Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Association between abnormalities in face-processing neural circuitry and clinical symptoms in patients with first-episode schizophrenia

Qijie Kuang
Guangzhou Psychiatric Hospital
Xue He
Guangzhou Psychiatric Hospital
Sumiao Zhou
Guangzhou Psychiatric Hospital
Zerui Liu
Guangzhou Psychiatric Hospital
Xiaohua Lu
Shenzhen Third People's Hospital
Xufei Zhu
Guangzhou Psychiatric Hospital
Jiaqi Liu
Guangzhou Psychiatric Hospital
Guangxing Deng
Guangzhou Psychiatric Hospital
Yingjun Zheng
Guangzhou Psychiatric Hospital
Shenglin She
shenglinshe@gzhmu.edu.cn

Guangzhou Psychiatric Hospital

Research Article

Keywords: schizophrenia, neuroimaging, fMRI, face perception, MFG

Posted Date: June 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9919468/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background Soial cognitive deficits in schizophrenia are linked to facial information processing difficulties, though the specific mechanisms remain unclear.

Method Thirty-one patients with first-episode schizophrenia (FES) and thirty-three healthy controls (HCs) underwent fMRI and structural MRI scans. Face-related brain regions were defined as areas where HCs showed stronger responses to upright faces versus disrupted faces. We compared activation values during tasks and resting-state to identify functional changes in FES patients and analyzed correlations with clinical symptoms.

Results HC scans defined bilateral inferior occipital-temporal (IOT) cortex, thalamus, middle frontal gyrus (MFG), and ventromedial prefrontal cortex as face-related regions. Compared to HCs, FES patients exhibited significantly decreased activation in the bilateral MFG in response to both upright and inverted face stimuli. Resting-state fMRI revealed decreased fALFF in the bilateral IOT and left thalamus, as well as decreased ReHo in the left IOT and thalamus. Crucially, bilateral MFG signal intensity was negatively correlated with negative symptom scores, while the left MFG correlated with positive symptom scores. Additionally, fALFF values in the left IOT and thalamus correlated with cognitive symptoms.

Conclusion FES patients show distinct functional alterations in facial-processing brain networks. These changes are significantly associated with clinical symptomatology, suggesting potential interactions between social cognitive deficits and schizophrenia symptom profiles.

Background

Schizophrenia (SZ) is a severe mental disorder with an unclear etiology. Its prevalence has increased by 65% over the past three decades, affecting approximately 1% of the global population [1, 2]. SZ is characterized by positive, negative, and cognitive symptoms, which severely impair patients' social functioning, impose a heavy economic burden on families, and rank SZ among the top ten leading causes of disability worldwide, resulting in substantial social costs.

Cognitive impairment represents the most prominent affected domain in SZ [1, 3]. Cognitive symptoms in SZ patients encompass neurocognitive and social cognitive deficits [4]. Social cognition refers to the ability to perceive others' intentions and emotions to guide social behaviors, which is critical for interpreting others' facial expressions, personal traits, interpersonal relationships, and behavioral cues. Patients with SZ commonly exhibit widespread social cognitive impairments, which are closely linked to poor functional outcomes, impaired interpersonal problem-solving ability, diminished social competence, a progressive disease course, higher relapse rates, and increased unemployment risk.

Face processing constitutes a core component of social cognition. Facial expressions convey abundant personal and communicative information; thus, the ability to recognize facial emotions and individual identities is indispensable for daily social interactions. Behavioral studies have demonstrated that SZ

patients show deficits in facial identity recognition, gender discrimination, age judgment, facial memory, and facial detection tasks [5]. Individuals with SZ display impaired facial information processing across all cognitive stages, which may be attributed to deficits in basic facial feature recognition, facial memory, facial detection, and emotional recognition processing [6]. She et al. verified facial recognition impairment in SZ patients via visual search and working memory tasks [7]. Facial inversion paradigms further revealed facial recognition deficits associated with impaired facial feature processing [8]. Lee et al. reported that facial emotion recognition deficits in SZ patients were correlated with the severity of negative symptoms [9]. Collectively, facial processing deficits in SZ may stem from compromised holistic face processing, which is closely mediated by face-selective brain regions such as the fusiform gyrus [6].

Face perception is one of the most sophisticated cognitive tasks of the human visual system and requires coordinated activation across multiple brain regions. Recent functional magnetic resonance imaging (fMRI) studies have elucidated the neural substrates of face processing and proposed a neurofunctional framework consisting of a core system and an extended system [10]. The core system comprises the occipital face area (OFA), fusiform face area (FFA), and posterior superior temporal sulcus (pSTS) [11], which are primarily responsible for early facial structure encoding [12], extraction of identity-related invariant facial representations, and processing of dynamic social cues, respectively [13]. The extended system not only participates in facial recognition but also interacts with attentional, emotional, and semantic memory circuits to support familiar face identification [14].

Most existing face processing studies have focused on healthy individuals; therefore, the neural mechanisms underlying facial processing deficits in SZ remain poorly understood. Previous studies have identified functional abnormalities in the fusiform gyrus during facial identity processing among SZ patients [15]. Quintana et al. observed reduced activation in the right FFA during face-matching tasks in SZ patients relative to healthy controls (HCs) [16]. Another study reported disrupted functional connectivity between the visual cortex and the right FFA in this population [17]. Structural imaging studies have detected decreased gray matter volume (GMV) in the bilateral fusiform gyrus, while inconsistent functional activation patterns indicate that functional abnormalities cannot be fully explained by structural atrophy alone [18]. Reduced activation has also been documented in the early visual cortices (V1–V3), hippocampus, and amygdala during facial discrimination and memory tasks in SZ patients [15].

Although neuroimaging studies have identified functional alterations in face-related brain regions in SZ, the reported findings remain inconsistent. To address these limitations, the present study systematically investigated neuroimaging alterations in face-associated brain regions in patients with first-episode schizophrenia (FES), and further explored the correlations between functional brain changes and clinical symptoms. Given that structural brain abnormalities may act as confounding factors for functional alterations, structural magnetic resonance imaging (sMRI) results were included as covariates in statistical analyses to control for structural confounding effects. This study aims to provide novel insights into the neurophysiological mechanisms underlying the pathogenesis of schizophrenia.

Materials and methods

Participants

The study included patients from the Affiliated Brain Hospital of Guangzhou Medical University. The inclusion criteria were as follows: (1) met DSM-IV criteria for SZ; (2) were aged 18–50 years; (3) were right-handed; (4) had a disease duration ≤ 2 years and medication history ≤ 6 months; (5) had a PANSS total score ≥ 50; and (6) had normal or corrected-to-normal visual acuity. Exclusion criteria comprised other DSM-IV psychiatric disorders, history of organic disease, MRI contraindications, or inability to complete the MRI protocol.

HCs were matched to patients on sex, age, and education, and were excluded if they had a personal or family history of psychiatric illness. Finally, thirty-one FES patients and 33 HCs were enrolled. All participants provided written informed consent in accordance with the hospital's Medical Ethics Committee. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Clinical evaluation

The Positive and Negative Symptom Scale (PANSS) was used to assess the psychotic symptoms of the patients[19]. This study was statistically analysed using the five-factor model proposed by Wallwork, which selected 22 of the entries in the PANSS to construct a five-factor model, including positive symptoms (P1, P3, P6, and G9), negative symptoms (N1, N2, N3, N4, N6, G7, G13, and G16), cognitive symptoms (P2, N5, and G11), excitement symptoms (P4, P7, and G8, and G14), and affective symptoms (G2, G3, and G6) [20]. Evaluations were performed by two attending physicians who passed the conformance test.

Functional MRI Task

During the task-state fMRI scan, each subject performed the one-back task. The stimuli were viewed through a screen during the task. The subject was asked to press the "1" key with the right index finger when the image appeared twice in a row to ensure that he or she was observing the image, and the button response could be observed by the tester in real time. If no button response was detected, a new acquisition was needed. Prior to the experiment, all faces were preprocessed in Photoshop to exclude distractors such as hair, ears, and facial contours, and nonface stimuli were also preprocessed to ensure that the luminance was the same as that of the face stimuli. This experiment used a block design that was run a total of five times, each containing 10 blocks, including five block stimuli for upright faces, inverted faces, happy faces, objects, and disorganized faces. Half of the face stimuli were male, and half were female. All the faces used in the experiment were selected from the Chinese Face Affective

Pictures System (CFAPS) [21], in which all subjects have provided written consent for publication. Cartoon images were used for the object pictures. The duration of each run was 252 seconds, and the duration of each block was 24 seconds. The subject was required to gaze at the “+" in the centre of the screen for 12 seconds before the blocks were presented. The blocks were then presented, each consisting of a stimulus that lasted 12 seconds and a blank screen that lasted 12 seconds. This procedure is shown in Fig. 1.

(Fig. 1)

MRI data acquisition

Imaging data were acquired by the attending or higher-level professional technicians of the Department of Radiology of the Affiliated Brain Hospital of Guangzhou Medical University. All the subjects were scanned with a Philips 3.0 T MRI system. T1 structural images were acquired first, and the images without obvious morphological abnormalities were entered into the subsequent scanning sequence. T1 structural images were obtained using a planar gradient echo imaging sequence with the following parameters: repetition time (TR) = 8.2 ms, echo time (TE) = 3.8 ms, flip angle = 7°, matrix = 256 × 256, thickness = 1.0 mm, and number of scanning layers = 165. The fMR images were acquired using a fast spin—echo planar T2-weighted imaging sequence with the following scanning parameters: TR = 2,000 ms, TE = 30 ms, flip angle = 90°, field of view = 192 × 192 mm, matrix = 64 × 64, thickness = 4.0 mm, and scanning layers = 33. The task-state fMRI data were acquired at a total of 126 time points, while the resting-state fMRI (rs-fMRI) data were acquired at 240 time points. During the scan, the head of the subject was immobilized with support foam pads and noise was minimized with rubber earplugs. The subjects were asked to remain awake during the scan.

Data preprocessing

Task-State fMRI

The fMRI data require head movements of less than 2 mm in translation and less than 2° in rotation. Task-state fMRI data were analysed and processed using SPM12 software (http://www.fl.ion.ucl.ac.uk/spm/software/spm12) in MATLAB 2013b (MathWorks Inc.). The preprocessing procedure included slice timing correction, realignment, spatial standardization (normalized by using the conventional EPI template), and smoothing with an 8-mm full width at half maximum Gaussian kernel.

The general linear model (GLM) was applied for the first-level fMRI analysis using Statistical Parametric Mapping software. Brain activation maps were obtained for upright faces, inverted faces, happy faces, objects, and disorganized faces by comparing blank stimuli to task stimuli using first-order analyses based on the stimulus appearance time. In a paired-samples t test, brain regions presenting increased

activation in HCs in response to upright face stimulation compared with those in response to disorganized face stimulation were defined as face-related brain regions. The results were subjected to family-wise error (FWE) correction, and $P < 0.05$ was defined as statistically significant. Face-related brain regions were defined as regions of interest (ROIs). Signals for the two groups of ROIs for upright faces, inverted faces, happy faces, and object stimuli were extracted using the RESTPLUS toolkit for subsequent between-group comparisons.

rs-fMRI

Rs-fMRI data were processed using the SPM12-based RESTplus toolkit. After discarding the first 10 volumes, the remaining steps included slice timing, realignment, normalization, detrending, nuisance regression, and smoothing (8-mm FWHM). Fractional amplitude of low-frequency fluctuations (fALFF) and regional homogeneity (ReHo) were calculated to assess spontaneous brain activity [22, 23]. Normalized fALFF is derived by transforming the time series into the frequency domain power spectrum via Fast Fourier Transform (FFA). In contrast, mReHo is calculated using Kendall's coefficient of concordance. Signal values within the predefined regions of interest (ROIs) are then extracted for subsequent analysis.

sMRI

T1-weighted images were processed using SPM8 (Version r6913) with the VBM8 toolbox. Images were segmented into grey matter (GM), white matter (WM), and CSF, and normalized to MNI space.GMV and WMV were obtained by multiplying the GM and WM concentration maps, respectively, with the nonlinear determinants derived from the spatial normalization step. Finally, GMV and WMV maps were smoothed (8-mm FWHM) and ROI-based signals were extracted.

Statistical analysis

Independent sample t tests and chi-square tests were used to analyse the basic demographic and descriptive characteristics. For categorical variables, the chi-square test was used. For continuous variables that conformed to a normal distribution, independent samples t tests were used. Two × four factor analysis of variance (ANOVA) was used to analyse activation values in the ROIs between the patient and healthy control subgroups under four visual conditions (upright face, inverted face, happy face, and object). The stimulation was a within-subject factor, and the group was a between-subject factor. If an interaction effect existed between the two factors, simple effects analysis was used to compare the between-group differences in ROI activation values; otherwise, independent samples t tests were used for comparison. ROI values with between-group differences were further correlated with clinical symptom scores.

Pearson’s correlation analysis was used when the variables were normally distributed, and Spearman’s correlation analysis was used when they were not normally distributed. After the identification of a correlation in Pearson’s correlation analysis, a partial correlation analysis was performed to exclude the effects of potential confounding variables, including sex, age, years of education, duration of illness, dose of antipsychotic drugs and structure. All continuous values are reported as the means ± SDs, and all statistical analyses were performed using two-sided tests with a significance level (α) of 0.05. Statistical analyses were performed using SPSS version 22.0.

Results

Demographic and clinical characteristics

A total of 33 HCs and 31 patients with FES participated in this study. However, 2 HCs were excluded from further analysis because of the complete absence of task-related fMRI results. No significant differences were observed between the two groups regarding sex ($\chi^2 = 0.58$; $P = 0.446$), age ($t = 0.34$; $P = 0.737$) or education ($t = 0.68$; $P = 0.507$). The equivalent doses of chlorpromazine in patients with FES were calculated according to the methods of Gardner et al. [24]. Detailed demographic data and patient characteristics are presented in Table 1.

Table 1
Demographic and clinical characteristics of the subjects

items	patients with FES (n = 31)	HCs (n = 31)	χ^2/t	*P value*
Gender (male/female)	17/14	14/17	0.58[b]	0.446
Age (years)	24.97 ± 6.83	24.45 ± 5.09	0.34[c]	0.737
Education (years)	11.10 ± 3.26	11.65 ± 3.21	0.68[c]	0.507
Duration of illness (months)	8.48 ± 7.00	-	-	-
Antipsychotics drug use (mg)[a]	222.15 ± 244.38	-	-	-
PANSS_Negative symptom	18.42 ± 4.76	-	-	-
PANSS_Cognitive symptom	4.19 ± 1.72	-	-	-
PANSS_Positive symptom	14.35 ± 4.03	-	-	-
PANSS_Excitement symptom	7.29 ± 3.48	-	-	-
PANSS_Affective Symptom	5.55 ± 2.35	-	-	-

Values are presented as mean (s ± d.). FES, first-episode schizophrenia; HC, healthy controls; SD, Standard Deviation; NA, not applicable; PANSS, positive and negative syndrome scale

a Chlorpromazine equivalent doses were calculated; b presents chi-square analysis; c presents independent samples *t*-test analysis

(Table 1)

Localization of face-related brain regions

Brain regions presenting increased activation in response to faces were identified and defined as face-related brain regions based on a comparison of both upright and disorganized faces in the task state analysis of HCs. The bilateral inferior occipital-temporal (IOT) cortex, bilateral thalamus, bilateral middle frontal gyrus (MFG), and ventral medial prefrontal cortex (VMPFC) showed significantly increased activation in response to upright faces compared with the response to disorganized faces (FWE-corrected, $P < 0.01$; > 20 voxels). These data are shown in Table 2 and Fig. 2E.

Table 2
Face-related brain regions

Brain region	Peak MNI coordinates			BA	t value	*P* (FWE_corrected)	Cluster size (voxel)
	x	y	z				
Right IOT cortex	45	-51	-24	-	9.671	< 0.01	181
Left IOT cortex	-39	-78	-12	-	10.118	< 0.01	132
Right thalamus	12	-12	9	-	9.255	< 0.01	85
Left thalamus	-18	-12	0	-	9.375	< 0.01	77
Right MFG	39	12	27	-	10.197	< 0.01	243
Left MFG	-42	0	57	6	8.985	< 0.01	97
VMPFC	6	18	51	8	9.613	< 0.01	174

MNI, Montreal Neurological Institute; BA, Brodmann Area; FWE, Family-Wise Error; IOT, inferior occipital-temporo; MFG, middle frontal gyrus; VMPFC, ventral medial prefrontal cortex

(Table 2)

Task-State Functional Responses of face-related brain regions in FES

We compared face-related brain region activation between two groups under different visual stimuli. The stimulus-group interaction was not significant (F = 0.71, *P* = 0.547), but the main effects of group (F = 5.77, *P* = 0.017) and stimulus (F = 6.38, *P* < 0.001) were significant. Bonferroni-corrected post hoc analyses showed inverted face stimuli induced significantly lower activation than upright faces, happy faces, and objects (all *P* < 0.01).

Given the non-significant interaction, we conducted follow-up t-tests for each stimulus. For upright and inverted face stimuli, patients exhibited significant hypoactivation in the bilateral MFG compared to HCs (*P* < 0.05).

Specifically, for upright faces, global activation was significantly reduced (t = 2.01, *P* = 0.049), and bilateral MFG activation decreased significantly (Right: t = 2.70, *P* = 0.009; Left: t = 3.44, *P* = 0.001). For inverted faces, although global activation did not reach significance (t = 1.98, *P* = 0.052), the specific deficit in bilateral MFG persisted (Right: t = 2.15, *P* = 0.035; Left: t = 2.76, *P* = 0.008). These results are shown in Fig. 2A & 2B.

Conversely, no significant global or regional differences were observed for happy face or object stimuli (all $P > 0.05$). While patients showed slight non-significant increases in IOT and VMPFC activation for these conditions, the overall patterns did not differ from HCs. These results are shown in Fig. 2C & 2D.

Rest-State Functional Responses of face-related brain regions in FES

Patients with FES showed significantly decreased global fALFF values in face-related regions compared to HCs ($t = 2.97$, $P = 0.004$). Region-specific analyses revealed reduced fALFF in the bilateral IOT (right: $t = 2.60$, $P = 0.013$; left: $t = 3.57$, $P = 0.001$) and left thalamus ($t = 2.87$, $P = 0.006$). Similarly, global ReHo values were lower in patients ($t = 2.35$, $P = 0.022$), driven by significant reductions in the left IOT ($t = 2.42$, $P = 0.019$) and left thalamus ($t = 3.40$, $P = 0.001$). No other regions showed significant group differences.

(Fig. 2)

Structure of face-related brain regions in FES

Global GMV was significantly reduced in FES patients compared to HCs ($t = 2.35$, $P = 0.022$), with specific deficits observed in the right MFG ($t = 2.58$, $P = 0.012$). In contrast, global WMV showed no significant group difference ($t = 0.01$, $P = 0.992$), and no other structural differences were detected in face-related regions.

Correlations of Visual Activation with Clinical Symptoms in FES

Face-related brain regions with differences in activation in response to visual stimuli between patients with FES and HCs were extracted for correlation with clinical symptom scores. The positive symptom scores, negative symptom scores and ROI signals were normally distributed; thus, Pearson’s correlation analyses were performed. However, the distributions of the cognitive symptom scores, excitement symptom scores, and affective symptom scores were skewed; thus, Spearman’s correlation analysis was performed.

Pearson’s correlation analysis revealed a negative correlation between the signals of the bilateral MFG in response to inverted facial stimulation and negative symptom scores for patients with FES (right MFG: $r = -0.38$, $P = 0.036$; left MFG: $r = -0.36$, $P = 0.045$). Spearman's correlation analysis showed a correlation between the fALFF values of the left IOT ($r = -0.36$; $P = 0.048$), left thalamus ($r = 0.38$; $P = 0.034$) and cognitive symptom scores for patients with FES. However, no correlation was observed between right IOT and cognitive symptom score ($r = -0.34$, $P = 0.060$).

A partial correlation analysis was performed with sex, age, education, duration of illness, antipsychotic drug use, GMV, and WMV as covariates to exclude the effects of potential confounding factors. The results showed that this negative correlation persisted in the partial correlation analysis (right: $r = -0.45$, $P = 0.026$; left: $r = -0.41$, $P = 0.049$). In addition, the left MFG was negatively correlated with positive

symptom scores (r = -0.48; *P* = 0.018), although Pearson's correlation analysis revealed no correlation. These correlation results are shown in Fig. 3.

(Fig. 3)

Discussion

This study used a one-back facial information processing task to locate face-processing brain regions, investigated functional changes in face-related regions in first-episode schizophrenia (FES) patients, and analyzed their correlations with clinical symptoms. Results showed that the bilateral inferior occipitotemporal (IOT) cortex, bilateral thalamus, bilateral middle frontal gyrus (MFG), and ventromedial prefrontal cortex (VMPFC) were closely involved in facial information processing. Compared with healthy controls (HCs), FES patients exhibited decreased activation in the bilateral MFG under both upright and inverted face stimuli, along with abnormal resting-state function and gray matter (GM) structure in these regions. After controlling for illness duration, medication, and brain structural variations, activation of the bilateral MFG during inverted face processing was significantly correlated with negative symptoms in FES patients, while left MFG activation was associated with positive symptoms.

The one-back task maintains attention while minimizing executive load. This paradigm reliably activates face-selective regions including the FFA, OFA, and pSTS [25], without the high proactive inhibition demands of 2-back or 3-back tasks [26, 27]. Its lower difficulty makes it ideal for FES patients, avoiding performance deficits that could mask neural group differences.

In this study, we found that, compared with disrupted faces, upright faces elicited significantly greater activation in HCs in the bilateral IOT, thalamus, MFG, and VMPFC. These findings indicate that these regions are involved in the recognition of upright faces in healthy individuals, partially aligning with previous research [27].

Our results align with the "core facial network" and "extended system" frameworks [10]. Specifically, the strong activation of the bilateral IOT is consistent with its role as a core node, overlapping with the OFA and FFA. The OFA is associated with the analysis of low-level facial features [11], while the FFA extracts higher-level identity and social information [28]. In the revised model proposed by Bernstein et al., the connections between the OFA and FFA constitute the ventral pathway for extracting form information from static facial images [13].

Furthermore, the VMPFC, encompassing the OFC and ACC, plays a crucial role in aesthetic evaluation, emotional value assessment, and attention [10], [14], [29], [30]. Furthermore, the thalamus and MFG, as components of the semantic network, likely participate in attentional modulation and social cognitive processing [25]. The thalamus serves as a sensory relay station, interconnecting with aforementioned regions to facilitate multiple stages of facial information processing.

FES patients showed globally reduced activation in face-related brain regions across visual stimuli compared with HCs, indicating severe impairment in processing facial and non-facial object information, consistent with most previous reports [15]. We also observed differential activation across four stimulus categories. Inverted faces evoked weaker activation than other stimuli, consistent with the face inversion effect reflecting disrupted configural face processing [31]. In SZ patients, this effect may be worsened by atypical tuning of face-selective networks, especially in early visual and frontal regions, suggesting reduced sensitivity to facial spatial and structural information [32].

FES patients displayed significantly decreased activation in the bilateral MFG under both upright and inverted face conditions, consistent with prior work. Li et al. reported right MFG hypoactivation in SZ patients during a dual n-back task [33]. These findings suggest SZ face-processing deficits largely stem from insufficient MFG recruitment.

The MFG supports working memory and attentional control. Reduced resting-state functional connectivity between the left MFG and left medial superior frontal gyrus is linked to impaired delayed memory [34]. The MFG also participates in facial memory [35]. Widespread frontal hypoactivation including the MFG has been reported in SZ patients during visual working memory tasks [36]. As our sample was first-episode patients, abnormal MFG activity during visual working memory tasks may represent a potential endophenotypic marker for SZ.

No significant group differences during happy face and object processing suggest basic emotional facial recognition pathways are relatively preserved in FES patients, or task demands were insufficient to reveal neural differences.

This study used fALFF and ReHo from rs-fMRI to compare resting-state functional characteristics of face-related regions between FES patients and HCs. Results showed functional abnormalities in occipitotemporal regions in SZ pa9tients, consistent with previous reports [15, 37]. Concurrent reductions in fALFF and ReHo in the occipitotemporal lobe and thalamus indicate diminished spontaneous neural activity, reduced regional synchronization, and disrupted thalamo-occipitotemporal connectivity in SZ patients.

Our findings clarify lateralization of dysfunctional face-processing networks in SZ. Face perception typically activates the lateral fusiform gyrus, which is mostly bilateral but often left-lateralized [10]. Left fusiform gyrus abnormalities may represent an early deficit in complex visual processing [16]. The right FFA contributes to face-nonface discrimination, while the left FFA processes lower-level facial similarity [38]. Reduced spontaneous neural activity in the left IOT and left thalamus in FES patients may reflect specific deficits in processing facial structural similarity.

Previous studies reported reduced GMV in the FFA in SZ patients. Goghari et al. found an 11% GMV reduction in the FFA in SZ patients versus HCs [39]. Our study demonstrated lower overall GMV in face-related regions in FES patients than HCs, especially significantly reduced cortical thickness in the right MFG [40].

As part of the DLPFC, the MFG supports high-order cognitive functions including working memory, attentional control, and social information processing. Reduced GMV or cortical thinning in the MFG has been reported in FES patients and first-degree relatives [40]. We found no significant volumetric changes in the FFA, possibly due to the short illness duration in our FES sample, suggesting FFA structural alterations are not fully developed. In contrast, reduced MFG volume may represent an earlier or more prominent neurodevelopmental abnormality, impairing attentional modulation and facial information integration and contributing to face recognition deficits in SZ.

A task-based fMRI study demonstrated that the bilateral MFG signals in response to inverted facial stimuli were negatively correlated with negative symptom scores in the FES group, and the findings also suggest that increased effective connectivity from the thalamus to the frontal cortex may be associated with negative symptoms and cognitive dysfunction in patients with SZ [41]. On the one hand, these findings may indicate that insufficient recruitment of the MFG is related to more severe negative symptoms (e.g., emotional withdrawal and apathy). Visual processing deficits have been confirmed to be associated with more prominent negative symptoms in patients with SZ. On the other hand, as reported by Chambon et al. [42], the strength of the inversion effect in emotional discrimination correlates with both positive and negative clinical symptoms, and the severity of symptoms is negatively associated with the magnitude of the inversion effect [31]. In addition, a rs-fMRI study combined with behavioural assessments revealed that the function of the right MFG was associated with both facial working memory and negative symptoms in patients with FSZ [35]. Furthermore, studies applying iTBS intervention in SZ have shown that the functional connectivity between the right MFG and the right superior temporal gyrus was enhanced after intervention, and this alteration was related to the improvement of positive and negative symptoms [43].

This study also revealed a negative correlation between the fALFF values in the left IOT region and left thalamus during the resting-state analysis and cognitive symptom scores. Previous research has indicated that face recognition deficits are associated with spatial working memory, sustained visual attention, and visual information processing and are correlated with the PANSS score for the cognitive subscale [15]. Top-down modulation may influence neural activity in the FFA. Thalamocortical dysregulation in patients with SZ is frequently implicated in clinical and cognitive symptoms [44]. One study demonstrated abnormal thalamic connectivity in patients with SZ who experienced persistent negative symptoms [45]. In a study of patients with FES, connectivity between the right medial thalamus and left middle temporal gyrus was correlated with negative symptom scores [41].

This study has limitations. First, the relatively small sample size in this study may limit the reliability of the findings. Second, the emotional task only compared happy and neutral faces, without including negative emotions, such as fear, anger, and sadness, which restricts the completeness of inferences regarding the "emotional valence-brain region-symptom" gradient. Furthermore, this neuroimaging study did not analyse differences in functional connectivity between distinct brain regions in individuals with SZ and HCs. Future studies should refine the experimental design to further investigate alterations in functional connectivity during face recognition in patients with FES.

In conclusion, our study revealed that face perception involves multiple brain regions. Patients with FES showed functional and structural changes in face-related brain regions compared with HCs. The potential effects of the brain region structure were determined, and some of these functional changes were associated with clinical symptoms, revealing interactions between clinical symptoms and social cognitive deficits in patients with SZ and providing insights into the underlying neurophysiological mechanisms of SZ.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Qijie Kuang: Writing - original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Funding acquisition. Xue He: Writing - original draft, Investigation, Data curation, Conceptualization. Sumiao Zhou: Writing - review & editing, Validation, Funding acquisition. Zerui Liu: Investigation, Data curation. Xiaohua Lu: Investigation, Data curation. Xufei Zhu: Investigation, Data curation. Jiaqi Liu: Investigation, Data curation. Guangxing Deng: Investigation, Data curation. Yingjun Zheng: Resources, Validation, Supervision, Software, Project administration, Funding acquisition, Data curation. Shenglin She: Writing - review & editing, Validation, Supervision, Software, Resources, Funding acquisition, Data curation.

Funding

This study was supported by the Medical Scientific Research Foundation of Guangdong Province, China (B202402), the Planed Science and Technology Projects of Guangzhou (2025A03J3353) and Guangzhou Key Clinical Specialty (Clinical Medical Research Institute).

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to partcipate

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national committees and with the Helsinki Declaration. The Institutional Review Board of the Affiliated Brain Hospital of Guangzhou Medical University approved the study, and the ethics approval number for our study is (2018) No. (002). The patients/participants provided written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

References

1. Leucht S, Siafis S, McGrath JJ, McGorry P, Howes OD, Tamminga C, Carr R, Bighelli I, Schneider-Thoma J, Priller J et al: Schizophrenia. Nat Rev Dis Primers 2025, 11(1):83.
2. Solmi M, Seitidis G, Mavridis D, Correll CU, Dragioti E, Guimond S, Tuominen L, Dargél A, Carvalho AF, Fornaro M et al: Incidence, prevalence, and global burden of schizophrenia - data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. Mol Psychiatry 2023, 28(12):5319-5327.
3. McCutcheon RA, Keefe RSE, McGuire PK: Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. Mol Psychiatry 2023, 28(5):1902-1918.
4. Takeda T, Umehara H, Matsumoto Y, Yoshida T, Nakataki M, Numata S: Schizophrenia and cognitive dysfunction. J Med Invest 2024, 71(3.4):205-209.
5. Chen Y, Ekstrom T: Visual and associated affective processing of face information in schizophrenia: A selective review. Curr Psychiatry Rev 2015, 11(4):266-272.
6. Maher S, Ekstrom T, Holt D, Ongur D, Chen Y: The Core Brain Region for Face Processing in Schizophrenia Lacks Face Selectivity. Schizophr Bull 2016, 42(3):666-674.
7. She S, Zhang B, Li X, Zhang X, Li R, Li J, Bi T, Zheng Y: Face-related visual search deficits in first-episode schizophrenia. Psychiatry Research 2017, 256:144-149.
8. Costa ALL, Costa DL, Pessoa VF, Caixeta FV, Maior RS: Systematic review of visual illusions in schizophrenia. Schizophr Res 2023, 252:13-22.
9. Lee JS, Park G, Song MJ, Choi K-H, Lee S-H: Early visual processing for low spatial frequency fearful face is correlated with cortical volume in patients with schizophrenia. Neuropsychiatr Dis Treat 2016, 12:1-14.
10. Yang C, Qi A, Yu H, Guan X, Wang J, Liu N, Zhang T, Li H, Zhou H, Zhu J et al: Different levels of facial expression recognition in patients with first-episode schizophrenia: A functional MRI study. Gen Psychiatry 2018, 31(2):e000014.
11. Thome I, García Alanis JC, Volk J, Vogelbacher C, Steinsträter O, Jansen A: Let's face it: The lateralization of the face perception network as measured with fMRI is not clearly right dominant. NeuroImage 2022, 263:119587.
12. Tsantani M, Kriegeskorte N, Storrs K, Williams AL, McGettigan C, Garrido L: FFA and OFA Encode Distinct Types of Face Identity Information. J Neurosci 2021, 41(9):1952-1969.
13. Bernstein M, Yovel G: Two neural pathways of face processing: A critical evaluation of current models. Neurosci Biobehav Rev 2015, 55:536-546.

14. Duchaine B, Yovel G: A Revised Neural Framework for Face Processing. Annu Rev Vis Sci 2015, 1(1):393-416.
15. Bortolon C, Capdevielle D, Raffard S: Face recognition in schizophrenia disorder: A comprehensive review of behavioral, neuroimaging and neurophysiological studies. Neuroscience & Biobehavioral Reviews 2015, 53:79-107.
16. Quintana J, Wong T, Ortiz-Portillo E, Marder SR, Mazziotta JC: Right lateral fusiform gyrus dysfunction during facial information processing in schizophrenia. Biological Psychiatry 2003, 53(12):1099-1112.
17. Maher S, Ekstrom T, Ongur D, Levy DL, Norton DJ, Nickerson LD, Chen Y: Functional disconnection between the visual cortex and right fusiform face area in schizophrenia. Schizophr Res 2019, 209:72-79.
18. Silverstein SM, All SD, Kasi R, Berten S, Essex B, Lathrop KL, Little DM: Increased fusiform area activation in schizophrenia during processing of spatial frequency-degraded faces, as revealed by fMRI. Psychol Med 2010, 40(7):1159-1169.
19. Kay SR, Fiszbein A, Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987, 13(2):261-276.
20. Fong TCT, Ho RTH, Wan AHY, Siu PJCY, Au-Yeung FSW: Psychometric validation of the consensus five-factor model of the Positive and Negative Syndrome Scale. Compr Psychiatry 2015, 62:204-208.
21. Gong X, Huang YX, Wang Y, Luo Yj: Revision of the Chinese facial affective picture system. Chin Ment Health 2011, 25(1):40-46.
22. Zou Q-H, Zhu C-Z, Yang Y, Zuo X-N, Long X-Y, Cao Q-J, Wang Y-F, Zang Y-F: An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. J Neurosci Methods 2008, 172(1):137-141.
23. Zang Y, Jiang T, Lu Y, He Y, Tian L: Regional homogeneity approach to fMRI data analysis. NeuroImage 2004, 22(1):394-400.
24. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ: International Consensus Study of Antipsychotic Dosing. AJP 2010, 167(6):686-693.
25. Zhen Z, Fang H, Liu J: The Hierarchical Brain Network for Face Recognition. PLoS One 2013, 8(3):e59886.
26. Zhu S, Wang Q, Kan C, Geng A, Sui Y, Zhuang R, Zhu Y, Wang T, Zhu L, Guo C: Age-related cerebral changes during different n-back tasks: a functional near-infrared spectroscopy study. Front Aging Neurosci 2024, 16:1437587.
27. Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, Benedetti F, Abbamonte M, Gasparotti R, Barale F et al: Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 2009, 34(6):418-432.
28. Borowiak K, Maguinness C, Von Kriegstein K: Dorsal-movement and ventral-form regions are functionally connected during visual-speech recognition. Human Brain Mapping 2020, 41(4):952-

972.

29. Goursaud A-PS, Bachevalier J: Altered face scanning and arousal after orbitofrontal cortex lesion in adult rhesus monkeys. Behav Neurosci 2020, 134(1):45-58.
30. Liang Y, Liu B, Xu J, Zhang G, Li X, Wang P, Wang B: Decoding facial expressions based on face-selective and motion-sensitive areas. Human Brain Mapping 2017, 38(6):3113-3125.
31. Romagnano V, Sokolov AN, Steinwand P, Fallgatter AJ, Pavlova MA: Face pareidolia in male schizophrenia. Schizophrenia (Heidelb) 2022, 8(1):112.
32. Pokorny VJ, Espensen-Sturges TD, Burton PC, Sponheim SR, Olman CA: Aberrant Cortical Connectivity During Ambiguous Object Recognition Is Associated With Schizophrenia. Biol Psychiatry Cogn Neurosci Neuroimaging 2021, 6(12):1193-1201.
33. Li X, Yi Z-h, Lv Q-y, Chu M-y, Hu H-x, Wang J-h, Zhang J-y, Cheung EEF, Chan RCK: Clinical utility of the dual n-back task in schizophrenia: A functional imaging approach. Psychiatry Research: Neuroimaging 2019, 284:37-44.
34. Yu L, Guo L, Fang X, Yang F, Chen Y, Wang Y, Wang D, Wu Z, Liu R, Tian X et al: Altered brain activity in the bilateral frontal cortices and neural correlation with cognitive impairment in schizophrenia. Brain Imaging Behav 2022, 16(1):415-423.
35. Zhou S, Kuang Q, Huang H, She S, Zheng Y, Li X: Resting-state degree centrality and Granger causality analysis in relation to facial working memory in patients with first-episode schizophrenia. BMC Psychiatry 2025, 25(1):147.
36. Stäblein M, Storchak H, Ghinea D, Kraft D, Knöchel C, Prvulovic D, Bittner RA, Reif A, Oertel-Knöchel V: Visual working memory encoding in schizophrenia and first-degree relatives: neurofunctional abnormalities and impaired consolidation. Psychol Med 2019, 49(1):75-83.
37. Wang Y, Jiang Y, Liu D, Zhang J, Yao D, Luo C, Wang J: Atypical Antipsychotics Mediate Dynamics of Intrinsic Brain Activity in Early-Stage Schizophrenia? A Preliminary Study. Psychiatry Investig 2021, 18(12):1205-1212.
38. Frässle S, Paulus FM, Krach S, Schweinberger SR, Stephan KE, Jansen A: Mechanisms of hemispheric lateralization: Asymmetric interhemispheric recruitment in the face perception network. NeuroImage 2016, 124:977-988.
39. Goghari VM, Macdonald AW, Sponheim SR: Temporal lobe structures and facial emotion recognition in schizophrenia patients and nonpsychotic relatives. Schizophr Bull 2011, 37(6):1281-1294.
40. Çabuk T, Zhang Y, Palaniyappan L, Şahin-Çevik D, Avcı H, Çakmak IB, Kafalı HY, Şenol B, Oğuz KK, Toulopoulou T: Formal thought disorder and familial risk in first-episode psychosis: A study of cortical thickness and neuroimaging-transcriptomic association analysis. Psychiatry Res Neuroimaging 2026, 357:112148.
41. Wang L-N, Lin S, Tian L, Wu H, Jin W-Q, Wang W, Pan W-G, Yang C-L, Ren Y-P, Ma X et al: Subregional thalamic functional connectivity abnormalities and cognitive impairments in first-episode schizophrenia. Asian J Psychiatr 2024, 96:104042.

42. Chambon V, Baudouin J-Y, Franck N: The role of configural information in facial emotion recognition in schizophrenia. Neuropsychologia 2006, 44(12):2437-2444.
43. Li L, Wang L, Wu H, Li B, Pan W, Jin W, Wang W, Ren Y, Liu C, Ma X: Effects of parietal iTBS on resting-state effective connectivity within the frontoparietal network in patients with schizophrenia: An fMRI study. Neuroimage Clin 2025, 45:103715.
44. Ramsay IS, Mueller B, Ma Y, Shen C, Sponheim SR: Thalamocortical connectivity and its relationship with symptoms and cognition across the psychosis continuum. Psychol Med 2023, 53(12):5582-5591.
45. Zhu T, Wang Z, Zhou C, Fang X, Huang C, Xie C, Ge H, Yan Z, Zhang X, Chen J: Meta-analysis of structural and functional brain abnormalities in schizophrenia with persistent negative symptoms using activation likelihood estimation. Front Psychiatry 2022, 13:957685.

Figures

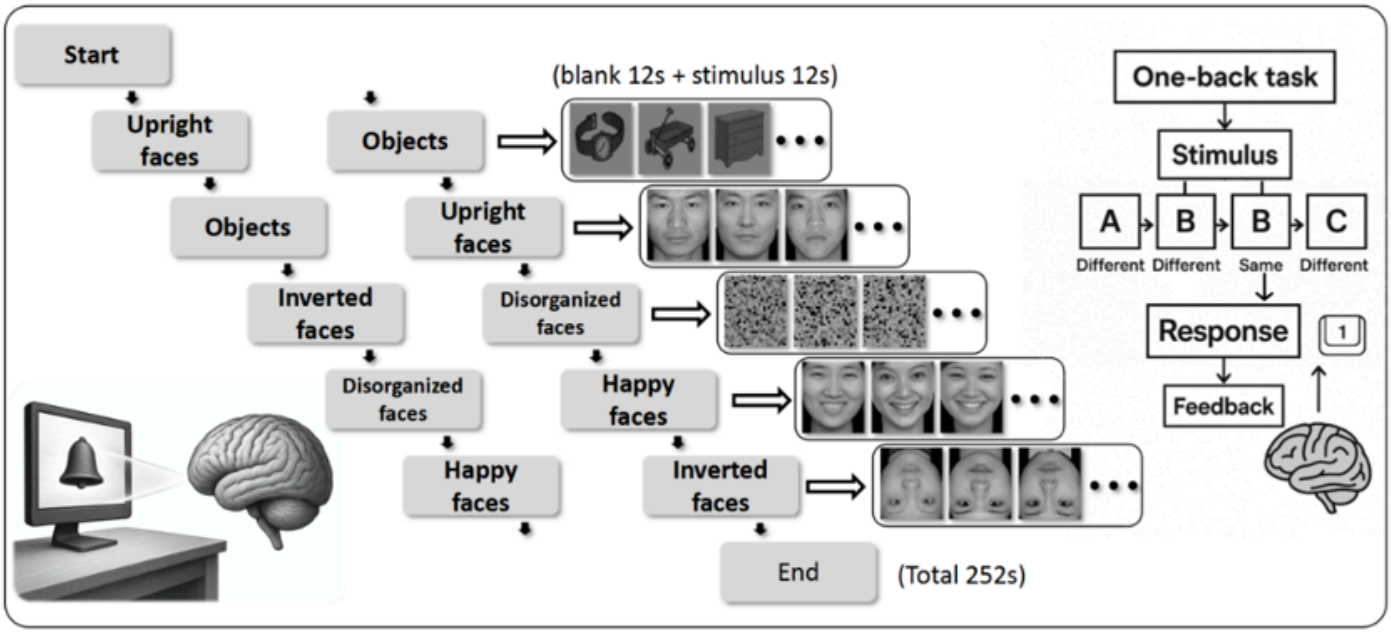


Figure 1

Visual one-back task paradigm in task-based fMRI. A block-design paradigm with a total duration of 252 s. Each run included 10 blocks (2 blocks for each condition: upright faces, inverted faces, happy faces, objects, disorganized faces). A 12-s fixation preceded each block, followed by 12-s stimulus and 12-s blank. Subjects responded to consecutive repeated stimuli

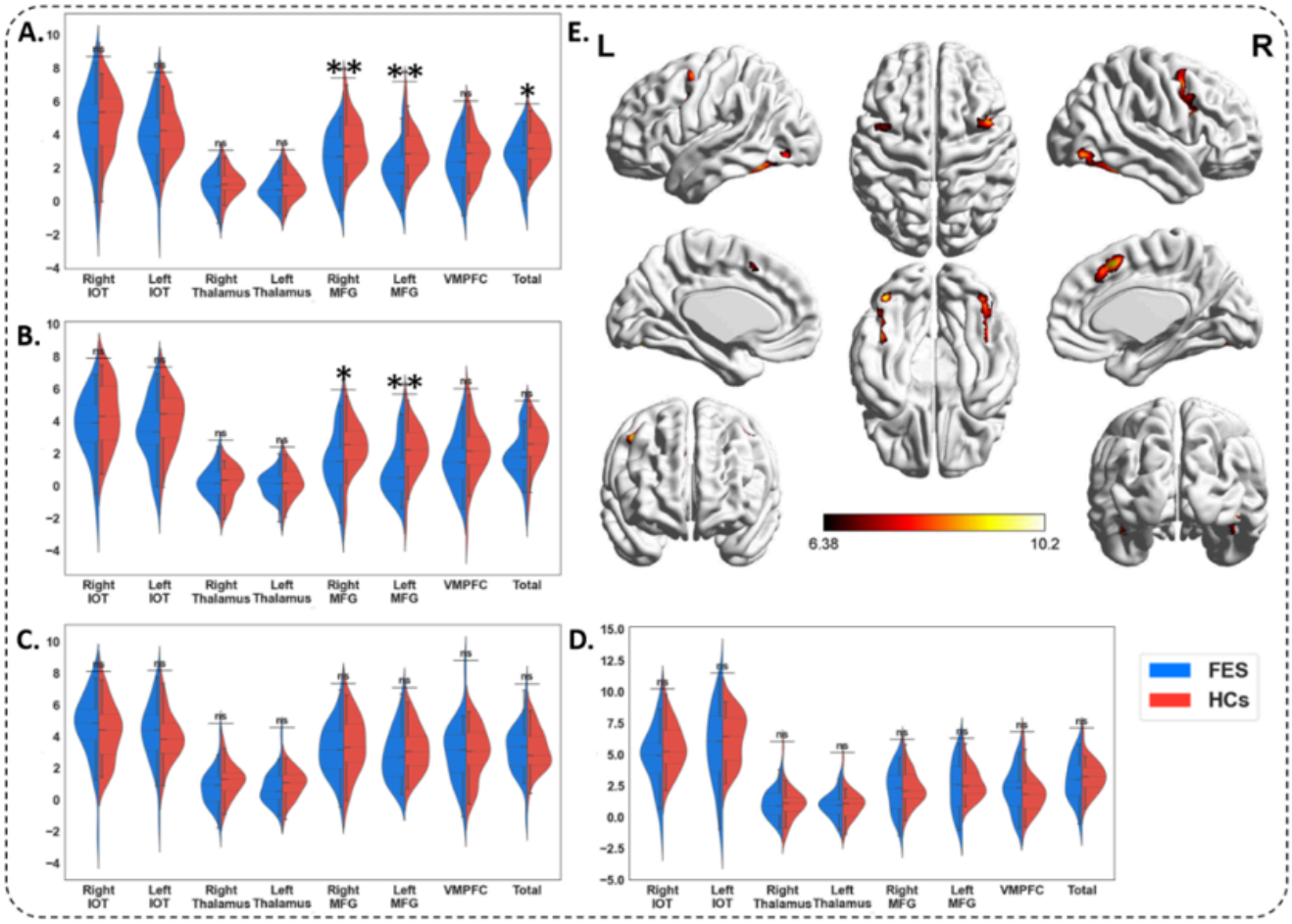


Figure 2

Task Functional differences in face-related brain regions between two groups. (A) Upright neutral faces; (B) Inverted neutral faces; (C) Upright happy faces; (D) Objects; (E) Face-related brain activation distribution, with a voxel-wise threshold of FWE-corrected P < 0.05 at the whole-brain level (FWE, family-wise error)

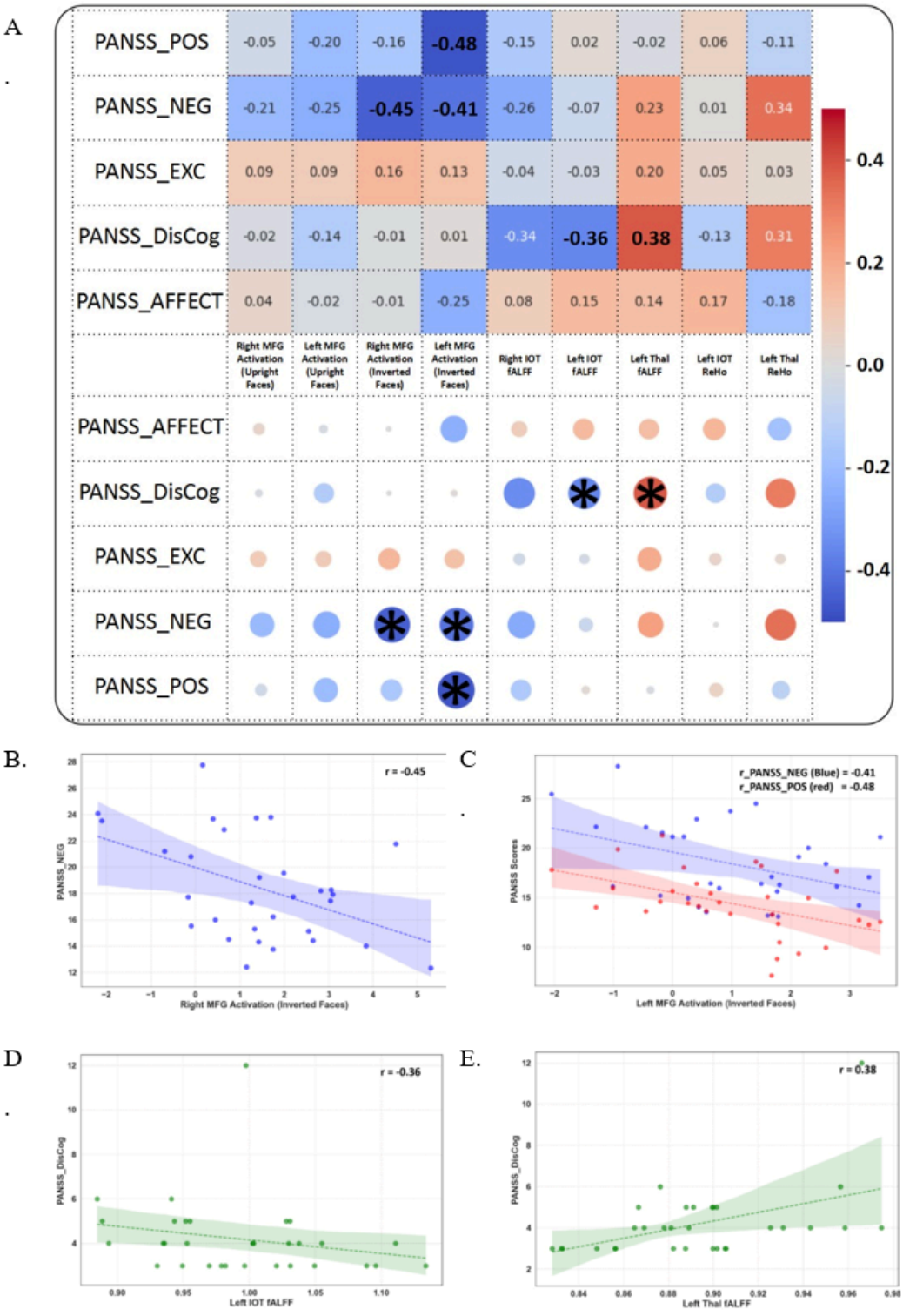


Figure 3

Correlation between functional alterations in differential brain regions and clinical symptoms. (A) Correlation matrix of regional activation, fALFF, ReHo with PANSS symptom scores; (B–E) Scatter plots showing correlations of bilateral MFG activation, left IOT fALFF, and left thalamus fALFF with clinical symptoms. Spearman's correlation and partial correlation were used separately; partial correlation was adjusted for sex, age, education, illness duration, medication, GMV, and WMV