

# Cortical Pathways or Mechanism in the Face Inversion Effect in Patients with First-Episode Schizophrenia

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**Objective:** Impaired face perception is considered as a hallmark of social disability in schizophrenia. It is widely believed that inverted faces and upright faces are processed by distinct mechanisms. Previous studies have identified that individuals with schizophrenia display poorer face processing than controls. However, the mechanisms underlying the face inversion effect (FIE) in patients with first-episode schizophrenia (FSZ) remain unclear.

**Methods:** We designed an fMRI task to investigate the FIE mechanism in patients with schizophrenia. Thirty-four patients with FSZ and thirty-five healthy controls (CON) underwent task-related fMRI scanning, clinical assessment, anhedonia experience examination, and social function and cognitive function evaluation.

**Results:** The patients with FSZ exhibited distinct functional activity regarding upright and inverted face processing within the cortical face and non-face network. These results suggest that the differences in quantitative processing might mediate the FIE in schizophrenia. Compared with controls, affected patients showed impairments in processing both upright and inverted faces; and for these patients with FSZ, upright face processing was associated with more severe and broader impairment than inverted face processing. Reduced response in the left middle occipital gyrus for upright face processing was related to poorer performance of social function outcomes evaluated using the Personal and Social Performance Scale.

**Conclusion:** Our data suggested that patients with FSZ exhibited similar performance in processing inverted faces and upright faces, but were less efficient than controls; and for these patients, inverted faces are processed less efficiently than upright faces. We also provided a clue that the mechanism under abnormal FIE might be related to an aberrant activation of non-face-selective areas instead of abnormal activation of face-specific areas in patients with schizophrenia. Finally, our study indicated that the neural pathway for upright recognition might be relevant in determining the functional outcomes of this devastating disorder.

**Keywords:** first-episode schizophrenia, face inversion effect, task-related fMRI, face recognition, social functional outcome

## Introduction

Successful social interactions require efficient decoding of information from facial expressions. Not surprisingly, impaired face perception is considered a hallmark of social disability in schizophrenia. Patients with schizophrenia present with psychotic symptoms, emotional and cognitive impairments, and abnormal social communication and interactions. Thus, dysfunction in face processing in schizophrenia seems to be correlated to social functioning impairment.

An increasing number of studies have identified that individuals with schizophrenia display poorer face processing performance than controls. For instance, according to studies using behavioral face processing tasks, self-face recognition is impaired in patients with schizophrenia.<sup>1</sup> These studies on self-face recognition have shown global impairment in famous faces recognition and self-face recognition,<sup>2,3</sup> associated with the theory of mind.<sup>4</sup> Eye-tracking research revealed that patients with schizophrenia present a restricted visual scanning strategy featured by fewer and longer fixations, reduced saccades, less attention to striking facial characteristics in the passive viewing, and avoidance of relevant face features.<sup>5,6</sup> However, the scan paths of patients with schizophrenia did not differ from that of controls when asked to focus on and determine the features of the faces.<sup>6</sup>

Most of previous studies have shown a dysfunction in the processing of upright faces in patients with schizophrenia;<sup>7–10</sup> however, little work has been done on the processing of inverted faces in those with this disorder.<sup>11</sup> Previous neuropsychological and developmental evidence suggests that the processing of inverted faces is qualitatively distinct from that of upright faces. For instance, prosopagnosia patients with a selective impairment of face perception paradoxically performed better at recognizing inverted faces than upright faces.<sup>12</sup> Patients with object agnosia and dyslexia caused by closed-head injuries showed normal recognition of upright faces, even though their processing of inverted faces was severely impaired.<sup>13,14</sup> These findings suggest that the recognition of inverted faces may engage mechanisms distinct from that of upright faces.

There is consistent evidence that face recognition involves a broadly distributed and interconnected brain networks, which include the fusiform face area (FFA)<sup>10</sup> located in the lateral fusiform gyrus and superior temporal sulcus,<sup>10,15</sup> as well as the occipital face area (OFA)<sup>10,16</sup> located in the inferior occipital gyrus, inferior frontal gyrus,<sup>17,18</sup> and the amygdala. Structural magnetic resonance imaging (sMRI) studies on FFA have found bilaterally reduced volume of gray matter in the fusiform gyrus in patients with schizophrenia,<sup>7,19</sup> and this volume reduction was significantly correlated with poor performance on delayed facial memory.<sup>7</sup> However, functional studies achieved mixed results regarding FFA activation, some showing greater activity in the fusiform gyrus when patients performed a gender discrimination task,<sup>20</sup> others exhibiting lower blood oxygen level dependent responses,

longer reaction times, and less accuracy during recognition of famous or unfamiliar faces.<sup>21</sup> Other functional studies found no activation of the fusiform gyrus in the facial discrimination task,<sup>22</sup> or showed sporadic activations when patients passively viewed face images.

The face-inversion effect (FIE) typically indicates more difficulty in recognizing inverted faces than recognizing upright faces. FFA is the most consistently observed brain locus involved in the FIE. However, the role of FFA in FIE is yet to be elucidated. One study found that only FFA positively correlated with the behavioral FIE and presented greater neural sensitivity to upright faces than inverted faces across healthy subjects.<sup>23</sup> Other studies found no change in the magnitude of response for inverted vs upright faces in the FFA.<sup>24</sup> The inconsistency of these imaging and behavioral data suggests that FIE may also be mediated by other face-selective areas, or even by non-face-selective areas.<sup>25</sup> The study of Epstein et al also revealed a greater response in lateral occipital object area and the right middle fusiform object area for recognition of inverted faces vs upright faces.<sup>24</sup>

Recent behavioral and computational evidence has shown that upright and inverted faces are processed by common mechanisms; quantitative processing differences may result in the FIE.<sup>26–28</sup> However, more recent research examined qualitative and quantitative processing differences for inverted faces vs upright faces recognition by using dynamic causal modeling and Bayesian model selection method in healthy participants.<sup>29</sup> The results indicated that upright and inverted faces were processed by distinct qualitative and quantitative pathways, with upright face processing involving isolated activation of the OFA/FFA with concurrent lateral inhibition of the lateral occipital cortex, and inverted face processing involving increased couplings to the intraparietal sulcus without inhibition of the lateral occipital cortex. In addition, the extent of effective connectivity within the pathways from the visual cortex to OFA could predict individual differences in behavioral FIE.

Recent behavioral experiments yielded mixed results of inversion on face recognition among most individuals with autism spectrum disorders (ASD).<sup>30,31</sup> However, the differences in the processing of inverted and upright faces and the mechanisms mediating FIE in patients with schizophrenia are still unclear. Face inversion is a well-established marker of holistic face processing, and could decrease the representativeness of facial identity and facial expressions.<sup>32,33</sup> Numerous researches on

configural face processing in healthy and schizophrenic subjects suggested that configural face processing is highly relevant to social functioning including memory and executive function.<sup>34</sup> Face recognition may rely more on configural processing, however, inversion could affect configural face processing.<sup>35</sup> Additionally, both upright and inverted faces are holistically processed, but inversion could lead to reduced overall processing efficiency.<sup>36</sup> By designing this study, we aim to better understand the mechanisms under FIE in patients with schizophrenia and to investigate the differences in the underlying mechanisms between patients with schizophrenia and controls from the community. In the present study, we investigated the neural basis during upright and inverted faces processing in schizophrenia patients and community controls using fMRI to characterize disease-specific face recognition markers. Using a task including images of upright, inverted, scrambled faces and objects, we contrasted the processing of upright and inverted faces, as well as their judgment of upright or inverted faces, compared to the judgment of scrambled or non-face object images. Our hypothesis is that, compared to community controls, schizophrenia patients would demonstrate abnormal processing of both upright and inverted faces.

## Materials and Methods

### Study Design

The study followed a prospective, non-randomized, experimental, and controlled design. G\*Power software was used to calculate the sample size of the study. The parameters are as follows: effect size: 0.8,  $\alpha=0.05$ , and test power: 0.9. Thus, each group should include at least 28 subjects.

### Patients

The study recruited 69 subjects, who were divided into two groups, with 34 patients in the first-episode schizophrenia (FSZ) group and 35 individuals in the healthy control (CON) group. All the subjects were recruited from the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangdong province. The diagnosis of schizophrenia was confirmed by experienced clinical psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria (DSM-IV).

All the participants were subject to strict inclusion management as the following criteria: 1) subjects aged 17 to 50 years at the time of diagnosis for both groups; 2) subjects in the patient group were diagnosed with schizophrenia for the first time, with an illness duration of no more than 2 years and had received antipsychotics for no more than one year before enrollment; 3) subjects received formal education for at least 6 years; 4) subjects in the control group were recruited from the community and did not meet the Criteria of Psychosis-risk Syndromes or DSM-IV for any mental disorders, and had no documented family history of psychiatric problems or medications. The demographic variables of age, gender and education were matched at the group level between the control group and the schizophrenia group.

The exclusion criteria for the subjects were 1) subjects who met DSM-IV criteria for any psychotic disorders, or had delirium, dementia, amnesia, or other severe cognitive impairments in the past or intellectual developmental disabilities ( $IQ<70$ ) before their schizophrenia diagnosis was made; 2) patients with clinically significant somatic diseases; 3) individuals with substance abuse in the past 3 months; 4) patients with a documented history of brain injury, epilepsy, or other known diseases of central nervous system; 5) patients who had received MECT therapy in the past 6 months.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Affiliated Brain Hospital of Guangzhou Medical University. All the participants provided written informed consent. In detail, for subjects under 18 years of age, informed consent obtained from a parent or legal guardian of each subject.

### Cognitive and General Psychiatric Assessments

All the participants completed a demographic questionnaire for us to obtain the demographic data such as age, gender, education level, marital status, body mass index (BMI), and family history of mental illness.

Psychotic symptoms were assessed in the schizophrenia group using the Positive and Negative Syndrome Scale (PANSS),<sup>37</sup> applied by two trained psychiatrists or psychologists. The Personal and Social Performance Scale (PSP)<sup>38</sup> was used to test the social function of patients with schizophrenia. The antipsychotic medication status at the time of testing was recorded in Table 1, including

**Table 1** Demographic, Clinical and Cognitive Characteristics

Characteristics	FSZ		CON		Statistic t, df, p
	n	Mean (S.D.)	n	Mean (S.D.)	
Age	31	25.0(6.8)	32	24.2(5.1)	t=0.536, df=61, p=0.594
Gender (M/F)	31	17/14	32	16/16	Chi square=0.148, p=0.802
Year of education	31	11.1(3.3)	32	11.7(3.1)	t=-0.692, df=61, p=0.492
Married (Y/N)	31	11/20	32	8/24	
Handedness (R/L)	31	30/1	32	30/2	
Family history (Y/N)	31	7/24	32	0/32	
Simple IQ	30	96.1(13.2)**	32	105.8(12.1)	t=3.015, df=60, p=0.004
Block diagram test	31	8.9(2.7)***	32	11.4(2.5)	t=-3.729, df=61, p=0.000
Vocabulary	30	9.7(2.7)	32	10.7(2.2)	t=-1.564, df=60, p=0.123
RBANS total	31	368.3(61.7)***	31	437.2(48.6)	t=-4.886, df=60, p=0.000
Immediate memory	31	57.1(16.8)***	32	74.9(13.8)	t=-4.602, df=61, p=0.000
Visual span	31	76.6(13.6)**	32	86.3(14.2)	t=-2.778, df=61, p=0.007
Language	31	71.8(19.8)***	32	88.7(15.8)	t=-3.753, df=61, p=0.000
Attention	31	92.7(17.9)*	31	103.2(13.7)	t=-2.577, df=60, p=0.012
Delayed memory	31	70.1(17.9)***	32	85.3(10.9)	t=-4.079, df=61, p=0.000
TMT-A	31	52.3(19.7)**	32	38.8(13.5)	t=-3.175, df=61, p=0.004
MSCEIT	31	80.3(9.6)	32	83.9(6.8)	t = 1.747, df=61, p=0.086
TEPS total	29	67.8(11.7)	32	72.9(9.5)	t=-1.883, df=59, p=0.065
SHAPS total	31	30.4(5.3)	32	33.0(5.2)	t=-1.984, df=61, p=0.052
BMI	31	20.7(3.1)	32	21.2(4.2)	t=-0.502, df=61, p=0.618
Duration of illness (months)	31	8.5(7.0)			
Age of first episode	31	24.0(6.8)			
Medication status at time of testing					
None medicated	8				
Antipsychotic	20				
Atypical	18				
Atypical+Traditional	2				
Antidepressant	1				
Unknown medication	2				
Duration of medication treatment (days)	31	26.4(37.2)			
Chlorpromazine Equivalents (mg)	31	222.1(244.4)			
PANSS total	31	65.6(15.0)			
PANSS positive	31	17.6(5.1)			
PANSS negative	31	13.7(4.1)			
PANSS general	31	34.3(8.6)			
PSP total	31	55.4(15.3)			
Past hospitalization history (Y/N)	31	3/28			
Auditory hallucination (Y/N)	31	20/11			

Notes: \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

Abbreviations: FSZ, patients with first-episode schizophrenia; CON, healthy controls; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test; RBANS, the Repeatable Battery for the Assessment of Neuropsychological Status; TMT-A, Trail-Making Test: Part A; TEPS, the Temporal Experience of Pleasure Scale; SHAPS, the Snaith-Hamilton Pleasure Scale; PANSS, the positive and negative syndrome scale; PSP, Personal and Social Performance; S.D., standard deviation.

types, duration and chlorpromazine equivalent doses of the medications. We also assessed all the patients for auditory hallucination.

We applied the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS),<sup>39</sup> Trail-Making Test: Part A (TMT-A) and Mayer-Salovey-Caruso Emotional Intelligence Test:

Managing Emotions (MSCEIT)<sup>40</sup> tests in the MATRICS Consensus Cognitive Battery (MCCB),<sup>41,42</sup> and block diagram test and vocabulary test were used to evaluate the cognitive performance of each subject. The cognitive evaluation was carried out by a trained and certified psychiatrist, psychologist or neuropsychological examiner.

The Temporal Experience of Pleasure Scale (TEPS)<sup>43</sup> and the Snaith–Hamilton Pleasure Scale (SHAPS)<sup>44</sup> were used to assess the anhedonia experience in patients with schizophrenia. The relationship between anhedonia and features of schizophrenia was also examined.

## Stimuli

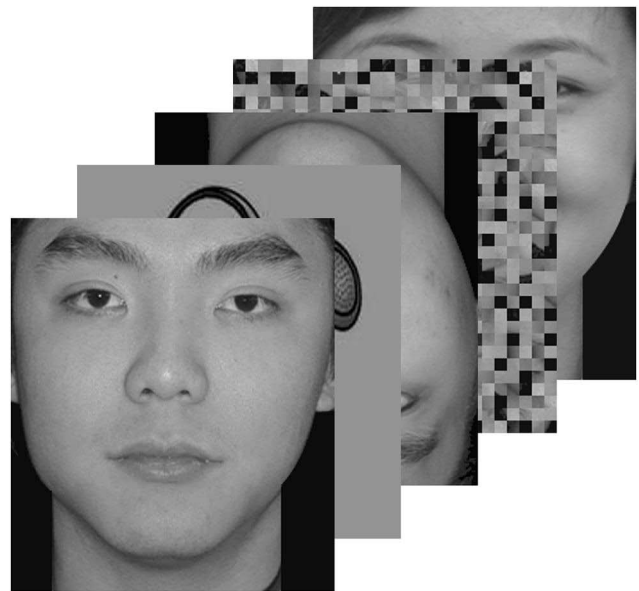
Stimuli consisted of grayscale images of upright and inverted faces with neutral expression, and happy faces, provided by Chinese Facial Affective Picture System (CFAPS),<sup>45</sup> as well as grayscale images of scrambled faces and objects. The scrambled faces were created by randomly mixing the neutral faces into squares of  $10 \times 10$ -pixel grids. All images subtended at  $6.2 \times 6.2^\circ$  of the visual angles and were presented at the center of the screen, with the mean brightness normalized (ie, the images were equalized in terms of brightness). We adopted a blocked design containing five categories displayed in the following sequence: upright faces, objects, inverted faces, scrambled faces and happy faces.

## Experimental Procedure

For each run, block trial began with a white point displayed at the center of the black screen, followed by image displays containing a sequence of upright faces, objects, inverted faces, scrambled faces, and happy faces that appeared at a rate of 2 Hz in blocks of 12s, with 12s of blank interval. Each image stimulus was presented for 300 ms, followed by a 200-ms interstimulus interval per block. The sum of the duration of fixation and sample displays was constant. Each 12s block presented 24 images per stimulus type, and the images were randomly selected from the same category type, with 30 images in each category. Faces image samples included female and male faces at a ratio of 1:1. According to the study protocol, each block type was presented for a total of 252 s per run. Subjects performed a one-back task during which they were asked to press a key to identify the same images (see Figure 1 for the illustration of the procedure, with samples provided).

## MRI Acquisition

A 3.0-T Philips Achieva MRI scanner (Philips, Netherlands) was used to obtain data of blood oxygenation level-dependent cortical activity. High-resolution fMRI brain images were obtained with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, field of view =  $220 \times 220$  mm<sup>2</sup>, voxel size =  $3.44$  mm  $\times$



**Figure 1** An illustration of the procedure. For each run, images sample displays containing a sequence of upright faces, objects, inverted faces, scrambled faces, and happy faces that appeared at a rate of 2 Hz in blocks of 12s and with 12s blank blocks interval at a time. Each image stimulus was presented for 300 ms, followed by a 200 ms interstimulus interval per block. The sum of the duration of fixation and sample displays was constant. Each block presented 24 images per stimulus type and lasted 12s. These images were randomly selected from the same category type. Each category contains 30 images. Faces images sample included female and male faces on each half.

$3.44$  mm, matrix size =  $64 \times 64$ , number of slices = 33, and slice thickness = 4 mm. A total of 126 functional full-brain volumes were collected per subject in each run.

Stimuli were presented with the Psychtoolbox 3.0 for MATLAB (<http://psychtoolbox.org>), and projected onto a screen viewed by the participants through a mirror fixed in the MRI scanner. All the subjects were instructed to keep their eyes opened, look at the pictures of the one-back task, and remain still in a supine position during the whole scanning. The MRI data were acquired at the Affiliated Brain Hospital of Guangzhou Medical University on the same day for clinical and cognitive assessments.

## Statistical Analysis

### Demographic, Clinical and Cognitive Data

The statistical analyses were performed with SPSS 23 software. Differences in demographic data (age, gender, education), clinical data and cognitive data were compared between groups using independent samples *t*-test and Chi square test; post-hoc test was applied as needed. Finally, Pearson correlations test was performed to compare the fMRI data and patient performance (clinical symptoms, medication dosages, and cognitive function). Benjamini

& Hochberg (BH) corrected significance level (at  $\alpha=0.05$ ) was used as the protected correction level for correlations.

### Preprocessing of fMRI Data

The fMRI data was analyzed using the general linear model for block designs in statistical parametric mapping version 12 (SPM12) software (the Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB (MathWorks). Functional images were preprocessed with correction of slice acquisition time, head motion correction (realignment), co-registration, and spatial normalization by using T1 image unified segmentation and resampled to voxel size of  $3\times 3\times 3$  mm<sup>3</sup>. Subsequently, the functional images underwent spatial smoothing with  $8\times 8\times 8$  mm<sup>3</sup> full-width at half-maximum (FWHM) Gaussian kernel. Subjects with a head motion of more than 2.5 mm and with an angular motion of more than 2° across the whole scan were excluded.

### First-Level and Second-Level Analysis

In the first-level analysis, the design matrix consisted of five regressors of interest, each representing the upright faces, objects, inverted faces, scrambled faces, and happy faces, with same display duration convolved with a canonical hemodynamic response function (HRF). Six head motion parameters were defined in the matrix as effects of no interest. Finally, a GLM HRF model was calculated for each subject. Within the FSZ or CON group, the upright face associated activation effect was defined using conjunctions of t-contrasts including upright faces > inverted faces, upright faces > scramble faces, and upright faces > objects. The inverted face associated activation effect was defined using conjunctions of t-contrasts including inverted faces > upright faces, inverted faces > scramble faces, and inverted faces > objects.

To further confirm the difference of brain activation between the FSZ group and the CON group, a second level two-sample *t* test was performed, with a threshold of significant difference being  $p < 0.05$  (false discovery rate (FDR) corrected, performed in DPABI version 4.0)<sup>46</sup> and a cluster threshold being no less than 10 voxels. Inter-group differences during each condition were tested with the contrast of CON vs FSZ. Firstly, we established the CON vs FSZ contrast during displays of upright faces, objects, inverted faces, scrambled faces, and happy faces. Then, we defined CON vs FSZ inter-group associated upright face activation effect (including t-contrast conjunctions of upright faces > inverted faces, upright faces >

scramble faces, and upright faces > objects) and inverted face activation effect (including t-contrast conjunctions of inverted faces > upright faces, inverted faces > scramble faces, and inverted faces > objects). We then masked the corrected SPM with a contrast-specific brain mask to limit findings to task activated regions for inter-group analysis. This mask was the combination of the activated voxels discovered in one-sample analysis in healthy controls and patients with schizophrenia under each contrast.

### Selection of Region of Interest (ROI)

Only voxels that reached the significance level for each contrast of inter-group analysis ( $p < 0.05$ , FDR corrected) were included in ROIs. We defined category-selective ROIs from contrasts between conditions of upright faces, inverted faces, scrambled faces, and objects. Upright face selective areas were extracted the t-contrast maps regarding conjunctions of upright faces > inverted faces, upright faces > scrambled faces, and upright faces > objects ( $p < 0.05$ , FDR corrected). Similarly, inverted-face selective areas were extracted from t-contrast maps regarding conjunctions of inverted faces > upright faces, inverted faces > scrambled faces, and inverted faces > objects ( $p < 0.05$ , FDR corrected). These ROIs were identified as spheres with a radius of 6 mm centered around the peak voxel of each activated cluster, and eigenvariate of the entire ROI region was extracted using the toolbox in SPM version 12 (see Table 5 for ROI information).

## Results

### Demographic, Clinical and Cognitive Results

Data from six subjects were excluded of the final analysis, including one who withdrew from the study, two who failed to finish non-imaging tests, and three with excessive head motion during the whole scan. A total of 63 subjects completed the behavioral experiments for analysis. Therefore, this data set included 31 FSZ patients and 32 CON subjects.

Demographic (age, gender, years of education, and medication status at the time of testing), and clinical data (PANSS symptom ratings) are presented in Table 1. There were no significant age, gender or education differences between the two groups. The patients with FSZ presented a disease duration of 8.5 months in average, and their doses of antipsychotics were converted to equivalent chlorpromazine dosage (CPZ). Cognitive performances are listed in Table 1. Patients with schizophrenia showed

clear deficits in TMT-A test and all the RBANs tests, while no difference from the controls was observed in the MSCEIT test. Additionally, patients also showed no differences in TEPS and SHAPS scores compared to healthy controls.

## Neuroimaging Results

### Conjunction Results of FIE

The conjunction analyses of upright and inverted face related contrasts of CON (see details in Table 3) and FSZ (see details in Table 2) revealed significant activation in various clusters comprising brain regions including fusiform, middle occipital gyrus, and inferior occipital gyrus, suggesting great activation in the FIE networks across groups.

(Tables 2 and 3 about here)

### Greater Functional Activities in the CON Group

Inter-group differences of upright face selective areas showed lower neural responses in the left parahippocampus, left hippocampus, left limbic lobe, left middle occipital gyrus, and left cuneus in patients with schizophrenia (see details in Table 4, and Figure 2A and C). Inter-group differences of inverted face selective areas showed lower neural responses in the left inferior parietal gyrus and left postcentral gyrus in the FSZ patients (see details in Table 4 and Figure 2B).

### Greater Functional Activities in the FSZ Group

Inter-group differences of upright face selective areas showed that higher neural responses were observed in left inferior parietal gyrus, left postcentral gyrus, right postcentral gyrus, and right parietal lobe in patients with schizophrenia, while no significant difference was observed in inverted face selective areas between patients and controls (see details in Table 4 and Figure 2C).

### ROIs for Correlation

Four ROIs were defined from the contrasts between the four face conditions (Table 5). A conjunction analysis using a conjunction-null hypothesis<sup>47</sup> was performed to identify common areas of activation across contrasts of upright faces > scrambled faces, upright faces > object, upright faces > inverted faces, and contrasts of inverted faces > scrambled faces, inverted faces > object, inverted faces > upright faces. According to the results, upright face processing was related to the left parahippocampus and left middle occipital gyrus, while inverted face processing was related to the left postcentral and inferior parietal lobule.

### Functional Activity - Correlation with Cognitive and Clinical Performance

In the FSZ group, the reduced functional activity of the left middle occipital gyrus showed negative correlation with PSP total performance ( $r = -0.495$ ,  $p = 0.005$ , two tailed, see details in Table 6 and Figure 3) and positive correlation with PANSS general scores ( $r = 0.396$ ,  $p = 0.05$ , two tailed, but failed the Benjamini and Hochberg correction, see details in Table 6), while the functional activity of the left postcentral gyrus was significantly associated with block diagram test scores ( $r = 0.431$ ,  $p = 0.016$ , two tailed, see details in Table 6 and Figure 3). (see all details in Table 6).

## Discussion

To our knowledge, the present study is the first to investigate the mechanisms underlying FIE in patients with first-episode schizophrenia. Our results suggest a distinct functional activity for upright and inverted face processing in FSZ patients, which located within the cortical face and non-face networks. According to our data, the patients with FSZ processed both inverted faces and upright faces less efficiently than controls; and for the patients, inverted faces are processed less efficiently than upright faces. Upright face recognition in schizophrenia patients was associated with activated face-selective network, including the fusiform, inferior occipital gyrus, and superior temporal gyrus. Non-face-specific areas were also activated in the patients, including the insula, precuneus, middle and inferior temporal gyrus, inferior and superior parietal lobule, middle occipital gyrus, and superior and middle frontal gyrus. On the other hand, inverted face recognition was not associated with activated fusiform and temporal face-selective areas, as well as the insula, parietal, and temporal non-face-selective brain regions. Inverted face recognition has induced slight and isolated activation of the occipital and frontal regions.

We concluded that turning faces upside down significantly decreased or suppressed the neural response of some face-processing related brain regions, especially the fusiform and the occipital face area (OFA), and temporal and parietal non-face selective areas. However, how the activation of these non-face-specific areas occurred is still unclear. Upright faces are identified in a holistic pathway, whereas inverted facial features are identified in a fragmented manner. Conversely, other findings predicted by an optimal Bayesian integrator study showed that whole faces were not recognized better than the sum of their components showed

**Table 2** Significantly Activated Regions During the Face Inversion Task in Patients with Schizophrenia

Regions	Cluster Size	T	MNI Coordinates		
			X	Y	Z
<b>Conjunction (upright &gt;inverted, upright &gt;scramble, upright &gt;objects)</b>					
<b>Upright &gt;inverted</b>					
Cluster 1					
Right insula	16	3.84	36	12	12
<b>Upright &gt;scramble</b>					
Cluster 1					
Right temporal lobe/fusiform gyrus	912	8.55	42	-48	-21
Cluster 2					
Left temporal lobe/fusiform gyrus	607	8.51	-42	-48	-21
Cluster 3					
Left insula	688	6.52	-30	21	3
Cluster 4					
Right insula	1013	7.70	33	21	6
Cluster 5					
Right superior parietal lobule	674	5.95	30	-57	51
Cluster 6					
Left inferior parietal lobule/postcentral lobule	736	6.87	-42	-33	48
Cluster 7					
Left cingulate gyrus	525	6.73	-6	12	45
<b>Upright &gt;objects</b>					
None					
<b>Conjunction (inverted &gt;upright, inverted &gt;scramble, inverted &gt;objects)</b>					
<b>Inverted &gt;upright</b>					
Cluster 1					
Right middle temporal gyrus/middle occipital gyrus	97	4.25	45	-69	27
Cluster 2					
Left middle occipital gyrus	98	4.69	-39	-78	27
Cluster 3					
Left middle frontal gyrus	155	5.50	-21	33	39
<b>inverted &gt;scramble</b>					
Cluster 1					
Left inferior occipital gyrus	445	6.77	-42	-78	-12
Cluster 2					
Right middle occipital gyrus/inferior occipital gyrus	681	7.91	42	-72	-12
Cluster 3					
Left inferior frontal gyrus	577	5.23	-33	21	9
Cluster 4					
Right insula/inferior frontal gyrus	84	4.28	30	24	0
Cluster 5					
Right inferior frontal gyrus/precentral gyrus	604	5.50	42	0	36
Cluster 6					
Left medial frontal gyrus/cingulate gyrus	438	6.07	0	12	48
Cluster 7					
Left inferior parietal gyrus	585	5.16	-27	-42	45
Cluster 8					
Right superior parietal lobule/inferior parietal lobule	607	5.45	30	-57	51
<b>Inverted &gt; objects</b>					
None					

**Notes:** The level of significance was set using a threshold of  $\alpha=0.05$  false discovery rate, FDR whole brain corrected.

**Abbreviation:** MNI, Montreal Neurological Institute.

**Table 3** Significantly Activated Regions During the Face Inversion Task in Healthy Controls

Regions	Cluster Size	T	MNI Coordinates		
			X	Y	Z
<b>Conjunction (upright &gt;inverted, upright &gt;scramble, upright &gt;objects)</b>					
<b>Upright &gt;inverted</b>					
Cluster 1					
Left temporal lobe/hippocampus	142	5.37	-33	-48	0
Cluster 2					
Left occipital lobe/cuneus	152	3.93	-9	90	3
<b>Upright &gt;scramble</b>					
Cluster 1					
Right temporal lobe/fusiform gyrus	2034	10.14	42	-51	-24
Cluster 2					
Right inferior frontal gyrus/middle frontal gyrus	1144	7.02	48	18	6
Cluster 3					
Left insula/inferior frontal gyrus	486	5.41	-33	21	0
Cluster 4					
Left inferior parietal lobule	161	4.83	-27	-57	39
Cluster 5					
Right inferior parietal lobule	338	5.41	39	-51	45
Cluster 6					
Right medial frontal gyrus	309	5.20	6	18	51
<b>Upright &gt;objects</b>					
None					
<b>Conjunction (inverted &gt;upright, inverted &gt;scramble, inverted &gt;objects)</b>					
<b>Inverted &gt;upright</b>					
Cluster 1					
Right precuneus/middle occipital lobule	136	4.29	33	-81	33
<b>Inverted &gt;scramble</b>					
Cluster 1					
Right middle occipital gyrus	953	9.42	42	-72	-12
Cluster 2					
Left inferior occipital gyrus/middle occipital gyrus	801	9.30	-39	-78	-12
Cluster 3					
Right middle temporal gyrus	183	-5.12	60	3	-12
Cluster 4					
Right occipital lobule/cuneus	3430	-7.40	6	-90	21
Cluster 5					
Left insula	161	5.28	-33	24	0
Cluster 6					
Left middle frontal gyrus	891	-6.08	-21	36	45
Cluster 7					
Right insula	1030	5.99	33	24	3
Cluster 8					
Left precentral gyrus	297	5.18	-39	-3	39
cluster 9					
Right medial frontal gyrus	524	6.48	9	15	51
cluster 10					
Right inferior parietal lobule	562	5.67	33	-51	45
Cluster 11					
Left parietal lobe/precuneus	359	5.55	-24	-60	45
<b>Inverted &gt;objects</b>					
None					

**Notes:** The level of significance was set using a threshold of  $\alpha=0.05$  false discovery rate, FDR whole brain corrected.

**Abbreviation:** MNI, Montreal Neurological Institute.

**Table 4** Significantly Activated Regions During the Face Inversion Task Between Patients with Schizophrenia and Healthy Controls

Regions	Cluster Size	T	MNI Coordinates		
			X	Y	Z
<b>CON&gt;FSZ</b> <b>upright &gt; inverted</b> Cluster 1 Left limbic lobe/parahippocampus/hippocampus	26	3.63	-24	-12	-15
<b>Upright &gt; scrambled</b> Cluster 1 Left middle occipital gyrus/cuneus	33	4.17	-21	-93	6
<b>Inverted &gt; upright</b> Cluster 1 Left postcentral/inferior parietal gyrus	33	4.37	-39	-33	45
<b>CON&lt;FSZ</b> <b>upright &gt; scrambled</b> Cluster 1 Left postcentral gyrus/parietal lobe/inferior parietal gyrus/supramarginal	225	-5.67	-39	-33	45
Cluster 2 Right postcentral/parietal lobe/supramarginal	39	-4.67	36	-27	39
<b>Other related contrasts</b> None					

**Note:** The level of significance was set using a threshold of  $\alpha=0.05$  false discovery rate, FDR contrast-specific brain mask corrected.

**Abbreviations:** MNI, Montreal Neurological Institute; CON, healthy controls; FSZ, patients with first-episode schizophrenia.

**Table 5** Three ROIs Selected for Correlations

Regions	Cluster Size	T	MNI Coordinates		
			X	Y	Z
<b>CON&gt;FSZ</b> <b>Upright&gt;inverted</b> Left parahippocampus	26	3.63	-24	-12	-15
<b>Inverted&gt;upright</b> Left postcentral/inferior parietal gyrus	33	4.37	-39	-33	45
<b>CON&lt;FSZ</b> <b>Upright&gt;scramble</b> Left middle occipital gyrus	33	4.17	-21	-93	6

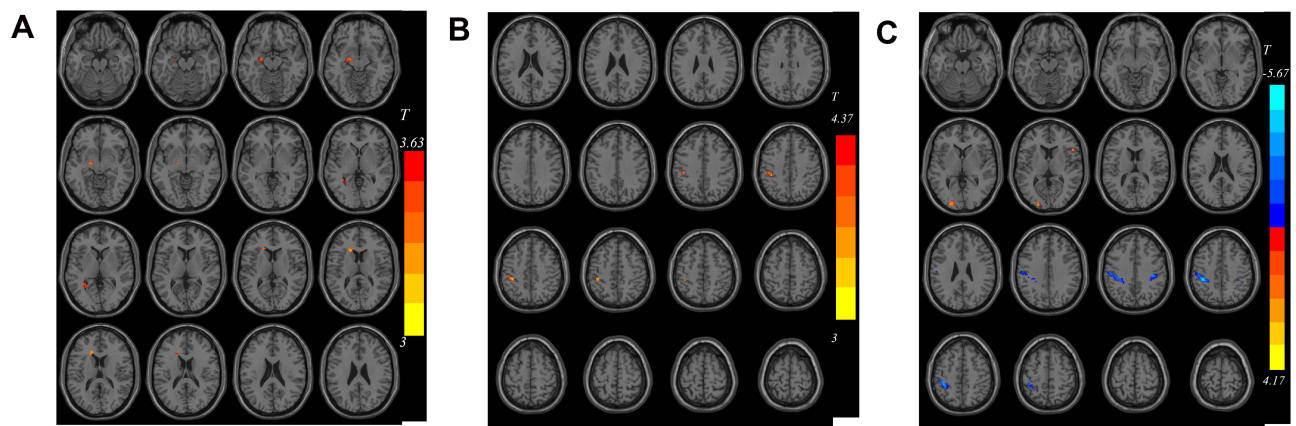
**Abbreviations:** MNI, Montreal Neurological Institute; CON, healthy controls; FSZ, patients with first-episode schizophrenia.

separately.<sup>48,49</sup> Still, other findings implied that inversion induces quantitative, rather than qualitative changes in the face recognition process. Upright features are, therefore, integrated more accurately and faster than inverted features. Face inversion disrupted the patient's ability to extract associated information when discriminating individual faces, and led to a significantly decreased response in recognition of faces.<sup>50</sup> Our results showed a reduced response in the cortical face network during recognition of inverted faces, which was consistent with previous findings. Conclusively, these

findings might suggest that inverted faces are processed similarly as upright faces, but inversion could lead to lower overall processing efficiency.<sup>51</sup>

Previous studies have examined the differences between the processing of upright and inverted faces in healthy controls. However, there is few available data regarding this process in individuals with major psychosis. Some behavioral experiments in individuals with ASD suggested a normal effect of inversion on face recognition.<sup>30,31</sup> A recent review summarized how the upright and inverted faces were processed and identified in individuals with ASD.<sup>52</sup> Our findings about processing differences for upright faces vs inverted faces in patients with schizophrenia are consistent with those ASD studies, suggesting that quantitative processing differences might be critical for how the upright and inverted faces are processed in patients with schizophrenia.

We also found that both processing for upright and inverted faces were impaired in patients with schizophrenia. For inverted faces processing, patients with schizophrenia showed reduced neural response only in the left inferior parietal gyrus and left postcentral gyrus; while, for upright face processing, more regions exhibited abnormal functional activity. Together, these results showed that



**Figure 2** (A) Functional activity differences of upright selective areas between patients with FES and controls (CON>FES). The color bar represents the t values of the functional activity group analysis. (B) Functional activity differences of upright selective areas between patients with FES and controls (CON<FES). The color bar represents the t values of the functional activity group analysis. (C) Functional activity differences of inverted selective areas between patients with FES and controls (CON>FES). The color bar represents the t values of the functional activity group analysis.

individuals with schizophrenia processed faces less efficiently than controls, and indicated that the impairment in upright face recognition was more severe and broader than in inverted face recognition in patients with schizophrenia.

There is evidence that regions for scene and object recognition, ie, the parahippocampal place area (PPA) and lateral occipital cortex, are both involved in the processing of inverted faces.<sup>53</sup> However, in this present study, we observed reduced response in the hippocampus in processing upright faces vs inverted faces, and reduced response in the middle occipital gyrus in the upright face processing. We also found reduced response in the inferior parietal gyrus in processing inverted faces vs upright faces in patients with schizophrenia. These findings provided a clue for the mechanism mediating the processing of upright and inverted features in patients with schizophrenia, which might be the aberrant activation of non-face-selective areas rather than abnormal activation of face-specific areas.

Additionally, our results showed that the reduced activity in the left middle occipital gyrus for upright processing was correlated with the performance of PSP, which reflected the social function outcomes for this devastating illness. One previous study reported functional activity in the occipital cortex, showing a correlation between poor social adjustment and impaired social cognition in patients with chronic schizophrenia.<sup>54</sup> Such findings are in line with the hypothesis that social functioning deficit may correlate with dysfunction in the processing of face information. We failed to find any correlation between inverted face processing and functional outcomes. As compromised inverted face processing could reduce the overall efficiency of face processing,<sup>36</sup> it may play a mediating role in the functional outcome of patients. Our findings have provided evidence for the neural pathway that might be involved in determining the functional outcomes of this disorder.

## Conclusion

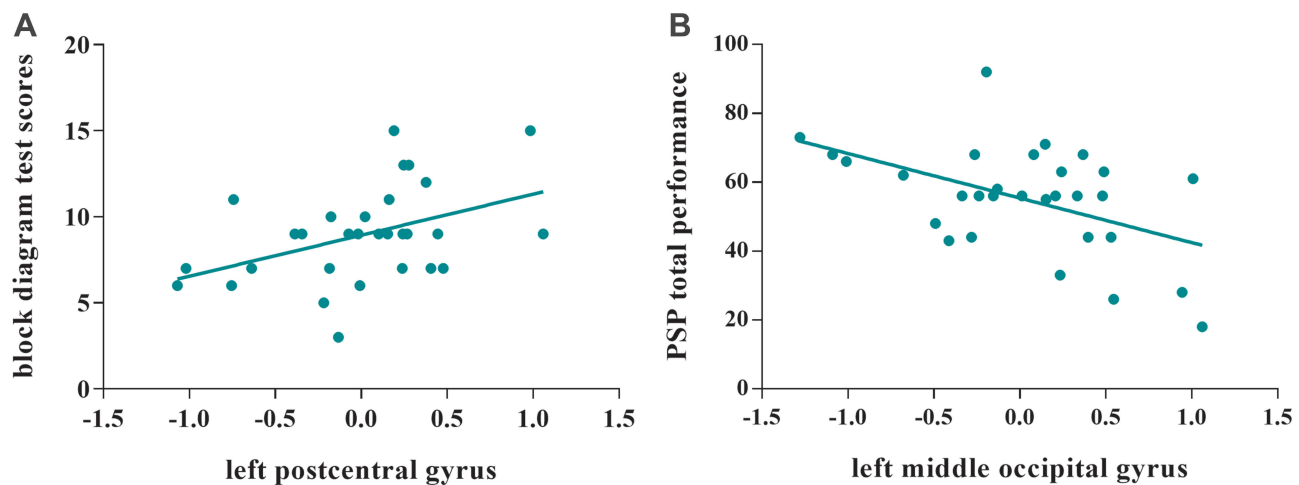
We have demonstrated the abnormal networks involved in upright and inverted face processing in patients with first-episode schizophrenia. Firstly, our results suggested that patients with FSZ process inverted faces and upright faces with similar performance, though inverted faces are processed a bit less efficiently than upright faces. Secondly, our data showed that upright face recognition impairment was more severe and broader than inverted face recognition in patients with schizophrenia. This shed light on the mechanism mediating the processing of upright and inverted features, which might be the aberrant activation of non-face-selective areas, rather than abnormal

**Table 6** Correlations Between Face Processing and Cognitive, Clinical Performances

Items	PSP Total	PANSS General	Block Diagram Test
Left postcentral/inferior parietal lobule	-0.003	-0.007	0.431*
Left middle occipital gyrus	-0.495**A	0.396*	0.225

**Notes:** A: Benjamini and Hochberg corrected  $p < 0.05/2 = 0.025$  significant; \* $p < 0.05$ , \*\* $p < 0.005$ .

**Abbreviations:** PANSS, the positive and negative syndrome scale; PSP, Personal and Social Performance.



**Figure 3** Correlations between the functional activity of the upright and inverted selective areas with cognitive and clinical performance. **(A)** represent the significant correlation between functional activity of the inverted selective areas and the scores of block diagram test. **(B)** represent the significant correlation between functional activity of the upright selective areas and the PSP total scores.

**Abbreviation:** PSP, The Personal and Social Performance Scale.

activation of face-specific areas. Furthermore, reduced neural response for upright face processing in the left middle occipital gyrus was correlated with social function outcomes, whereas no correlation was found between regions involved in inverted face processing. Therefore, the dysfunction of upright face processing rather than inverted face recognition might play a critical role in determining the functional outcome of this devastating disorder.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest.

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