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# Abnormalities in cognitive-related functional connectivity can be used to identify patients with schizophrenia and individuals in clinical high-risk

Yangpan Ou[1†], Zhaobin Chen[1†], Ying Wang[2*], Huabing Li[3], Feng Liu[4], Ping Li[5], Dongsheng Lv[6], Yong Liu[1], Bing Lang[1], Jingping Zhao[1] and Wenbin Guo[1*]

## Abstract

**Background** Clinical high-risk (CHR) refers to prodromal phase before schizophrenia onset, characterized by attenuated psychotic symptoms and functional decline. They exhibit similar but milder cognitive impairments, brain abnormalities and eye movement change compared with first-episode schizophrenia (FSZ). These alterations may increase vulnerability to transitioning to the disease. This study explores cognitive-related functional connectivity (FC) and eye movement abnormalities to examine differences in the progression of schizophrenia.

**Methods** Thirty drug-naive FSZ, 28 CHR, and 30 healthy controls (HCs) were recruited to undergo resting-state functional magnetic resonance imaging (rs-fMRI). Connectome-based predictive modeling (CPM) was employed to extract cognitive-related brain regions, which were then selected as seeds to form FC networks. Support vector machine (SVM) was used to distinguish FSZ from CHR. Smooth pursuit eye-tracking tasks were conducted to assess eye movement features.

**Results** FSZ displayed decreased cognitive-related FC between right posterior cingulate cortex and right superior frontal gyrus compared with HCs and between right amygdala and left inferior parietal gyrus (IPG) compared with CHR. SVM analysis indicated a combination of BACS-SC and CFT-A scores, and FC between right amygdala and left IPG could serve as a potential biomarker for distinguishing FSZ from CHR with high sensitivity. FSZ also exhibited a wide range of eye movement abnormalities compared with HCs, which were associated with alterations in cognitive-related FC.

†Yangpan Ou and Zhaobin Chen contributed equally to this work.

*Correspondence:
Ying Wang
wangying@csu.edu.cn
Wenbin Guo
guowenbin76@csu.edu.cn

Full list of author information is available at the end of the article

**Conclusions** FSZ and CHR exhibited different patterns of cognitive-related FC and eye movement alteration. Our findings illustrate potential neuroimaging and cognitive markers for early identification of psychosis that could help in the intervention of schizophrenia in high-risk groups.

**Keywords** Cognitive function, Clinical high-risk, Schizophrenia, Eye movement, Connectome-based predictive modeling (CPM)

## Background

Clinical high-risk (CHR) phase is a prodromal period before psychosis onset, marked by attenuated, transient, or intermittent psychotic symptoms and a decline in function in non-psychiatric individuals [1, 2]. Almost 22% of CHR would convert to full-blown psychosis within 1 year and 36% over 3 years [3]. Study on CHR may provide a window of opportunity for better understanding the trajectory from elevated risk to well-established illness and decrease the rate of transition to psychosis through appropriate detection and intervention in the early stage of non-specific mental distress [4, 5].

Notably, generalized cognitive impairments are an independent core feature of schizophrenia, including impairments in neurocognition (e.g., processing speed, attention, working memory) and social cognition (e.g., mentalizing, social perception) [6, 7]. These impairments are observed earlier before the emergence of typical psychotic symptoms, deteriorate throughout development, and stabilize in the chronic state [8]. Evidence indicated that cognitive impairments are present in a considerable number of CHR and first-episode schizophrenia (FSZ) [9–11]. CHR performs worse in cognitive tasks like verbal fluency and processing speed compared to healthy controls (HCs), with impairments similar to FSZ [11–14]. Several studies showed that CHR displays a modest degree of cognitive impairments intermediated between FSZ and HCs [15–17]. CHR who did transition to schizophrenia at follow-up tended to have more severe cognitive impairments than those who did not [17–19], suggesting cognitive impairments may be driven by a more severely damaged subgroup that is at risk of psychosis. These findings support cognitive function as a candidate marker for predicting conversion of psychosis [20, 21].

The neurodevelopmental hypothesis suggests that cognitive impairments in schizophrenia result from problems with cognitive acquisition caused by persistent brain developmental abnormalities from an early age [8]. Neuroimaging technologies, such as functional magnetic resonance imaging (fMRI), have tried to link cognitive impairments to localized brain activity and revealed specific brain abnormalities in different cognitive tasks [22–24]. For example, reduced activation in the middle frontal gyrus (MFG), parahippocampal gyrus, and medial frontal gyrus has been observed in CHR during verbal memory tasks [25]. Other studies highlight alterations in the prefrontal cortex, temporal lobes, hippocampus, and caudate during various cognitive activities [26–28]. Our previous study showed that decreased functional connectivity strength (FCS) in the MFG and increased FCS in the calcarine were positively correlated to cognitive measures in CHR [24].

Connectome-based predictive modeling (CPM) is a novel data-driven machine-learning method for generating predictive models of brain-behavior relationships from whole-brain FC patterns at the individual level [29]. Unlike traditional FC analysis, CPM provides more comprehensive information on all brain connectivity rather than individual regions [29, 30]. With built-in cross-validation methods, CPM can efficiently protect against overfitting and increase replicability and adaptability in a new sample. Moreover, CPM identifies predictive networks with the most relevant features from neuroimaging data [29]. This modeling has been successfully applied to extract behavior-related brain areas and to make predictions at individual levels, such as compulsive behavior in obsessive-compulsive disorder [31], memory deficits in psychiatric disorders [32], and social disorder in attention-deficit/hyperactivity disorder [33].

As a non-invasive neuropsychological test, eye movement detection can be used to explore visual processing under various conditions, offering insights into the mechanisms underlying human cognitive and psychological functions. Previous studies have consistently shown that eye movement abnormalities, including deficits in smooth pursuit eye movement (SPEM), free-viewing, and fixation stability tasks, are well-recognized in schizophrenia and are often associated with cognitive impairments, particularly in attention and executive function tasks [34–36]. These impairments reflect dysfunction in brain regions such as the frontal and parietal cortices [37, 38]. However, eye movement studies in CHR remain limited. Pervious study discovered that error rates in antisaccade tasks in CHR were intermediate between schizophrenia and HCs, suggesting that eye movement dysfunction may emerge early in the disease [39].

In this study, CPM was implemented to explore cognitive-related brain regions among FSZ, CHR, and HCs. The most relevant regions were selected as seeds to construct FC networks. Thus, we collected eye movement data from SPEM tasks to examine whether eye movement abnormalities could reflect different cognitive-related FC patterns among the patients. Based on previous studies

[24, 40, 41], we predicted that CHR and FSZ would show significantly disrupted cognitive-related FC in specific brain regions, with these alterations serving as a potential marker for classification.

## Methods

### Participants

Thirty outpatients suffering from schizophrenia were recruited from the Second Xiangya Hospital of Central South University, diagnosed by two senior psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. All patients were diagnosed with their first episode of the disorder and were under three years of its onset. Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of psychiatric symptoms. Twenty-eight participants were recruited from the outpatient clinics of the hospital for investigation of CHR. To confirm the presence of CHR, the Structured Interview for Prodromal Syndromes (SIPS) was administered to all participants. Patients who had a prior neurological condition, a history of head injury, or whose eye movement data were excluded from this analysis. Thirty-one HCs were procured from the broader community. Notwithstanding, none of them had a prior psychiatric history or a first-degree familial history of psychosis. HCs were excluded if they exhibited epilepsy or any other neurological disorders, diabetes, used substances within the last six months, or had a history of head injury leading to loss of consciousness for more than five minutes. All individuals enrolled in the survey were identified as possessing the following characteristics: right-handedness, age between 16 and 45 years, and the ability to understand the survey material.

The Second Xiangya Hospital of Central South University Ethics Committee reviewed and approved the research protocol. The study adhered to the principles of ethical research, and the investigator meticulously explained the potential risks and benefits to the participants before enrollment, and all participants provided written informed consent.

### Cognitive tests

The Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB), a standardized tool used to evaluate cognitive function, is widely utilized and has been translated into the Chinese language. The Trail Making Test-Part A (TMT-A), Brief Assessment of Cognition in Schizophrenia-Symbol Coding (BACS-SC), and the Category Fluency Test-Animal (CFT-A) were administered to evaluate participants' speed of processing. The Wechsler Memory Scale-spatial span (WMS-SS) was used to assess working memory. The Neuropsychological Assessment Battery (NAB) was conducted to evaluate reasoning and problem-solving abilities. Attention and vigilance were evaluated using the Continuous Performance Test-Identical Pairs (CPT-IP). The word learning ability was assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R). The Brief Visuospatial Memory Test (BVMT-R) was administered to measure visual learning ability. The exclusion of social cognition from our analyses was a result of the fact that the Mayer-Salovey-Caruso Emotional Intelligence Test-managing emotions test (MSCEIT) was limited to individuals under a certain age. In addition, we administered a complementary test of memory by administering a Stroop Colour Word Test (SCWT). The duration for each subject to complete the MCCB ranged from 1 to 1.5 h. After administering the MCCB, raw scores were converted into scale scores and subsequently translated to Chinese normalized T scores.

### Smooth pursuit eye-tracking tasks

Studies on SPEM are typically divided into two phases: the initiation phase (within the first 100ms) and the maintenance phase (after 100ms). The initiation phase primarily is associated with perceptual-motor functions. During this phase, the participant receives the movement signal from the target via the retina, which is then transmitted to higher brain regions and converted into eye movement signals, initiating the pursuit [42]. This process is believed to involve both perceptual-motor integration and higher cognitive functions, as participants not only follow the target with their eyes but also predict its speed, direction, and position [43].

Eye movements were recorded using an EyeLink 1000 eye tracker (SR Research, Ontario, Canada). The hole-in-the-card test was used to determine the dominant eye. Tracking of the dominant eye was achieved through a 25 mm camera lens. The stimuli were presented on a 24-inch screen with a resolution of 1920 × 1080 pixels and a refresh rate of 144 Hz. Participants were 70 cm away from the screen and positioned their heads on a chin/forehead rest to minimize head movements. A 9-point calibration mode was used to begin each task, and drift correction was automatically applied throughout each task.

We administered four quizzes in SPEM tasks, each consisting of horizontal and Lissajous tracking for two modes. In all tasks, participants were instructed to maintain their gaze on a 0.5-degree circular target before tracking it as it moved across the screen. For the horizontal SPEM task, the target moved horizontally at a frequency of 0.4 Hz (HS4). In the color count horizontal task (HS4X), the target color changed randomly during movement. For the Lissajous smooth pursuit task, the target moved across the screen at a frequency of 0.2 Hz following the Lissajous graph (LS2). In the complex

background Lissajous SPEM task (LS2B), the target stimulus followed a 0.2 Hz Lissajous trajectory, but with a large stationary distractor of the same size as the target in the background.

### Image acquisition and preprocessing

All participants underwent scanning with a Siemens 3.0T machine. Participants were instructed to lie supine, keep their eyes closed, and remain awake. Foam padding and earplugs were used to minimize head motion. Resting-state fMRI data were acquired using an echo planar imaging sequence with specified parameters. TR/TE = 2000ms/30ms, flip angle = 90°, field of view = 220 mm×220 mm, 64 × 64 matrix, 4 mm slice thickness, 39 slices, and 200 volumes. A toolbox for Data Processing & Analysis for Brain Imaging (DPABI, https://rfmri.org/DPABI) software was used for data preprocessing [44]. To obtain more stable data, the first 10 time points were discarded. Subsequently, slice timing and motion correction were performed. Next, the corrected data were normalized to the Montreal Neurological Institute (MNI) space to improve the signal-to-noise ratio and smoothed with a 4 mm full-width half-maximum isotropic Gaussian kernel. Finally, the data were bandpass filtered between 0.01 Hz and 0.08 Hz and linearly detrended to remove high-frequency noise interference.

### Connectivity matrices

The fMRI data was parcellated into 246 regions of interest (ROIs) using the Human Brainnetome Atlas [45], which divides the brain into 210 cortical and 36 subcortical subregions based on anatomical and functional connectivity. Averaging fMRI time series in each ROI produced a representative time series for each subject. Consequently, a 246 × 246 FC matrix or edges was obtained for each participant.

### CPM construction

CPM was performed using MATLAB scripts [29]. The data were split into training and testing sets (30 FSZ data, 28 CHR data, and 31 HC data) for cross-validation, employing a leave-one-subject-out method. Correlations between edges and MCCB and its subscales were computed using Pearson correlation analysis in the training set. Significant edges were selected based on their linear association with clinical data using the thresholds $p < 0.001$. The selected edges were summarized for each subject in the training set, resulting in single summary values for both positive and negative edge sets. A predictive model was then fitted. The model was used to predict MCCB and its subscales scores for the subjects in the testing set, separately for positive and negative edge sets. The accuracy of the predictive model was evaluated in the testing set using permutation testing (5000 permutations).

### Least absolute shrinkage and selection operator (Lasso) regression analysis

Lasso regression is a linear regression method that uses L1 regularization to reduce model complexity [46]. Considering that the CPM model selected many features, we used Lasso regression for feature dimensionality reduction. We performed a correlation analysis between the previously selected predictive network features and the MCCB scores and their subscales of FSZ and CHR participants, which allowed us to select the edges most relevant to the cognitive functions of FSZ and CHR.

### Seed-based FC analysis

We used the features selected in the previous step as seeds to compare the differences in seed-based FC analysis among three groups. We employed a one-way analysis of variance (ANOVA) with age, sex, education years, and head motion as covariates. Post hoc *t*-tests were conducted on the analysis results, followed by false discovery rate (FDR) correction ($p < 0.05$).

### Classification analysis

Support vector machine (SVM) is a supervised discriminative classification algorithm in machine learning, which has been widely applied in classification and prediction of various psychiatric disorders, such as schizophrenia, depression, bipolar disorder, and autistic spectrum disorders [47–49]. The core of SVM is constructing a hyperplane that maximizes the distances of the nearest sample point to separate the data into different groups optimally [50]. In this work, SVM analysis was used to investigate whether cognitive-related FCs and cognitive features could identify FSZ from CHR by using the LIBSVM software package (http://www.csie.ntu.edu.tw/$\sim$cjlin/libsvm/) in MATLAB. The "5-fold cross-validation" method was used to train the classifier and select the optimal feature combination to achieve the highest sensitivity and specificity.

### Statistical analysis

Analysis of variance (ANOVA) was performed to analyze group differences in age, education years, eye movement parameters, MCCB and its subscales scores across three groups using SPSS26.0 (LSD between two group comparisons). A chi-square test was used to compare sex distributions. The significance level was set at $p < 0.05$.

Correlation analysis was conducted to explore the correlations between abnormal FC and eye movement characteristics in FSZ and CHR, and the results were FDR-corrected at $p < 0.05$.

**Table 1** Participants demographics and clinical characteristics (M ± SD)

| | FSZ(*N* = 30) | CHR(*N* = 28) | HC(*N* = 31) | F/$\chi^2$ | *p* | |
|---|---|---|---|---|---|---|
| Sex [a] (M/F) | 14/16 | 11/17 | 21/10 | $\chi^2 = 5.227$ | 0.073 | |
| Age (years) | 22.40 ± 5.71 | 17.36 ± 4.39 | 21.68 ± 5.70 | $F_{(2,88)} = 7.533$ | 0.001 | ** |
| Education (years) | 9.93 ± 4.08 | 7.96 ± 3.16 | 12.65 ± 1.92 | $F_{(2,88)} = 16.32$ | 0.001 | ** |
| PANSS | 74.73 ± 20.77 | | | | | |
| Positive | 18.23 ± 6.33 | | | | | |
| Negative | 18.60 ± 6.11 | | | | | |
| General | 37.90 ± 11.75 | | | | | |
| SIPS | | 32.75 ± 9.86 | | | | |
| Positive | | 11.32 ± 4.07 | | | | |
| Negative | | 12.04 ± 4.98 | | | | |
| Disorganization | | 5.29 ± 2.62 | | | | |
| General | | 6.71 ± 3.57 | | | | |

FSZ: first-episode schizophrenia, CHR: clinical high-risk, HC: healthy controls, PANSS: Positive and Negative Syndrome Scale, SIPS: Structured Interview for Psychosis-risk Syndromes

[a] The classification variables were statistically tested by chi-square test

* $0.01 < p \leq 0.05$, ** $0.001 < p \leq 0.01$, *** $p \leq 0.001$

**Table 2** Differences in cognitive function across the three groups

| | | | | | | FSZ vs. CHR | FSZ vs. HC | CHR vs. HC |
|---|---|---|---|---|---|---|---|---|
| **EM** | **FSZ** | **CHR** | **HC** | **F** | ***p*** | ***p*** | ***p*** | ***p*** |
| TMT | 43.90 ± 8.37 | 46.54 ± 12.10 | 50.94 ± 11.02 | 3.445 | 0.036 | 0.346 | 0.011 | 0.114 |
| BACS: Symbol Coding | 35.53 ± 11.83 | 38.11 ± 10.80 | 46.55 ± 11.56 | 7.759 | 0.001 | 0.394 | 0.000 | 0.006 |
| HVLT-R | 37.27 ± 9.43 | 45.93 ± 12.35 | 46.10 ± 10.85 | 6.406 | 0.003 | 0.003 | 0.002 | 0.953 |
| WMS-III: Spatial Span | 45.90 ± 9.82 | 46.25 ± 12.69 | 46.58 ± 5.74 | 0.037 | 0.963 | 0.891 | 0.785 | 0.897 |
| NAB: Mazes | 46.83 ± 12.90 | 49.18 ± 13.36 | 52.06 ± 8.70 | 1.512 | 0.226 | 0.450 | 0.086 | 0.350 |
| BVMT-R | 44.13 ± 13.63 | 44.04 ± 10.82 | 53.42 ± 10.22 | 6.476 | 0.002 | 0.975 | 0.003 | 0.003 |
| Animal naming Fluency | 35.37 ± 11.58 | 40.04 ± 10.49 | 48.97 ± 12.76 | 10.683 | 0.000 | 0.132 | 0.000 | 0.004 |
| CPT-IP | 50.83 ± 8.89 | 72.11 ± 27.08 | 53.16 ± 10.28 | 13.329 | 0.000 | 0.000 | 0.597 | 0.000 |
| Stroop Word Reading | 47.30 ± 14.32 | 66.18 ± 20.56 | 53.65 ± 12.64 | 10.320 | 0.000 | 0.000 | 0.126 | 0.004 |
| Stroop Color Naming | 41.90 ± 10.74 | 41.68 ± 8.22 | 48.45 ± 9.75 | 4.806 | 0.011 | 0.931 | 0.010 | 0.009 |
| Stroop Color Word | 41.67 ± 9.61 | 41.46 ± 12.06 | 50.35 ± 10.46 | 6.788 | 0.002 | 0.943 | 0.002 | 0.002 |
| Speed of Processing | 38.30 ± 7.54 | 41.54 ± 8.56 | 48.58 ± 8.33 | 12.704 | 0.000 | 0.134 | 0.000 | 0.001 |
| Attention Vigilance | 50.83 ± 8.89 | 72.11 ± 27.08 | 53.16 ± 10.28 | 13.329 | 0.000 | 0.000 | 0.597 | 0.000 |
| Working Memory | 45.90 ± 9.82 | 46.25 ± 12.69 | 46.58 ± 5.74 | 0.037 | 0.963 | 0.891 | 0.785 | 0.897 |
| Verbal Learning | 37.27 ± 9.43 | 45.93 ± 12.34 | 46.10 ± 10.85 | 6.406 | 0.003 | 0.003 | 0.002 | 0.953 |
| Visual Learning | 44.00 ± 13.61 | 43.96 ± 10.81 | 53.42 ± 10.22 | 6.636 | 0.002 | 0.991 | 0.002 | 0.002 |
| Reasoning and Problem Solving | 46.83 ± 12.91 | 49.18 ± 13.36 | 52.06 ± 8.70 | 1.512 | 0.226 | 0.450 | 0.086 | 0.350 |

FSZ: first-episode schizophrenia, CHR: clinical high-risk, HC: healthy controls. TMT: Trail Making Test: Part A, BACS: Brief Assessment of Cognition in Schizophrenia, HVLT-R: Hopkins Verbal Learning Test Revised, WMS-III: Wechsler Memory Scale Third Edition, NAB: Neuropsychological Assessment Battery, BVMT-R: Brief Visuospatial Memory Test Revised, CPT-IP: Continuous Performance Test-Identical Pairs

## Results

### Demographic and clinical characteristics

Table 1 outlines the demographic and clinical characteristics of three groups. CHR exhibited a lower age than FSZ and HCs ($p < 0.001$). A significant difference in education years between CHR and other groups was observed ($p < 0.001$). Consistent with expectations, the PANSS and SIPS scores of FSZ and CHR align with their respective disease characteristics. The following table (Table 2) exhibits significant inter-group disparities in various tests, including TMT, BACS, HVLT-R, BVMT-R, CPT-IP, and SCWT. Table S3 reflects the significant differences in eye movements across three groups. During SPEM task, FSZ showed significantly longer higher peak velocity in HS4X, LS2, LS2B tasks compared to CHR. Compared with HCs, FSZ also showed increased peak velocity in HS4X, LS2 tasks and increased saccadic amplitude in HS4X and LS2B tasks.

### CPM results based on cognitive domains and Lasso regression analysis

After linear regression of edges and cognitive traits of three groups, 19 edges were selected for negative correlation with the BACS-SC scores, and 17 edges were selected for negative correlation with the CFT-A scores (Fig. 1). Single-subject summary values of significant

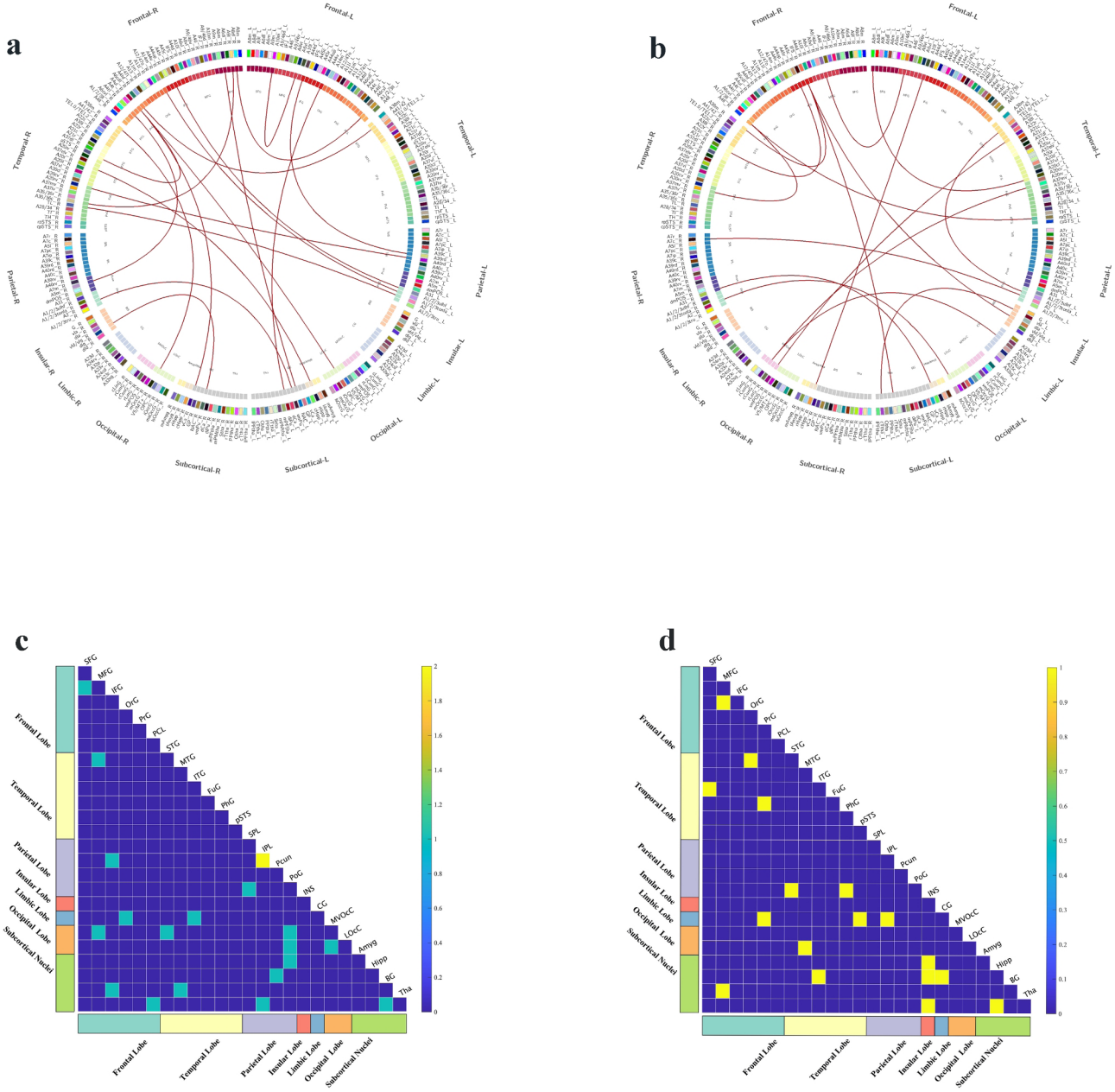


**Fig. 1** Visualizing selected connectivity features. (**a**) and (**b**) Circle plots: 19 edges (**a**) negative correlated with the Brief Assessment of Cognition in Schizophrenia: Symbol Coding scores of the MCCB, and 17 edges (**b**) negative correlated with the Animal naming Fluency scores of the MCCB with a typical significance threshold of $p = 0.001$. (**c**) and (**d**) Matrix plots: The cells of the matrix plots represent the difference between the total number of negative edges connecting the nodes in different brain regions. c represents the number of negative edges related to the Brief Assessment of Cognition in Schizophrenia: Symbol Coding scores. d represents the number of negative edges related to the Animal naming Fluency scores of the MCCB. MCCB: Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery

edges were set as independent variables and behavioral variables as dependent variables to generate CPM. Permutation testing showed that CPM raising from the summary value of 19 edges could accurately predict individual BACS-SC scores ($r = 0.53$, $p < 0.001$), and CPM raising from the summary value of 17 edges could predict individual CFT-A scores ($r = 0.46$, $p = 0.024$) (Fig. 2). After Lasso regression with significant edges and MCCB and their subscales scores, we obtained 9 edges most associated with patients' cognitive features (Figure S1 and Table S1).

### Seed-based FC differences between groups

Seven significant edges were found to be connected with the basal nucleus. Thus, we selected 7 nudes as seeds to construct FC networks. Table S2 and Fig. 3 reflect the

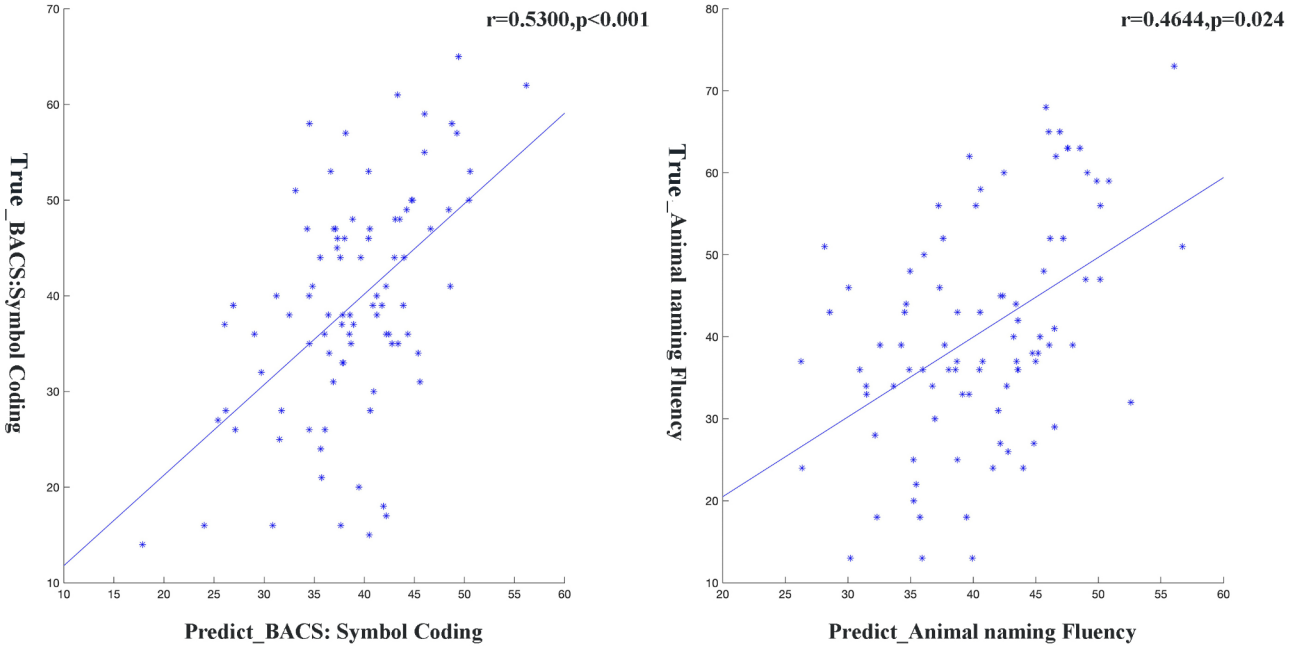


**Fig. 2** The CPM model predicted the Brief Assessment of Cognition in Schizophrenia: Symbol Coding scores of the MCCB (left), and the Animal naming Fluency scores of the MCCB (right). CPM: Connectome-based predictive modeling, MCCB: Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery

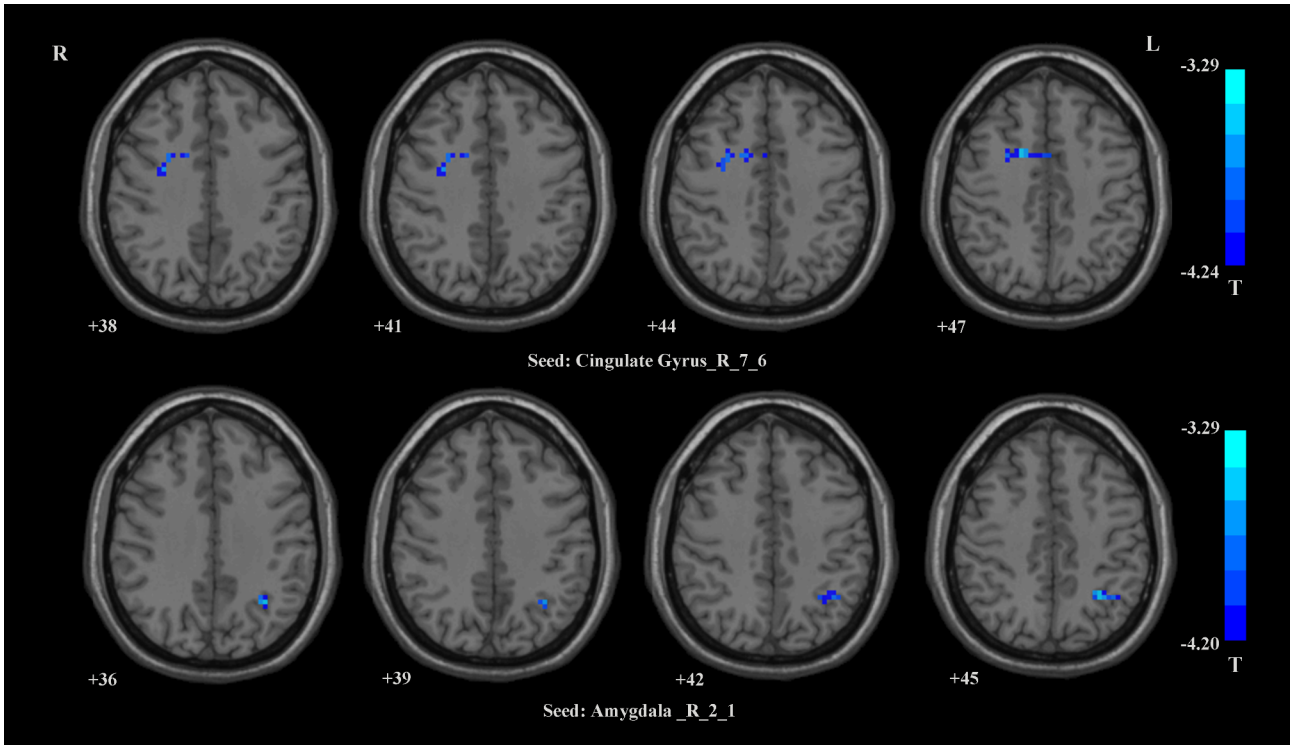


**Fig. 3** Differences in seed-based functional connectivity (FC) across the three groups. The patients with FSZ showed decreased FC between the Cingulate Gyrus_R_7_6 (Brainnetome Atlas) and the Right Superior frontal gyrus compared with the HC, and showed decreased FC between the Amygdala _R_2_1 (Brainnetome Atlas) and the Left Inferior parietal gyrus compared with the patients with CHR. The significance level of *p* value was corrected by false discovery rate (FDR) (corrected $p < 0.05$). FSZ: first-episode schizophrenia, CHR: clinical high-risk, HC: healthy control

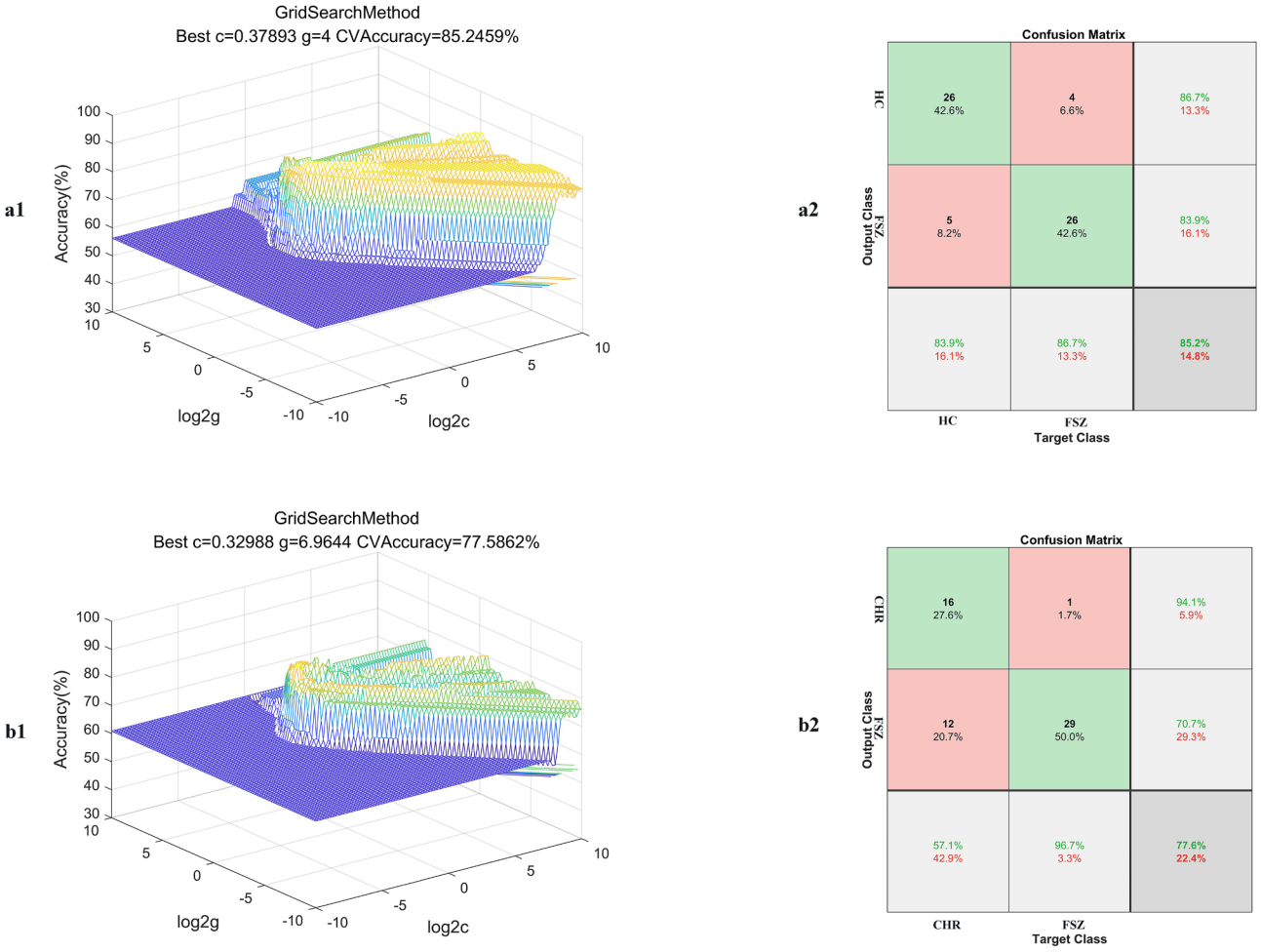


**Fig. 4** 3D view of the classified accuracy with the best parameters using seed-based FC, the BACS: Symbol Coding scores, and the Animal naming Fluency scores as features. **a**1 and **a**2: To identify the patients with FSZ from the HC using the A23c_R-SFG_R, the BACS: Symbol Coding scores, and the Animal naming Fluency scores as features. **b**1 and **b**2: To identify the patients with FSZ from the patients with CHR using the mAmyg_R-IPG_L, the BACS: Symbol Coding scores, and the Animal naming Fluency scores as features. FC: functional connectivity, FSZ: first-episode schizophrenia, CHR: clinical high-risk, HC: healthy control, mAmyg_R: Right Amygdala, SFG_R: Right Superior frontal gyrus, IPG_L: Left Inferior parietal gyrus

significant differences in seed-based FC patterns among three groups after FDR correction. Relative to HCs, FSZ had decreased FC between the right posterior cingulate cortex (PCC) and right superior frontal gyrus (SFG). Compared with CHR, FSZ had decreased FC between the right amygdala and left inferior parietal gyrus (IPG).

### Identify FSZ patients using seed-based FC and cognitive scores

SVM analysis showed that FC between the right PCC and right SFG, BACS-SC and CFT-A scores as features could be used to discriminate FSZ from HC with an accuracy of 83.05%, a sensitivity of 86.67%, and a specificity of 83.87%. Similarly, a combination of FC between the right amygdala and left IPG, BACS-SC and CFT-A scores could discriminate FSZ from CHR with an accuracy of 77.59%, a sensitivity of 96.67% and a specificity of 57.14% (Fig. 4).

### Correlations between FC of rois and eye-tracking data

For FSZ and CHR, FC between the right amygdala and left IPG were negatively correlated with the amplitude of saccades in HS4 and LS2 tasks with background interference ($r$ = -0.28, $p < 0.05$; $r$ = -0.29, $p < 0.05$), and peak velocity of saccades in HS4 and LS2 tasks with background interference ($r$ = -0.27, $p < 0.05$; $r$ = -0.29, $p < 0.05$) after the FDR correction (Figure S2).

## Discussion

The predominant findings support our hypothesis that FSZ displayed decreased cognitive-related FC between the right PCC and right SFG compared with HCs and between the right amygdala and left IPG compared with CHR. Moreover, the BACS-SC and CFT-A scores combined with FC between the right amygdala and left IPG could serve as a potential biomarker for distinguishing FSZ from CHR with high sensitivity. In addition, FSZ

exhibited eye movement abnormalities in SPEM tasks compared with HCs, and eye movement patterns of CHR are similar to HC. These eye movement alterations were associated with cognitive-related FC.

Consistent with previous researches [16, 17], CHR has mild to moderate global cognitive impairments between FSZ and HCs. However, the level of attention and vigilance observed in CHR was higher than FSZ and HCs, suggesting that CHR were in an increased state of attention and vigilance to new stimuli in the environment [51]. Using the CPM algorithm, two cognitive features (BACS-SC and CFT-A) were selected to generate the prediction model, both of which were used to evaluate processing speed. Confirmatory factor analysis in the structure of MCCB indicated that processing speed was a factor in the three-factors MCCB model, and symbol coding was the best single predictor for general cognitive performance [52]. Additionally, another study demonstrated that processing speed and social cognition could best discriminate schizophrenia from HCs [53]. It is reasonable that processing speed reflects the comprehensive application of other cognitive functions, such as executive function, memory, and verbal fluency [8, 53–55]. In this study, both CHR and FSZ showed significant decreases in processing speed compared with HCs, suggesting processing speed is an early and sensitive cognitive indicator for schizophrenia [56].

In the present study, FSZ showed a decrease in FC between the right amygdala and left IPG compared with CHR. As the role of processing threat and learning fear, amygdala serves a more general role in responding to salient stimuli to facilitate the adaptation to goal-related situations, and links to regulate and modulate a diversity of cognitive functions, such as attention, explicit memory, and perception [57, 58]. For example, activated amygdala function was associated with faster performance during the high cognitive load in the working memory task [59]. Prior researches showed that volumes of lateral and basal amygdala nuclei were smaller in FSZ, whereas CHR only had volume deficits in lateral nuclei compared to HCs, suggesting abnormal structural changes in the amygdala were engaged in schizophrenia progression [60, 61]. IPG, consisting of the supramarginal gyrus and adjacent angular gyrus, is a key neural convergence zone of various mental processes involving spatial attention, sensory information, and semantic processing [62, 63]. Previous studies have provided evidence to support the left anterior IFG was activated during semantic processing [64]. Virtual lesions on the left IPG in HCs were reported to interfere with semantic tasks during language comprehension [65, 66]. Other studies have focused on social cognitive function in participants and found activation between the amygdala and IPG was associated with the processing of faces without awareness and gesture planning and execution [67–69]. Our study found that function of attention and verbal learning in FSZ is significantly worse than in CHR, which is consistent with the performance of the IPG and amygdala impairments. Therefore, we speculate that decreased FC between the IPG and amygdala may represent comprehensive cognitive function impairments in FSZ.

Related to HCs, decreased FC between the right PCC and right SFG in FSZ was another important finding in this study, reflecting alterations specific to schizophrenia. PCC is a key component of the default mode network (DMN), implicated in a host of cognitive and affective processing [70]. Prior studies have found that PCC was deactivated during attention and externally directed thought tasks and active during tasks involving internally directed thought, such as daydreaming and memory recollection [71, 72]. SFG is a subarea of the dorsolateral prefrontal cortex (DLPFC), which has extensive interconnections with almost all cortical and subcortical structures. Recent studies on FSZ found that destroyed FCs between the SFG and essential nodes of DMN were associated with processing speed [73]. Thus, we speculate that differences in cognitive function, particularly processing speed, between FSZ and HCs may be due to disturbed neural activity in the right PCC and right SFG.

Results of SVM analysis further supported a combination of FC between the right amygdala and left IPG, BACS-SC and CFT-A scores could serve as early markers for discriminating FSZ from CHR with a high sensitivity of 96.67%, although specificity was relatively low. Similarly, FC between the right PCC and right SFG, BACS-SC and CFT-A scores could be applied as a potential maker for discriminating FSZ from HCs with a sensitivity of 86.67% and a specificity of 83.87%. Previous studies suggested that sensitivity should be more than 70% [74]. Therefore, the sensitivities in this study are acceptable. However, we did not discriminate CHR from HCs for no significant cognitive-related FC features. This result may be partly explained by the attenuation in symptoms and functional abnormalities in CHR. Future studies should include other specific features to distinguish them.

In SPEM tasks, when a participant's eye movement speed is slower than target speed, they compensate for the gap by generating catch-up saccades, which increases peak velocity [75]. FSZ showed decreased accuracy in tracking targets compared to CHR and HCs, as evidenced by significantly higher amplitude and faster saccades. These findings are consistent with previous studies reporting smooth pursuit impairments in schizophrenia and their relatives [76, 77]. In contrast, saccade performance in CHR was more similar to HCs. Although several studies have reported eye movement abnormalities in CHR, our study did not find such abnormalities [39, 78], which may be attributed to differences in task

strategies and disease stage. Additionally, aberrant peak velocities of saccades were observed only in FSZ, suggesting that CHR did not yet exhibit the compensatory catch-up saccades seen in FSZ, and peak velocities of saccades may be a distinguishing feature of fully developed schizophrenia. Furthermore, FC between the right amygdala and left IPG was negatively correlated with saccades' amplitude and peak velocity. It has been suggested that abnormalities in brain regions such as the parietal cortex, prefrontal cortex, thalamus, and basal ganglia may play a crucial role in smooth pursuit impairments in schizophrenia [79, 80]. Parietal cortex is crucial for saccadas control; for instance, stimulation of neurons in the lateral intraparietal sulcus in monkeys triggers saccades [81]. Similarly, stimulation of the parietal eye fields can initiate smooth pursuit eye movements [82], and these fields contain neurons that project to the pursuit region of the frontal eye fields [83]. The amygdala, primarily involved in processing facial features and emotional cues, plays a key role in directing visual attention toward socially relevant stimuli [84]. However, its involvement in non-facial or non-emotional tasks remains unclear. Our results confirm that IPG and amygdala may be involved in SPEM.

This study had several strengths worth noting. For example, FSZ and CHR were recruited in our study to limit potential confounding effects caused by substance and medication use, long illness duration, and age-related neural changes. Second, only a few previous studies have established the relationship between brain regions and clinical features in schizophrenia (e.g., positive symptoms, individualized response to antipsychotic treatment) utilizing the CPM method [85, 86]. To our knowledge, the present research is the first to explore brain-cognitive relationships from whole-brain FC patterns in the early phases of psychosis. Recent studies have shown that mapping intrinsic brain connectivity networks offers valuable insights into human behavior, cognition, and psychiatric disorders [87–89]. Viewing mental illnesses from a symptom network or connectivity perspective may offer a better understanding of their development. Third, the relationships between eye movements and FC network were established, providing a new perspective for in-depth research into alterations in cognitive function.

Some limitations could be listed. First, sample size in our study was small, although the cross-validation method was used to increase reliability and reproducibility [90]. Second, social cognitive function was not evaluated by using appropriate scales for the broad age range of the participants. Finally, our study is a cross-sectional design, which had no information about transitions to psychosis in CHR. CHR includes both patients who may convert to psychosis and those who may not, and the possibility of two independent patterns of brain function could not be excluded. Thus, findings in CHR should be interpreted with caution. Future research should focus on larger sample sizes and longitudinal studies that track the progression of CHR over time.

## Conclusions

This study showed that FSZ and CHR exhibited different patterns of cognitive-related FC and eye movements. Moreover, combining cognitive-related FC and cognitive features may be a reliable biomarker for distinguishing FSZ from CHR. Our findings illustrate potential neuroimaging and cognitive markers for early identification of psychosis that could help prevent schizophrenia in at-risk populations.

### Abbreviations

| | |
|---|---|
| CHR | Clinical high-risk |
| FSZ | First-episode schizophrenia |
| HCs | Healthy controls |
| fMRI | Functional magnetic resonance imaging |
| MFG | Middle frontal gyrus |
| FCS | Functional connectivity strength |
| CPM | Connectome-based predictive modeling |
| SPEM | Smooth pursuit eye movement |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition |
| PANSS | Positive and Negative Syndrome Scale |
| SIPS | Structured Interview for Prodromal Syndromes |
| MCCB | Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery |
| TMT-A | Trail Making Test-Part A |
| BACS-SC | Brief Assessment of Cognition in Schizophrenia-Symbol Coding |
| CFT-A | Category Fluency Test-Animal |
| WMS-SS | Wechsler Memory Scale-spatial span |
| CPT-IP | Continuous Performance Test-Identical Pairs |
| HVLT-R | Hopkins Verbal Learning Test-Revised |
| BVMT-R | Brief Visuospatial Memory Test |
| MSCEIT | Mayer-Salovey-Caruso Emotional Intelligence Test-managing emotions test |
| SCWT | Stroop Colour Word Test |
| ROIs | Regions of interest |
| Lasso | Least Absolute Shrinkage and Selection Operator |
| FDR | False discovery rate |
| SVM | Support vector machine |
| PCC | Posterior cingulate cortex |
| SFG | Superior frontal gyrus |
| IPG | Inferior parietal gyrus |
| DMN | Default mode network |
| DLPFC | Dorsolateral prefrontal cortex |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06747-x.

Supplementary Material 1

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Not applicable.

### Author contributions

ZBC and YPO performed the data analysis and wrote the initial draft. HBL and FL conceptualized the study. PL and DSL preprocessed the MRI data. YW, YL, BL, JPZ, and WBG were responsible for all final revisions and editing.

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**Data availability**
Data is provided within the manuscript or supplementary information files. The remaining data that support the findings of this study are available from the corresponding author upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and relevant Chinese regulations. All participants signed informed consent to study protocols approved by the Ethics Committee of the Second Xiangya Hospital of Central South University.

**Consent for publication**
Written informed consent for publication was obtained from all participants.

**Competing interests**
The authors declare no competing interests.

**Author details**
[1]Department of Psychiatry, National Clinical Research Center for Mental Disorders, and National Center for Mental Disorders, The Second Xiangya Hospital of Central South University, Changsha 410011, Hunan, China
[2]Department of Mental Health Center of Xiangya Hospital, Central South University, Changsha 410008, Hunan, China
[3]Department of Radiology, The Second Xiangya Hospital of Central South University, Changsha 410011, Hunan, China
[4]Department of Radiology, Tianjin Medical University General Hospital, Tianjin 300000, China
[5]Department of Psychiatry, Qiqihar Medical University, Qiqihar 161006, Heilongjiang, China
[6]Center of Mental Health, Inner Mongolia Autonomous Region, Hohhot 010010, China

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**References**

1. Dutt A, Tseng H-H, Fonville L, Drakesmith M, Su L, Evans J, Zammit S, Jones D, Lewis G, David AS. Exploring neural dysfunction in 'clinical high risk' for psychosis: A quantitative review of fMRI studies. J Psychiatr Res. 2015;61:122–34.
2. Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rössler A, Schultze-Lutter F, Keshavan M, Wood S, Ruhrmann S, Seidman LJ et al. The psychosis High-Risk state. JAMA Psychiatry 2013, 70(1).
3. Buckley PF. Predicting psychosis: Meta-analysis of transition outcomes in individuals at high clinical risk. Yearbook Psychiatry Appl Mental Health. 2013;2013:111–2.
4. Fusar-Poli P, Yung AR, McGorry P, van Os J. Lessons learned from the psychosis high-risk State: towards a general staging model of prodromal intervention. Psychol Med. 2013;44(1):17–24.
5. Glenthøj LB, Hjorthøj C, Kristensen TD, Davidson CA, Nordentoft M. The effect of cognitive remediation in individuals at ultra-high risk for psychosis: a systematic review. Npj Schizophrenia 2017, 3(1).
6. McCutcheon RA, Keefe RSE, McGuire PK. Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. Mol Psychiatry. 2023;28(5):1902–18.
7. Javitt DC. Cognitive impairment associated with schizophrenia: from pathophysiology to treatment. Annu Rev Pharmacol Toxicol. 2023;63(1):119–41.
8. Sheffield JM, Karcher NR, Barch DM. Cognitive deficits in psychotic disorders: A lifespan perspective. Neuropsychol Rev. 2018;28(4):509–33.
9. Catalan A, Salazar de Pablo G, Aymerich C, Damiani S, Sordi V, Radua J, Oliver D, McGuire P, Giuliano AJ, Stone WS et al. Neurocognitive functioning in individuals at clinical high risk for psychosis. JAMA Psychiatry 2021, 78(8).
10. Gold S, Arndt S, Nopoulos P, O'Leary DS, Andreasen NC. Longitudinal study of cognitive function in First-Episode and Recent-Onset schizophrenia. Am J Psychiat. 1999;156(9):1342–8.
11. Bora E, Murray RM. Meta-analysis of cognitive deficits in Ultra-high risk to psychosis and First-Episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis? Schizophr Bull. 2013;40(4):744–55.
12. Üçok A, Direk N, Koyuncu A, Keskin-Ergen Y, Yüksel Ç, Güler J, Karadayı G, Akturan E, Devrim-Üçok M. Cognitive deficits in clinical and Familial high risk groups for psychosis are common as in first episode schizophrenia. Schizophr Res. 2013;151(1–3):265–9.
13. Anda L, Brønnick KK, Johannessen JO, Joa I, Kroken RA, Johnsen E, Rettenbacher M, Fathian F, Løberg E-M. Cognitive profile in ultra high risk for psychosis and schizophrenia: A comparison using coordinated norms. Front Psychiatry 2019, 10.
14. Liu Y, Wang G, Jin H, Lyu H, Liu Y, Guo W, Shi C, Meyers J, Wang J, Zhao J, et al. Cognitive deficits in subjects at risk for psychosis, first-episode and chronic schizophrenia patients. Psychiatry Res. 2019;274:235–42.
15. Chu AOK, Chang WC, Chan SKW, Lee EHM, Hui CLM, Chen EYH. Comparison of cognitive functions between first-episode schizophrenia patients, their unaffected siblings and individuals at clinical high-risk for psychosis. Psychol Med. 2018;49(11):1929–36.
16. Hou C-L, Xiang Y-T, Wang Z-L, Everall I, Tang Y, Yang C, Xu M-Z, Correll CU, Jia F-J. Cognitive functioning in individuals at ultra-high risk for psychosis, first-degree relatives of patients with psychosis and patients with first-episode schizophrenia. Schizophr Res. 2016;174(1–3):71–6.
17. Hauser M, Zhang J-P, Sheridan EM, Burdick KE, Mogil R, Kane JM, Auther A, Carrión RE, Cornblatt BA, Correll CU. Neuropsychological test performance to enhance identification of subjects at clinical high risk for psychosis and be most promising for predictive algorithms for conversion to psychosis. J Clin Psychiatry. 2017;78(01):e28–40.
18. Cui H, Giuliano AJ, Zhang T, Xu L, Wei Y, Tang Y, Qian Z, Stone LM, Li H, Whitfield-Gabrieli S, et al. Cognitive dysfunction in a psychotropic medication-naïve, clinical high-risk sample from the ShangHai-At-Risk-for-Psychosis (SHARP) study: associations with clinical outcomes. Schizophr Res. 2020;226:138–46.
19. Zheng W, Zhang Q-E, Cai D-B, Ng CH, Ungvari GS, Ning Y-P, Xiang Y-T. Neurocognitive dysfunction in subjects at clinical high risk for psychosis: A meta-analysis. J Psychiatr Res. 2018;103:38–45.
20. Bolt LK, Amminger GP, Farhall J, McGorry PD, Nelson B, Markulev C, Yuen HP, Schäfer MR, Mossaheb N, Schlögelhofer M, et al. Neurocognition as a predictor of transition to psychotic disorder and functional outcomes in ultra-high risk participants: findings from the NEURAPRO randomized clinical trial. Schizophr Res. 2019;206:67–74.
21. Joyce EM, Roiser JP. Cognitive heterogeneity in schizophrenia. Curr Opin Psychiatry. 2007;20(3):268–72.
22. Meyer-Lindenberg A. From maps to mechanisms through neuroimaging of schizophrenia. Nature. 2010;468(7321):194–202.
23. Vucurovic K, Caillies S, Kaladjian A. Neural correlates of mentalizing in individuals with clinical high risk for schizophrenia: ALE Meta-Analysis. Front Psychiatry 2021, 12.
24. Li RR, Lyu HL, Liu F, Lian N, Wu RR, Zhao JP, Guo WB. Altered functional connectivity strength and its correlations with cognitive function in subjects with ultra-high risk for psychosis at rest. CNS Neurosci Ther. 2018;24(12):1140–8.
25. Allen P, Seal ML, Valli I, Fusar-Poli P, Perlini C, Day F, Wood SJ, Williams SC, McGuire PK. Altered prefrontal and hippocampal function during verbal encoding and recognition in people with prodromal symptoms of psychosis. Schizophr Bull. 2009;37(4):746–56.
26. Allen P, Luigjes J, Howes OD, Egerton A, Hirao K, Valli I, Kambeitz J, Fusar-Poli P, Broome M, McGuire P. Transition to psychosis associated with prefrontal and subcortical dysfunction in ultra High-Risk individuals. Schizophr Bull. 2012;38(6):1268–76.
27. Sabb FW, van Erp TGM, Hardt ME, Dapretto M, Caplan R, Cannon TD, Bearden CE. Language network dysfunction as a predictor of outcome in youth at clinical high risk for psychosis. Schizophr Res. 2010;116(2–3):173–83.
28. Marjoram D, Job DE, Whalley HC, Gountouna V-E, McIntosh AM, Simonotto E, Cunningham-Owens D, Johnstone EC, Lawrie S. A visual joke fMRI investigation into Theory of Mind and enhanced risk of schizophrenia. *NeuroImage* 2006, 31(4):1850–1858.
29. Shen X, Finn ES, Scheinost D, Rosenberg MD, Chun MM, Papademetris X, Constable RT. Using connectome-based predictive modeling to predict individual behavior from brain connectivity. Nat Protoc. 2017;12(3):506–18.

30. Sui J, Jiang R, Bustillo J, Calhoun V. Neuroimaging-based individualized prediction of cognition and behavior for mental disorders and health: methods and promises. Biol Psychiatry. 2020;88(11):818–28.
31. Wu X, Yang Q, Xu C, Huo H, Seger CA, Peng Z, Chen Q. Connectome-based predictive modeling of compulsion in obsessive–compulsive disorder. Cereb Cortex. 2023;33(4):1412–25.
32. Barron DS, Gao S, Dadashkarimi J, Greene AS, Spann MN, Noble S, Lake EMR, Krystal JH, Constable RT, Scheinost D. Transdiagnostic, Connectome-Based prediction of memory constructs across psychiatric disorders. Cereb Cortex. 2021;31(5):2523–33.
33. Lake EMR, Finn ES, Noble SM, Vanderwal T, Shen X, Rosenberg MD, Spann MN, Chun MM, Scheinost D, Constable RT. The functional brain organization of an individual allows prediction of measures of social abilities transdiagnostically in autism and Attention-Deficit/Hyperactivity disorder. Biol Psychiatry. 2019;86(4):315–26.
34. Morita K, Miura K, Fujimoto M, Yamamori H, Yasuda Y, Kudo N, Azechi H, Okada N, Koshiyama D, Ikeda M, et al. Eye movement abnormalities and their association with cognitive impairments in schizophrenia. Schizophr Res. 2019;209:255–62.
35. Hutton SB. Cognitive control of saccadic eye movements. Brain Cogn. 2008;68(3):327–40.
36. Beedie SA, Benson PJ, Giegling I, Rujescu D, St. Clair DM. Smooth pursuit and visual scanpaths: independence of two candidate oculomotor risk markers for schizophrenia. World J Biol Psychiatry. 2011;13(3):200–10.
37. Gottlieb JP, MacAvoy MG, Bruce CJ. Neural responses related to smooth-pursuit eye movements and their correspondence with electrically elicited smooth eye movements in the primate frontal eye field. J Neurophysiol. 1994;72(4):1634–53.
38. Ilg UJ, Thier P. The neural basis of smooth pursuit eye movements in the rhesus monkey brain. Brain Cogn. 2008;68(3):229–40.
39. Obyedkov I, Skuhareuskaya M, Skugarevsky O, Obyedkov V, Buslauski P, Skuhareuskaya T, Waszkiewicz N. Saccadic eye movements in different dimensions of schizophrenia and in clinical high-risk state for psychosis. BMC Psychiatry 2019, 19(1).
40. Ma X, Zheng W, Li C, Li Z, Tang J, Yuan L, Ouyang L, Jin K, He Y, Chen X. Decreased regional homogeneity and increased functional connectivity of default network correlated with neurocognitive deficits in subjects with genetic high-risk for schizophrenia: A resting-state fMRI study. Psychiatry Res 2019, 281.
41. Zarogianni E, Storkey AJ, Johnstone EC, Owens DGC, Lawrie SM. Improved individualized prediction of schizophrenia in subjects at Familial high risk, based on neuroanatomical data, schizotypal and neurocognitive features. Schizophr Res. 2017;181:6–12.
42. Krishna N, O'Neill H, Sánchez-Morla EM, Thaker GK. Long range frontal/posterior phase synchronization during remembered pursuit task is impaired in schizophrenia. Schizophr Res. 2014;157(1–3):198–203.
43. Agathos CP, Bernardin D, Huchet D, Scherlen A-C, Assaiante C, Isableu B. Sensorimotor and cognitive factors associated with the age-related increase of visual field dependence: a cross-sectional study. Age 2015, 37(4).
44. Yan C-G, Wang X-D, Zuo X-N, Zang Y-F. DPABI: data processing & analysis for (Resting-State) brain imaging. Neuroinformatics. 2016;14(3):339–51.
45. Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L, Yang Z, Chu C, Xie S, Laird AR, et al. The human brainnetome atlas: A new brain atlas based on connectional architecture. Cereb Cortex. 2016;26(8):3508–26.
46. Kaushik S, Sabharwal A, Grover G. Extracting relevant predictors of the severity of mental illnesses from clinical information using regularisation regression models. Stat Transition New Ser. 2022;23(2):129–52.
47. Yassin W, Nakatani H, Zhu Y, Kojima M, Owada K, Kuwabara H, Gonoi W, Aoki Y, Takao H, Natsubori T et al. Machine-learning classification using neuroimaging data in schizophrenia, autism, ultra-high risk and first-episode psychosis. Translational Psychiatry 2020, 10(1).
48. Orrù G, Pettersson-Yeo W, Marquand AF, Sartori G, Mechelli A. Using support vector machine to identify imaging biomarkers of neurological and psychiatric disease: A critical review. Neurosci Biobehavioral Reviews. 2012;36(4):1140–52.
49. Yu JS, Xue AY, Redei EE, Bagheri N. A support vector machine model provides an accurate transcript-level-based diagnostic for major depressive disorder. Translational Psychiatry. 2016;6(10):e931–931.
50. Vieira S, Gong Q-y, Pinaya WHL, Scarpazza C, Tognin S, Crespo-Facorro B, Tordesillas-Gutierrez D, Ortiz-García V, Setien-Suero E, Scheepers FE, et al. Using machine learning and structural neuroimaging to detect first episode psychosis: reconsidering the evidence. Schizophr Bull. 2020;46(1):17–26.
51. Kim W-S, Shen G, Liu C, Kang N-I, Lee K-H, Sui J, Chung Y-C. Altered amygdala-based functional connectivity in individuals with attenuated psychosis syndrome and first-episode schizophrenia. Sci Rep 2020, 10(1).
52. Burton CZ, Vella L, Harvey PD, Patterson TL, Heaton RK, Twamley EW. Factor structure of the MATRICS consensus cognitive battery (MCCB) in schizophrenia. Schizophr Res. 2013;146(1–3):244–8.
53. Kern RS, Gold JM, Dickinson D, Green MF, Nuechterlein KH, Baade LE, Keefe RSE, Mesholam-Gately RI, Seidman LJ, Lee C, et al. The MCCB impairment profile for schizophrenia outpatients: results from the MATRICS psychometric and standardization study. Schizophr Res. 2011;126(1–3):124–31.
54. Bachman P, Reichenberg A, Rice P, Woolsey M, Chaves O, Martinez D, Maples N, Velligan DI, Glahn DC. Deconstructing processing speed deficits in schizophrenia: application of a parametric digit symbol coding test. Schizophr Res. 2010;118(1–3):6–11.
55. Xiao Y, Liao W, Long Z, Tao B, Zhao Q, Luo C, Tamminga CA, Keshavan MS, Pearlson GD, Clementz BA, et al. Subtyping schizophrenia patients based on patterns of structural brain alterations. Schizophr Bull. 2022;48(1):241–50.
56. Dickinson D, Ramsey ME, Gold JM. Overlooking the Obvious. Arch Gen Psychiatry 2007, 64(5).
57. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. Nat Rev Neurosci. 2009;10(6):423–33.
58. West HV, Burgess GC, Dust J, Kandala S, Barch DM. Amygdala activation in cognitive task fMRI varies with individual differences in cognitive traits. Cogn Affect Behav Neurosci. 2021;21(1):254–64.
59. Schaefer A, Braver TS, Reynolds JR, Burgess GC, Yarkoni T, Gray JR. Individual differences in amygdala activity predict response speed during working memory. J Neurosci. 2006;26(40):10120–8.
60. Fan F, Xiang H, Tan S, Yang F, Fan H, Guo H, Kochunov P, Wang Z, Hong LE, Tan Y. Subcortical structures and cognitive dysfunction in first episode schizophrenia. Psychiatry Research: Neuroimaging. 2019;286:69–75.
61. Armio R-L, Laurikainen H, Ilonen T, Walta M, Salokangas RKR, Koutsouleris N, Hietala J, Tuominen L. Amygdala subnucleus volumes in psychosis high-risk state and first-episode psychosis. Schizophr Res. 2020;215:284–92.
62. Torrey EF. Schizophrenia and the inferior parietal lobule. Schizophr Res. 2007;97(1–3):215–25.
63. Chieffi S, Ilardi CR, Iavarone A. Parietal lobe dysfunction in schizophrenia: A review. Curr Psychiatry Reviews. 2018;14(2):71–83.
64. Numssen O, Bzdok D, Hartwigsen G. Functional specialization within the inferior parietal lobes across cognitive domains. Elife 2021, 10.
65. Hartwigsen G, Bzdok D, Klein M, Wawrzyniak M, Stockert A, Wrede K, Classen J, Saur D. Rapid short-term reorganization in the Language network. Elife 2017, 6.
66. Sliwinska MW, James A, Devlin JT. Inferior parietal lobule contributions to visual word recognition. J Cogn Neurosci. 2015;27(3):593–604.
67. Stegmayer K, Bohlhalter S, Vanbellingen T, Federspiel A, Wiest R, Müri RM, Strik W, Walther S. Limbic interference during social action planning in schizophrenia. Schizophr Bull. 2018;44(2):359–68.
68. Troiani V, Schultz RT. Amygdala, pulvinar, and inferior parietal cortex contribute to early processing of faces without awareness. Front Hum Neurosci 2013, 7.
69. Rizzo G, Milardi D, Bertino S, Basile GA, Di Mauro D, Calamuneri A, Chillemi G, Silvestri G, Anastasi G, Bramanti A, et al. The limbic and sensorimotor pathways of the human amygdala: A structural connectivity study. Neuroscience. 2018;385:166–80.
70. Busler JN, Yanes JA, Bird RT, Reid MA, Robinson JL. Differential functional patterns of the human posterior cingulate cortex during activation and deactivation: a meta-analytic connectivity model. Exp Brain Res. 2019;237(9):2367–85.
71. Singh KD, Fawcett IP. Transient and linearly graded deactivation of the human default-mode network by a visual detection task. NeuroImage. 2008;41(1):100–12.
72. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network. Ann N Y Acad Sci. 2008;1124(1):1–38.
73. Qiu X, Lu S, Zhou M, Yan W, Du J, Zhang A, Xie S, Zhang R. 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.
74. Gong Q, Li L, Tognin S, Wu Q, Pettersson-Yeo W, Lui S, Huang X, Marquand AF, Mechelli A. Using structural neuroanatomy to identify trauma survivors with and without post-traumatic stress disorder at the individual level. Psychol Med. 2013;44(1):195–203.

75. Levy DL, Sereno AB, Gooding DC, O'Driscoll GA. Eye tracking dysfunction in schizophrenia: characterization and pathophysiology. Behav Neurobiol Schizophrenia its Treat 2010.
76. Lyu H, St Clair D, Wu R, Benson PJ, Guo W, Wang G, Liu Y, Hu S, Zhao J. Eye movement abnormalities can distinguish First-Episode schizophrenia, chronic schizophrenia, and prodromal patients from healthy controls. Schizophrenia Bull Open 2023, 4(1).
77. Ivleva EI, Moates AF, Hamm JP, Bernstein IH, O'Neill HB, Cole D, Clementz BA, Thaker GK, Tamminga CA. Smooth pursuit eye movement, prepulse Inhibition, and auditory paired stimuli processing endophenotypes across the Schizophrenia-Bipolar disorder psychosis dimension. Schizophr Bull. 2014;40(3):642–52.
78. Lee K-H, Williams LM. Eye movement dysfunction as a biological marker of risk for schizophrenia. Australian New Z J Psychiatry. 2018;34(1suppl):A91–100.
79. Kaufmann L. The Oxford handbook of eye movements. Perception. 2011;40(11):1393–4.
80. Hikosaka O, Takikawa Y, Kawagoe R. Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol Rev. 2000;80(3):953–78.
81. Thier P, Andersen RA. Electrical microstimulation distinguishes distinct saccade-related areas in the posterior parietal cortex. J Neurophysiol. 1998;80(4):1713–35.
82. Kurylo DD, Skavenski AA. Eye movements elicited by electrical stimulation of area PG in the monkey. J Neurophysiol. 1991;65(6):1243–53.
83. Stanton GB, Friedman HR, Dias EC, Bruce CJ. Cortical afferents to the smooth-pursuit region of the macaque Monkey's frontal eye field. Exp Brain Res. 2005;165(2):179–92.
84. Cao R, Li X, Brandmeir NJ, Wang S. Encoding of facial features by single neurons in the human amygdala and hippocampus. Commun Biology 2021, 4(1).
85. Cao H, Lencz T, Gallego JA, Rubio JM, John M, Barber AD, Birnbaum ML, Robinson DG, Malhotra AK. A functional Connectome-Based neural signature for individualized prediction of antipsychotic response in First-Episode psychosis. Am J Psychiat. 2023;180(11):827–35.
86. Yuan L, Ma X, Li D, Li Z, Ouyang L, Fan L, Yang Z, Zhang Z, Li C, He Y et al. Abnormal brain network interaction associated with positive symptoms in Drug-Naive patients with First-Episode schizophrenia. Front Psychiatry 2022, 13.
87. Zhang X, Xu R, Ma H, Qian Y, Zhu J. Brain structural and functional damage network localization of suicide. Biol Psychiatry. 2024;95(12):1091–9.
88. Cheng Y, Cai H, Liu S, Yang Y, Pan S, Zhang Y, Mo F, Yu Y, Zhu J. Brain network localization of Gray matter atrophy and neurocognitive and social cognitive dysfunction in schizophrenia. Biol Psychiatry. 2025;97(2):148–56.
89. Mo F, Zhao H, Li Y, Cai H, Song Y, Wang R, Yu Y, Zhu J. Network localization of state and trait of auditory verbal hallucinations in schizophrenia. Schizophr Bull. 2024;50(6):1326–36.
90. Chen X, Lu B, Yan CG. Reproducibility of R-fMRI metrics on the impact of different strategies for multiple comparison correction and sample sizes. Hum Brain Mapp. 2017;39(1):300–18.

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