of interest and structural volumes. ROI-to-ROI correlational analysis was carried out by CONN toolbox and SPM8. The preprocessing of the functional images considered of band-pass filtering of 0.008-0.09 Hz, motion correction, registration to structural images and spatial normalization to the MNI template. Then to reduce the physiological noise source, a Component-Based Noise Correction Method (CompCor) has been used[22]. CompCor can be used for the reduction of noise in both blood oxygenation level dependent and perfusion-based functional magnetic resonance imaging data. False discovery rate correction is used for multiple hypothesis testing. Number of PCA components to be extracted for each ROI is set to one. It means the time-series of interest is defined as the average BOLD activation within the ROI voxels, but it's possible to define it as the principal eigenvariates of the time-series within the ROI voxels. Regions of interest and all the Brodmann areas defined by Talairach daemon assigned to all subjects. By segmentation of structural image for each subject, grey matter, white matter, and CSF masks were generated. Bivariate correlation is used as a functional connectivity measure between two areas. General linear model (GLM)[23] used for comparison of connectivity results between genders and between control and Schizophrenia patients.

Table 2. The connectivity contrast values between the PerCG right and the targets (*P* = 0.05)
(the complete list of the effects size is provided in the supplementary data)

Analysis Unit	Statistic	p-unc	p-FDR
Seed intensity = 18.77, size = 5	PreCG r	F(30)(113) = 3.17	0.0000
PreCG r -Hippocampus l	T(142) = 4.16	0.0001	0.0074
PreCG r -Thalamus l	T(142) = -3.92	0.0001	0.0093
PreCG r -pPaHC l	T(142) = 3.62	0.0004	0.0151
PreCG r -Thalamus r	T(142) = -3.54	0.0005	0.0151
PreCG r -pSMG r	T(142) = -3.53	0.0006	0.0151

ROI based analysis

We investigated the hypothesis of connectivity difference in schizophrenia and used ROI analyzing for the PreCG region of the brain. Two-sample *t*-test analyzes computed via SPM8[24] to compare the connectivity results of patients *vs.* controls and male patient *vs.* women patient to compare the connectivity across two groups. Connectivity values (Fisher-transformed correlation coefficients) between the seed and the identified ROI was extracted from the connectivity map. The different source of interest can be defined for analyzing.

First level voxel-based analysis

For a subject or condition, it is possible to perform voxel-to-voxel analyzing that applies the matrix of voxel-to-voxel connectivity values and there is no need for the prior region of interest or seed analysis. In this method, we can investigate whole-brain connectivity. The voxel-based analyzing can be on connectivity pattern (principal component analysis) between a voxel and the rest of the brain (MVPA). Another voxel-based measure is available in CONN toolboxes is indexed that calculates the average local connectivity between each voxel and its neighbors (integrated local correlation)[25] or instead of average, the spatial asymmetry of the local connectivity can be used (radial correlation contrast)[26]. Also, instead of local connectivity, global connectivity pattern between a voxel and the rest of the brain can be used (e.g., radial similarity contrast)[27]. More details about measuring the index can be found in[28].

Second level analysis

In the second level analysis step, the between-subject contrast can be considered (e.g., to compare different groups like male *vs.* female to see main effects in the connectivity within each group). In the ROI-to-ROI analyze, the first-level connectivity-measure matrix is used and the results can be a threshold at the desired *P*-value threshold. In this step by graph theoretical analyzing method provides the network measures like efficiency, centrality, and cost/degree to test the between-subject contrast.

RESULTS

The connectivity contrast values between the PreCG right and the targets show the PreCG has abnormal communication with thalamus, hippocampus, pPaHC, pSMG and mPFC (*P* = 0.05). Figure 2 shows ROI-level results for PreCG left and right PreCG. Effects size for each region is shown by the dot size. We compared the functional connectivity difference between the left and right PreCG between healthy controls and schizophrenia patients. Results show that the connectivity of the left Hippocampus with both left and right PreCG decreased in schizophrenia [Figure 3]. More details about the connectivity impairment of PreCG and the rest of the brain is demonstrated in the [Tables 2 and 3]. We also compared schizophrenia affects the PreCG in the male and female patients [Figures 4 and 5].

DISCUSSION

The present study supports the notion of the functional connectivity abnormal connectivity of the precentral gyrus in schizophrenia[1,2,8-11]. We have shown that PreCG alteration and its abnormal connectivity are not the
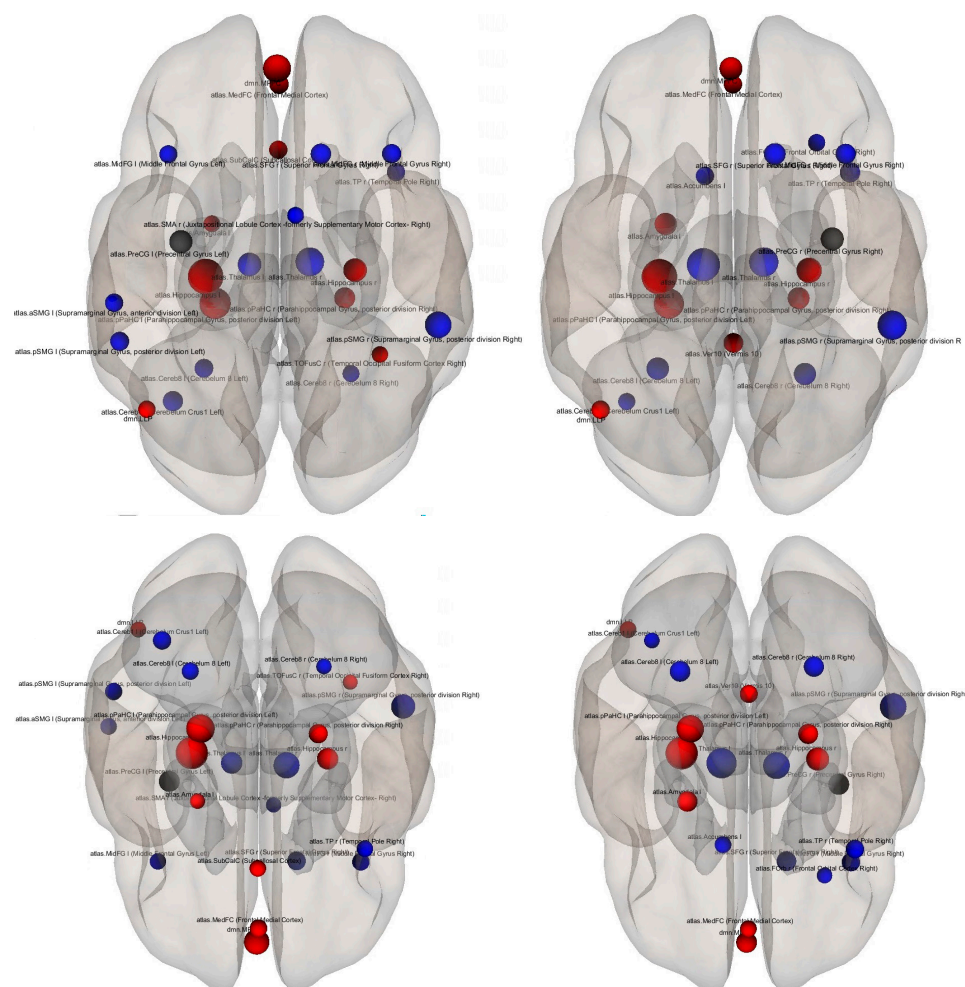
Figure 2. The superior (top) and the posterior views of the ROI-level results for each target ROI. The selected sources (precentral gyrus left and right) are shown by black dots and the targets are blue (control > schizophrenia) and red (control < schizophrenia). Effects size for each region is shown by the dot size

Table 3. The connectivity contrast values between the PerCG left and the targets (*P* = 0.05)
(the complete list of the effects size is provided in the supplementary data)

Analysis Unit	Statistic	p-unc	pFDR
Seed intensity = 25.55, size= 7	PreCG l	F(30)(113) = 3.41	0.0000
PreCG l -Hippocampus l	T(142) = 4.47	0.0000	0.0022
PreCG l -pPaHC l	T(142) = 4.02	0.0001	0.0063
PreCG l -Thalamus r	T(142) = -3.72	0.0003	0.0128
PreCG l -dmn.MPFC	T(142) = 3.64	0.0004	0.0131
PreCG l -pSMG r	T(142) = -3.48	0.0007	0.0179
PreCG l -Hippocampus r	T(142) = 3.12	0.0022	0.0450
PreCG l -Thalamus l	T(142) = -3.10	0.0023	0.0450

same in the male and female patients with schizophrenia. The resting-state functional magnetic resonance imaging data of healthy control subjects and patients with schizophrenia from the Centers of Biomedical Research Excellence dataset are used to examine the aberrant functional brain connectome in schizophrenia. Our results show precentral gyrus has abnormal communication with thalamus, hippocampus, pPaHC, pSMG and mPFC (pFDR = 0.05).
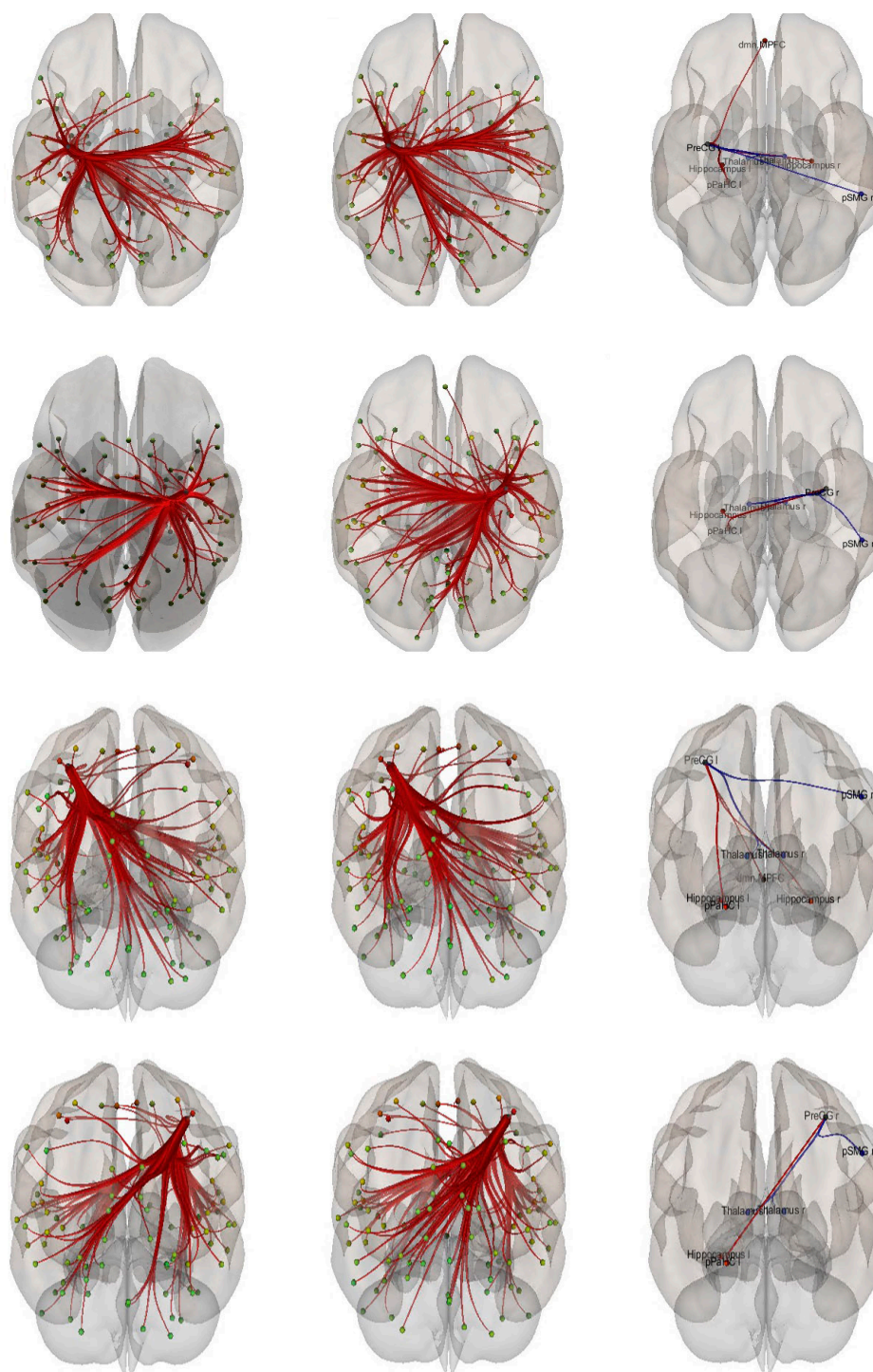
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Figure 3. Functional connectivity difference between the left and right precentral gyrus between healthy controls *vs*. patients with schizophrenia (controls > schizophrenia). The PreCG connectivity in the healthy control, patients with schizophrenia, and their difference are shown in the first, second and the last column respectively and the two top rows are the superior views and the two-bottom row are the posterior views

Here, we investigated abnormal connectivities of left and right precentral gyrus in male and female patients with schizophrenia. The region of interest based analysis carried out for the healthy control and patients with Schizophrenia data. To do this resting state functional magnetic resonance imaging data of healthy control subjects and patients with schizophrenia from Center for Biomedical Research Excellence are used
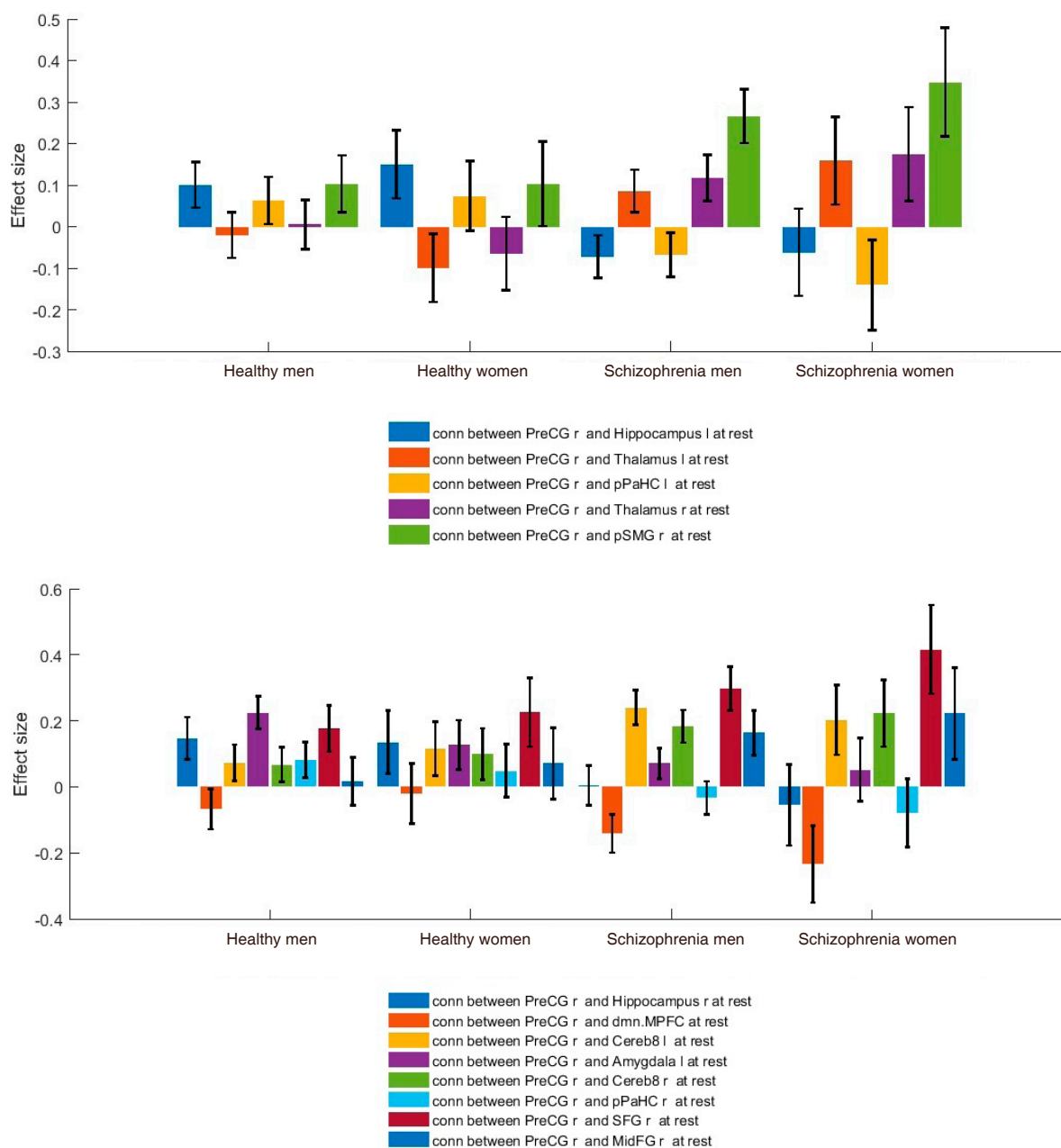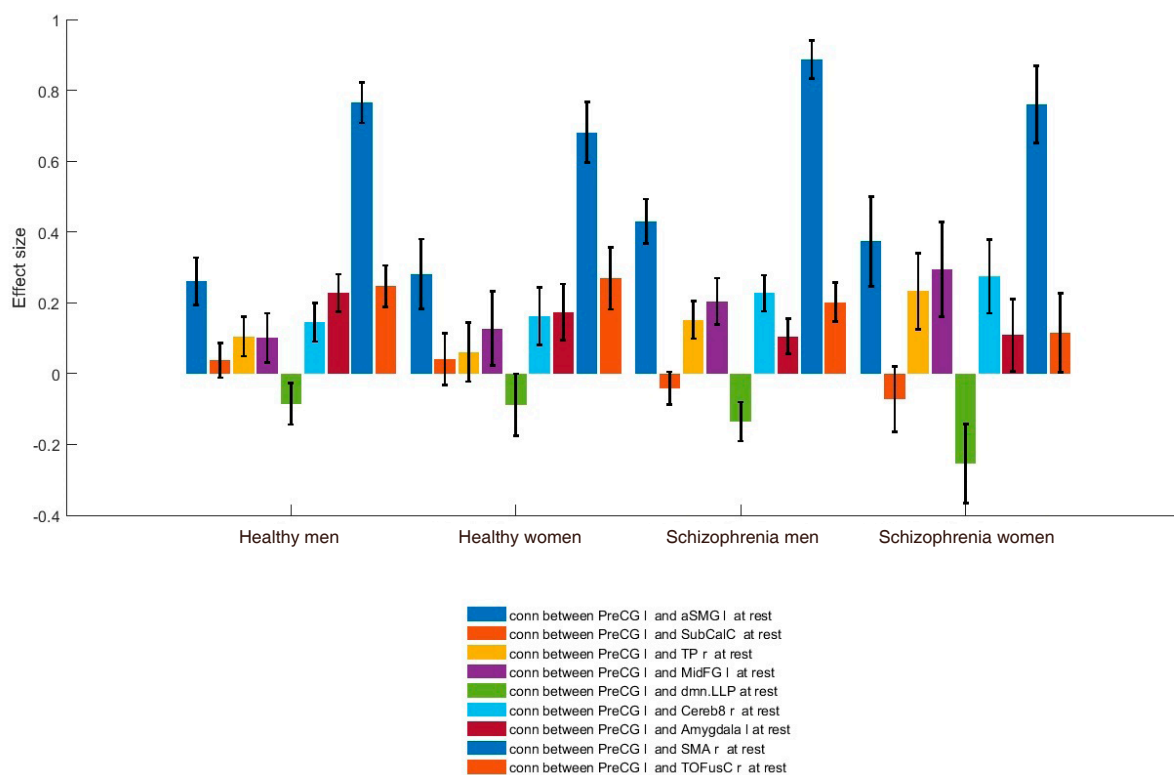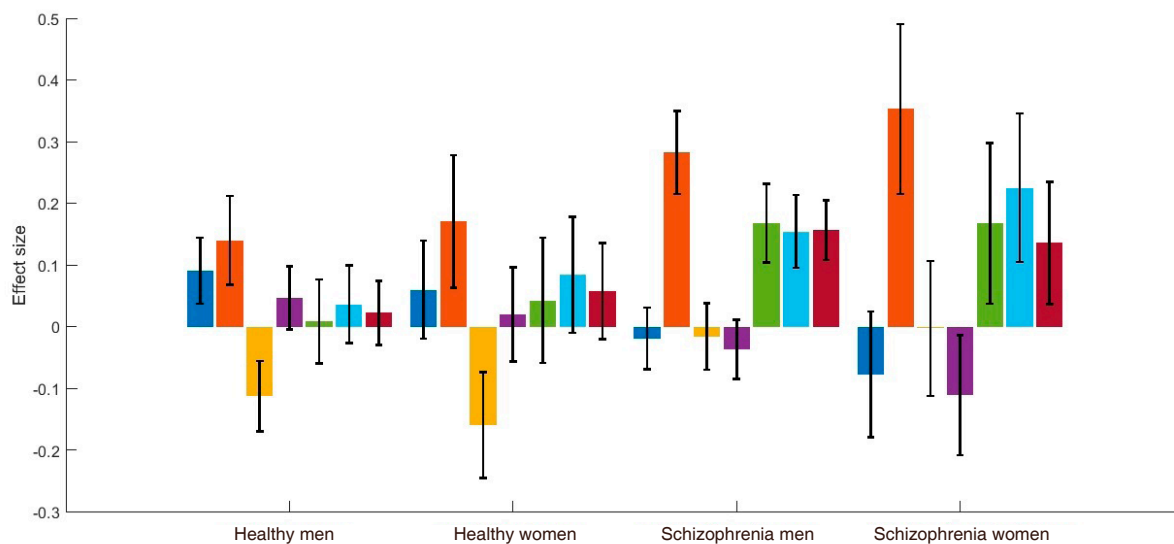
Figure 4. Right precentral gyrus functional connectivity difference between healthy controls and patients with schizophrenia (controls > schizophrenia)

to examine the aberrant functional brain connectome in schizophrenia which contains raw anatomical and functional MR data from 72 patients with schizophrenia and 75 healthy controls, ranging in age from 18 to 65 years old. We can summarize our results as follows: The precentral gyrus has abnormal communication with thalamus, hippocampus, pPaHC, pSMG and mPFC ($P = 0.05$). The right precentral gyrus has unusual connectivities with Hippocampus l, pPaHC l Thalamus l, Thalamus r and pSMG r. The right precentral gyrus has unbalanced connectivities with Hippocampus l, pPaHC l, Thalamus r, MPFC, pSMG r, Hippocampus r and Thalamus l. The connectivity impairments of the PreCG in schizophrenia are different for male and female patients. This information is expected to provide a better understanding of altered functional connectivity of primary motor cortex in schizophrenia.

Legend (top chart):
- conn between PreCG l and pPaHC r at rest
- conn between PreCG l and SFG r at rest
- conn between PreCG l and Cereb1 l at rest
- conn between PreCG l and MedFC at rest
- conn between PreCG l and MidFG r at rest
- conn between PreCG l and pSMG l at rest
- conn between PreCG l and Cereb8 l at rest

Legend (bottom chart):
- conn between PreCG l and aSMG l at rest
- conn between PreCG l and SubCalC at rest
- conn between PreCG l and TP r at rest
- conn between PreCG l and MidFG l at rest
- conn between PreCG l and dmn.LLP at rest
- conn between PreCG l and Cereb8 r at rest
- conn between PreCG l and Amygdala l at rest
- conn between PreCG l and SMA r at rest
- conn between PreCG l and TOFusC r at rest

Legend:
- conn between PreCG l and Hippocampus l at rest
- conn between PreCG l and pPaHC l at rest
- conn between PreCG l and Thalamus r at rest
- conn between PreCG l and dmn.MPFC at rest
- conn between PreCG l and pSMG r at rest
- conn between PreCG l and Hippocampus r at rest
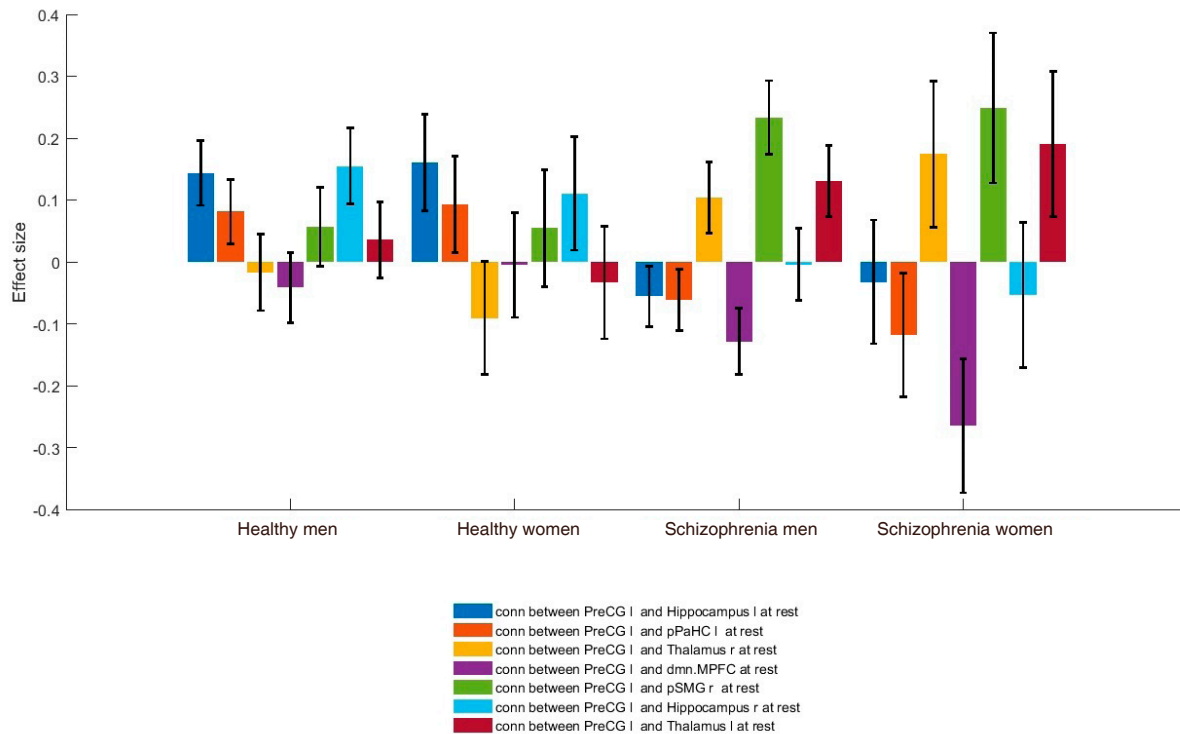- conn between PreCG l and Thalamus l at rest

Figure 5. Left precentral gyrus functional connectivity difference between healthy controls and patients with schizophrenia (controls > schizophrenia)

DECLARATIONS

Authors' contributions
The author contributed solely to the paper.

Data source and availability
Datas presented here are from the Center for Biomedical Research Excellence data set (COBRE). This data set is available at a previous study[7] and contains raw anatomical and functional MR data from patients with Schizophrenia and healthy controls, ranging in age from 18 to 65 years old. Resting fMRI, anatomical MRI, phenotype data for every participant including gender, age, handedness and diagnostic information are released.

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Conflicts of interest
There are no conflicts of interest.

Patient consent
Not applicable.

Ethics approval
Not applicable.

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