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ORIGINAL RESEARCH

Facial emotion perception abilities are related to grey matter volume in the culmen of cerebellum anterior lobe in drug-naïve patients with first-episode schizophrenia

Xiaoxin Zhao[1] · Jingjing Yao[2] · Yiding Lv[3] · Xinyue Zhang[4] · Chongyang Han[3] · Lijun Chen[3] · Fangfang Ren[3] · Qun Zhou[3] · Zhuma Jin[3] · Yuan Li[3] · Yasong Du[1] · Yuxiu Sui[3]

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Abstract

Impaired capability for understanding and interpreting the expressions on other people's faces manifests itself as a core feature of schizophrenia, contributing to social dysfunction. With the purpose of better understanding of the neurobiological basis of facial emotion perception deficits in schizophrenia, we investigated facial emotion perception abilities and regional structural brain abnormalities in drug-naïve patients with first-episode schizophrenia, and then examined the correlation between them. Fifty-two drug-naive patients with first-episode schizophrenia and 29 group-matched healthy controls were examined for facial emotion perception abilities assessed with the Facial Emotion Categorization and performed magnetic resonance imaging. The Facial Emotion Categorization data were inserted into a logistic function model so as to calculate shift point and slope as outcome measurements. Voxel-based morphometry was applied to investigate regional grey matter volume (GMV) alterations. The relationship between facial emotion perception and GMV was explored in patients using voxel-wise correlation analysis within brain regions that showed a significant GMV alterations in patients compared with controls. The schizophrenic patients performed differently on Facial Emotion Categorization tasks from the controls and presented a higher shift point and a steeper slope. Relative to the controls, patients showed GMV reductions in the superior temporal gyrus, middle occipital gyrus, parahippocampa gyrus, posterior cingulate, the culmen of cerebellum anterior lobe, cerebellar tonsil, and the declive of cerebellum posterior lobe. Importantly, abnormal performance on Facial Emotion Categorization was found correlated with GMV alterations in the culmen of cerebellum anterior lobe in schizophrenia. This study suggests that reduced GMV in the culmen of cerebellum anterior lobe occurs in first-episode schizophrenia, constituting a potential neuropathological basis for the impaired facial emotion perception in schizophrenia.

Keywords Schizophrenia · Facial emotion perception · Grey matter volume

Introduction

It is generally recognized that facial emotion perception (FEP) is an important component of social cognition and sound FEP ability is essential to successful social relationships (de la Torre-Luque et al., 2022). FEP is defined as an individual's understanding and interpretation of facial expressions (Marco-Garcia et al., 2019). A large body of evidence has revealed that the difficulties in recognizing facial expressions contribute to the development of aggressiveness and paranoid symptoms, barrier in personal communication, and a poor functional outcome among patients with schizophrenia (Bulgari et al., 2020; Comparelli et al., 2014; Mitrovic et al., 2020).

✉ Yasong Du
yasongdu2020@126.com

✉ Yuxiu Sui
suiyuxiu@aliyun.com

1 Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China

2 Kangning Hospital, Ningbo 315000, China

3 Nanjing Brain Hospital, Nanjing Medical University, Nanjing 210029, China

4 Kangning Hospital, Shenzhen 518000, China

Previous studies have reported that FEP deficits, consistent and pervasive, exist in patients with schizophrenia (Comparelli et al., 2013; Huang & Hsiao, 2017; Kohler et al., 2010). However, most FEP paradigms adopt pictures that presented different types of basic emotions characterized by full signal strength, and more attention was paid to the accuracy of determining someone's emotions based on their facial expression. Accordingly, previous work in this area may thus have its limitation since they failed to examine the judgments of subtle and ambiguous facial expressions that are frequently experienced in the real world. To address this limitation, we applied an emotional continuum paradigm of morphed facial expression images that anchored with two different basic emotions at both ends to examine whether schizophrenic patients showed abnormal pattern of categorical perception.

Several studies evaluating the association between psychiatric symptoms and FEP in schizophrenia have had inconsistent results. Some studies showed that severity of both positive symptoms (Arguedas et al., 2006; Bosnjak Kuharic et al., 2019; Chen et al., 2009; McBain et al., 2010; Tseng et al., 2013) and negative symptoms (Chen et al., 2012; Kitoko et al., 2019; Leszczyńska, 2015; Romero-Ferreiro et al., 2016; She et al., 2017) have been associated with worse FEP. Some studies (Bozikas et al., 2004; Lee et al., 2015; Ventura et al., 2013) suggested that the severity of the cognitive symptom relates to the deficits on FEP. However, some studies failed to replicate these findings (Baudouin et al., 2002; Caharel et al., 2007). Thus, the picture emerging is that the correlations between clinical symptoms and FEP deserve further examination in patients with schizophrenia.

For approximately the past decade, magnetic resonance imaging (MRI) has undergone rapid growth in its use as a technique to characterize neuroanatomical differences in patients with schizophrenia. Previous morphometric studies have repeatedly reported multiregional grey matter volume (GMV) reductions in schizophrenic patients. A number of structural studies have indicated the disproportionate GMV reductions in multiple regions of prefrontal and temporal lobes in the way of manual volumetry (Shenton et al., 2001; Suzuki et al., 2005). Voxel-based morphometry (VBM) (Ashburner & Friston, 2000) is an assumption-free method for detecting differences in regional GMV throughout the brain, without the necessity of a priori selection of predetermined regions for study, and thus has obvious advantages for the exploratory nature of the present study. A recent meta-analysis of VBM study suggested GMV alterations in such regions as the gyrus rectus, superior temporal gyrus (STG), supramarginal gyrus, middle temporal gyrus, hippocampus, and median cingulate/paracingulate gyrus (Shah et al., 2017). While many studies showed neuroanatomical alterations, the results are inconsistent due to methodological differences and certain confounding factors such as demographic characteristics, long-term exposure to antipsychotics and the possible confounding influences of unmeasured factors (Hashimoto et al., 2018; Liu et al., 2020). It is worthwhile mentioning that the diffeomorphic anatomical registration through an exponentiated Lie algebra (DARTEL) algorithm, developed by Ashburner (2007), is capable of more accurately evaluating GMV by dint of a more precise inter-subject alignment, contributing to a more correct realignment of small inner structure compared with the standard VBM (Whitwell, 2009). Therefore, the picture emerging is that GMV alterations are definitely worth further researching with the DARTEL-based VBM in first-episode schizophrenia.

Several studies have examined the relationships between some of these regional GMV alteration and psychosis severity in individuals with schizophrenia, with mixed results. For instance, GMV alterations were found to be related with negative symptoms (Bora et al., 2011; Ota et al., 2017; Zhang et al., 2015) or positive symptoms (Rao et al., 2010; Roalf et al., 2017) in several discrete region. However, some authors reported that GMV alteration was associated with both positive and negative symptoms (Berge et al., 2011; Koutsouleris et al., 2008), or even failed to find any correlations between regional GMV alterations and the psychopathology of schizophrenia (Fannon et al., 2000). Although relationships between brain morphometric abnormalities and various neurocognitive deficits such as attention, working memory and executive function have been examined in schizophrenia (Antonova et al., 2004; Kelly et al., 2019; Penadés et al., 2019), relatively few attempts have been made to investigate the associations between regional structural alterations and socio-cognitive impairment in schizophrenic individuals.

Realizing the significance of understanding the neuropathology of FEP deficits in schizophrenia, a few pioneering researchers have begun to investigate this potential correlation. A growing body of evidence suggested that poor performance on FEP may involve in the possible abnormalities in the FEP network in schizophrenia, including anterior cingulate cortex (ACC), insula, fusiform gyrus, amygdala, and inferior occipital gyrus (Li et al., 2010). ACC is one of the critical neural structures involved in FEP processing in individuals with schizophrenia (Fan et al., 2011; Kowal et al., 2013). Moreover, evidence indicated that schizophrenia patients showed the deficits in the processing of emotional information and the abnormal response to facial expressions of disgust, which were significantly correlated with the alterations of the insula (Lindner et al., 2014; Wylie & Tregellas, 2010). The fusiform gyrus has been considered to play an important role in FEP in humans (Zhao et al., 2020), and a recent study reported that fusiform gyrus volume reduction was significantly associated with abnormal FEP in patients with schizophrenia spectrum

psychosis (Jung et al., 2021). Patients with schizophrenia showed reduced amygdala activation when exposed to aversive emotional stimuli (Anticevic et al., 2012), or underwent FEP tasks (Gur et al., 2007; Pinkham et al., 2008). Additionally, impaired recognition of fearful facial expressions has been associated with oxytocin by enhancing activities in inferior occipital gyrus in schizophrenia (Dey & Rao, 2017). Rigucci et al. (2013) observed that temporo-occipital GMV decrease was correlated with impaired FEP in first-episode schizophrenia. The discrepancies in these studies could be due, partly, to the small sample size, various sample characteristics (first-episode vs chronic, or naive vs medicated), and several methodological limitations. In accordance with previous studies, the aim of this study was to further investigate the correlation between FEP deficits and structural abnormalities of cerebral regions in naïve patients with first-episode schizophrenia, with a larger population. We employed an advanced FEP test and VBM based on high-resolution structural MRI to investigate voxel-based relationship between them. Furthermore, we also examined the association between the five-factor model PANSS scores and both GMV variations and FEP performance.

Our hypotheses were that: 1) schizophrenic individuals would show regional GMV abnormalities; 2) schizophrenic individuals would exhibit specific FEP deficits; 3) on the condition that the two above-mentioned hypotheses are true, we further hypothesized that FEP deficits would correlate with GMV alterations in specific brain regions in schizophrenia.

Materials and methods

Participants

We recruited 63 patients (44 males,19 females) with schizophrenia and 30 healthy controls (17 males, 13 females) matched for age, sex and education for participation in the study ("American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder (4th edn) (DSM-IV)," 1994). All participants were Han Chinese, and classified as right-handers according to the Annett Handedness Scale (Annett, 1967). The patients were never-medicated with a first episode and recruited from the Nanjing Brain Hospital. Diagnosis was established according to the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P) (First et al., 1996) and confirmed by an associate doctor of psychiatry. The patients had a mean ± SD age of 23.4 ± 5.1 years (range, 17–44), a mean ± SD duration of illness of 10.9 ± 9.2 months (range, 1–24), and a mean ± SD education of 12.7 ± 2.7 years (range, 2–20).

Healthy volunteers were enrolled from the hospital staff and the local community. All controls were interviewed for recruitment using the SCID-I/NP (non-patient version) to exclude individuals with any current or previous neurological or psychiatric disorder. Participants were also excluded if their first-degree relatives had a prior medical history of any psychotic episodes. The controls had a mean ± SD age of 22.1 ± 3.6 years (range, 18–31) and a mean ± SD education of 13.8 ± 2.8 years (range, 9–20).

Subjects were excluded if they had a history of head injury, cerebrovascular disease, neurological disorder such as seizure, were pregnancy, had severe psychiatric illnesses, or are alcohol or drug abusers/addicts. The study is in strict conformity to the ethical standards of the Declaration of Helsinki. The ethical review board of Nanjing Brain Hospital approved the study and written informed consent was obtained from all participants.

Assessment

Clinical symptoms in patients with schizophrenia

The Clinical status was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The PANSS produces a total score and factor scores of five underlying dimensions: positive, negative, disorganized/concrete, excited, and depressed factor (Wallwork et al., 2012). Increasing evidence implicates that the five-factor model better captured the PANSS structure in schizophrenic individuals (Jerrell & Hrisko, 2013a, b; Lancon et al., 2000; Wallwork et al., 2012). To ensure reliability and consistency of assessing across the study, two associate doctors of psychiatry received a training on the use of the PANSS before the study began and were required to reach an intra-class correlation coefficient (ICC) of 0.80 for the repeatability of the PANSS assessments.

Morphed emotional stimuli

The facial emotion images were created from facial emotion photographs of happy and angry developed by Ekman and Friesen (Ekman & Friesen, 1976). Using a computer algorithm, the prototype photographs were morphed in 25% increments in signal-strength to create a linear continuum of five facial images between two endpoints (e.g. 100% happy and 100% angry). For the continuum, pertinent anatomical areas such as the mouth, eyes, nose, and hairline were used as control points. To create the morphed transformation, the pixels around key points were changed from their positions in the start image to their positions in the end image. Importantly, in the morph procedure control points are shifted by an equal percentage of the total distance between their initial and final positions (Pollak & Kistler, 2002). Consequently, facial emotion images were comprised of five levels of facial expressions in each continuum (Fig. 1).

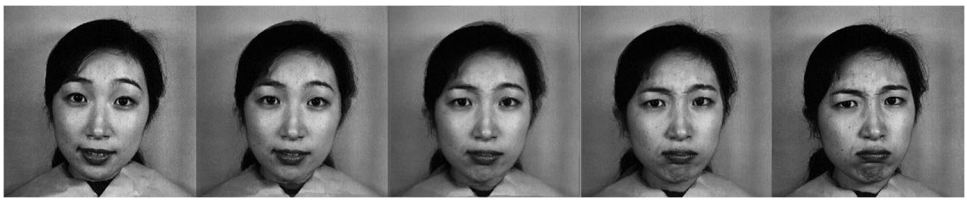

Fig. 1 The illustration of the FEC paradigm. Facial expressions ranging from 100%happy to 100% angry. The expressions located in the middle are ambiguous expressions with morphed features of happy (50%) and angry (50%)

The happy-to-angry continuum were selected because they conformed well in two basic psychological dimensions: pleasant-unpleasant(Tsui et al., 2013).

Facial emotion categorization (FEC)

FEC is a computer-based task to assess FEP (Huang et al., 2011). During FEC task, a facial image was presented centrally on a computer screen with two different labels of emotion appearing beneath the image. the participants were instructed to make a force-choice to determine whether the facial expression was happy or angry as accurately and as quickly as possible to maintain focus and approximate the real life timing of judgments. The facial image remained in view until a response was made. Four practice trials were followed by 60 actual trials, and each level of facial expression presented 12 times in random order. We would record the proportion of response that identifies the image as being "angry" from one prototypical facial emotion to the other (signal strengths 1–5).

Imaging acquisition

All MR data were collected using a 3-Tesla Siemens Verio scanner with a standard head array receive coil. The T1-weighted sagittal images were acquired using a three-dimensional magnetization-prepared rapid acquisition gradient echo (3D-MPRAGE) with parameters: repetition time (TR) = 2530 ms, echo time (TE) = 2.30 ms, field of view (FOV) = 256 mm × 256 mm, acquisition matrix = 256 × 256, slice thickness = 1.0 mm with 0.5 mm gap and slices = 192. All brain scans were examined by an experienced neuroimaging physician and were found to be free from organic brain pathology (for example, tumors, infarcts, bleeding, and obstructive hydrocephalus).

Data processing and statistical analysis

FEC data analysis

FEC data were analyzed using a method described previously by Pollak and Kistler (Pollak & Kistler, 2002). The FEC data were plotted on a graph, with the x-axis representing levels 1–5 signal-strength of the facial expressions and the y-axis representing the percentage of identification within the facial expressions as being "angry". The group level data that were plotted on the graphs generated a sigmoid curve. The data of each participant were also subjected to logistic function models and simple algebraic transformations in order to calculate the parameters "c" (shift point) and "d" (slope) in the light of the formula that is shown below, and then compare group means on these two parameters. However, visual inspection of the data indicated that a logistic model did not fit some patients. The unfitness or invalid data could be owing to the careless or random selection during the task and should be excluded to ensure the genuineness and reliability. The shift point indicated when the subjects' emotion judgments began to change and the slope indicated how rapidly these changes happened at the shift point in the emotion continuum. A greater shift point indicates the "late" perception in the emotion continuum and a greater slope indicates the clearer demarcation and the greater sensitivity towards the emotional intensity.

$$y = a + b/(1 + e^{-|(x-c)/d|})$$

- y probability of the identification of an "angry" emotion
- x signal strength (1–5), with reference to the % of "angry" emotion signals
- a lower asymptote
- b difference between upper and lower asymptotes
- e exponential function
- c shift point
- d slope

Voxel-based morphometry analysis

GMV alterations were examined on T1 images using Voxel-based morphometry (VBM) toolbox in Statistical Parametric Mapping software (SPM, http://www.fil.ion.ucl.ac.uk/spm). To improve the registration of the MRI images, we applied the diffeomorphic anatomical registration through an exponentiated Lie algebra (DARTEL; Ashburner,

2007) algorithm, which facilitates precise reorganization of small subcortical structures and has been shown to be more sensitive to regional changes in brain volume than standard VBM methods (Klein et al., 2009). All the processing steps were performed as suggested by Ashburner (2010). (1) the raw anatomic images were first manually reoriented so that the coordinate of the anterior commissure matched the origin (0, 0, 0), and were approximately aligned with Montreal Neurological Institute (MNI) space. (2) T1-weighted images were segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the 'new-segment' option implemented in SPM8. (3) Flow fields and a series of template images were generated by running the 'DARTEL (create templates)' routine using DARTEL imported versions of GM and WM generated in the previous step. (4) In this step, DARTEL increases the accuracy of inter-subject alignment by modeling the shape of each brain using millions of parameters (three parameters for each voxel). DARTEL works by aligning gray matter among the images, while simultaneously aligning white matter. This is achieved by generating increasingly crisp average template data to which the data are iteratively aligned. The final voxel resolution after DARTEL was 3 mm × 3 mm × 3 mm. (4) Modulated, smoothed (full width at half maximum = 8 mm), spatially normalized tissue images were generated in MNI space by running the 'normalize to MNI space' option using the flow fields and the final template image created in the previous step. At the end of this pre-processing, modulated, smoothed, normalized images were obtained for statistical analysis.

Group-level analyses were carried out to examine GMV abnormalities in schizophrenia. The GMV over the whole-brain structures were compared between the patient and control subjects using permutation-based statistical analysis with 5000 permutations, with age, gender, education, and the total intracranial volume as covariates. Statistical significance was defined as $p < 0.005$, correcting for multiple comparisons by threshold-free cluster enhancement (TFCE) (Smith & Nichols, 2009). The GMV reduction/increase areas in patients were used as inclusion masks to perform the following voxel-wise correlation analysis.

Correlation analysis

Voxel-wise correlation analyses were carried out to explore the grey matter regions that correlated with the severity of symptoms (the total PANSS score, and positive, negative, disorganized/concrete, excited, and depressed factor) and each FEC parameter (shift point and slope) in patients. Age, gender, education, illness duration, and the total intracranial volume were considered as covariates of no interest. The above-mentioned masks were used to include only those voxels that showed significant group differences. The randomized permutation-based nonparametric inference was undertaken with 5000 permutations. The significance threshold was set to a p-value of 0.05 corrected for multiple comparisons using family wise error rate (FWE).

Partial correlation analyses between FEC performance and clinical variables in schizophrenic patients were performed in SPSS and control for the effects of age, gender, education, and illness duration. To correct for multiple tests a Bonferroni was applied. Since we used 6 components of PANSS (total score and five factor scores) and both FEC parameter (shift point and slope), a P value less than 0.0042 (0.05/12) was considered statistically significant after Bonferroni's correction.

To examine the correlation between FEC performance and GMV in controls, the same correlation analyses were conducted for the whole brain of healthy controls. Within controls, the threshold for statistical significance was set at $P < 0.05$ for correction of multiple comparisons using FEW, given the exploratory nature of this study.

Results

Demographic and symptom data

Table 1 shows the demographic data and clinical variables of schizophrenic patients and the controls. There were no statistically significant differences between patients and controls regarding age, gender, and education.

FEC data

Figure 2 shows the sigmoid curves based on the raw data obtained from the FEP performance of patients and controls. To evaluate when and how rapidly the subjects began to identify facial expressions as angry, we compared the mean shift point and slope of the two groups. There were significantly difference between patients and controls with respect to both shift point and slope as shown in Table 1. The patients showed a higher shift point in FEC, namely, a "late" categorization when the facial expression turning from happy to angry compared with controls, indicating that schizophrenic patients were more likely to categorize subtle facial expressions as "happy" rather than "angry". For the analysis of slope, the patients exhibited a greater slope in FEC, namely, a steeper response slope when the facial expression shifting from happy to angry compared with controls, suggesting that schizophrenic patients had a clearer demarcation along the happy-to-angry continuum.

Table 1 Demographic data, clinical information and FEC measures in patients with schizophrenia and health controls

	FES ($n=52$)[a]		HC ($n=29$)[a]			Statistics
	Mean	S.D	Mean	S.D	t/x^2	p value
Age, years	23.4	5.1	22.1	3.6	1.218	0.227[b]
Gender (male/female)	38/14		17/12		1.785	0.182[c]
Handedness (right/left)	52/0		29/0		-	-
Education, years	12.7	2.7	13.8	2.8	-1.847	0.068[b]
DUP, months	10.9	9.2	NA		-	-
PANSS						
Total	101.5	18.0	NA		-	-
Positive factor	15.2	3.6	NA		-	-
Negative factor	24.7	7.1	NA		-	-
Disorganized/ concrete factor	10.4	3.0	NA		-	-
Excited factor	9.6	4.4	NA		-	-
Depressed factor	8.9	3.4	NA		-	-
FEC						
Shift point	3.11	0.30	2.90	0.44	2.297	0.023[b]
Slope	0.21	0.21	0.11	0.12	2.691	0.009[b]

There was no significant difference between patient and healthy control groups in age, gender, and education (all p values > 0.05)

FES first-episode schizophrenia, *HC* healthy control, *DUP* Duration of untreated psychosis, *PANSS* Positive and Negative Syndrome Scale, *FEC* Facial emotion categorization, *NA* not applicable

[a]Seven schizophrenic patients and one control subject were excluded because the data did not fit a logistic curve pattern, likely due to careless or random selection of response during the FEC task. Four other schizophrenic patients were excluded due to poor quality of data. The excluded patients included 6 males and 5 females, and the excluded controls included 1 females

[b]Two-tailed t-tests

[c]Two-tailed chi-square tests

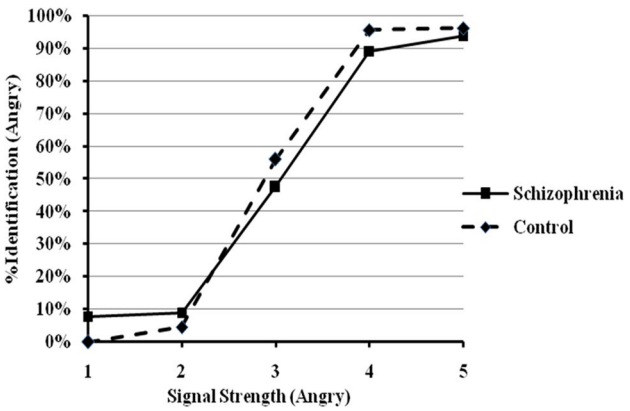

Fig. 2 Performance on the happy-angry continuum for schizophrenia and control groups. The x-axis represents the level of signal strength of the emotion continuum, ranging from level 1 (100% happy and 0% angry) to level 5 (0% happy and 100% angry). Level 3 is the ambiguous emotion with 50% happy and 50% angry. The y-axis represents the proportion of response that identifies the image as being angry

Regional GMV reductions in schizophrenia compared with controls

Compared to healthy controls, schizophrenia patients reported GMV reductions mainly located in temporal, occipital, limbic, and cerebellar grey. Large clusters of GMV reductions were identified as containing the left STG, left middle occipital gyrus (MOG), right parahippocampa gyrus, left posterior cingulate, the culmen of right cerebellum anterior lobe (CAL), left cerebellar tonsil, and the decisive of left cerebellum posterior lobe (CPL) (Table 2 and Fig. 3). There were no significant GMV increase in schizophrenia patients.

Correlation analyses

The voxel-wise correlation analyses showed that, in the patient group, the negative factor was significantly negative correlated with GMV in the left MOG ($r=-0.480$, $P<0.05$, FWE-TFCE-corrected; Fig. 4A). The PANSS total score, positive factor, disorganized factor, excited factor, and depressed factor did not correlate significantly with the

Table 2 Brain areas with significant GMV reductions between schizophrenia patients and healthy controls

Region	Hemisphere	Cluster size (voxel)	MNI coordinates (mm)			t value
			x	y	z	
Temporal Lobe						
STG	Left	193	-55.5	-15	9	-4.31
Occipital Lobe						
MOG	Left	3552	-46.5	-81	-15	-4.17
Limbic Lobe						
Parahippocampa Gyrus	Right	45	22.5	-40.5	-10.5	-3.67
Posterior Cingulate	Left	26	-19.5	-69	15	-3.22
Cerebellum						
CAL (Culmen)	Right	98	12	-57	-24	-3.10
CPL (Cerebellar Tonsil)	Left	185	0	-49.5	-46.5	-2.33
CPL (Declive)	Left	43	-3	-66	-28.5	-2.64

$P < 0.005$, corrected by TFCE

MNI Montreal Neurological Institute, *STG* superior temporal gyrus, *MOG* middle occipital gyrus, *CPL* cerebellum posterior lobe, *CAL* cerebellum anterior lobe

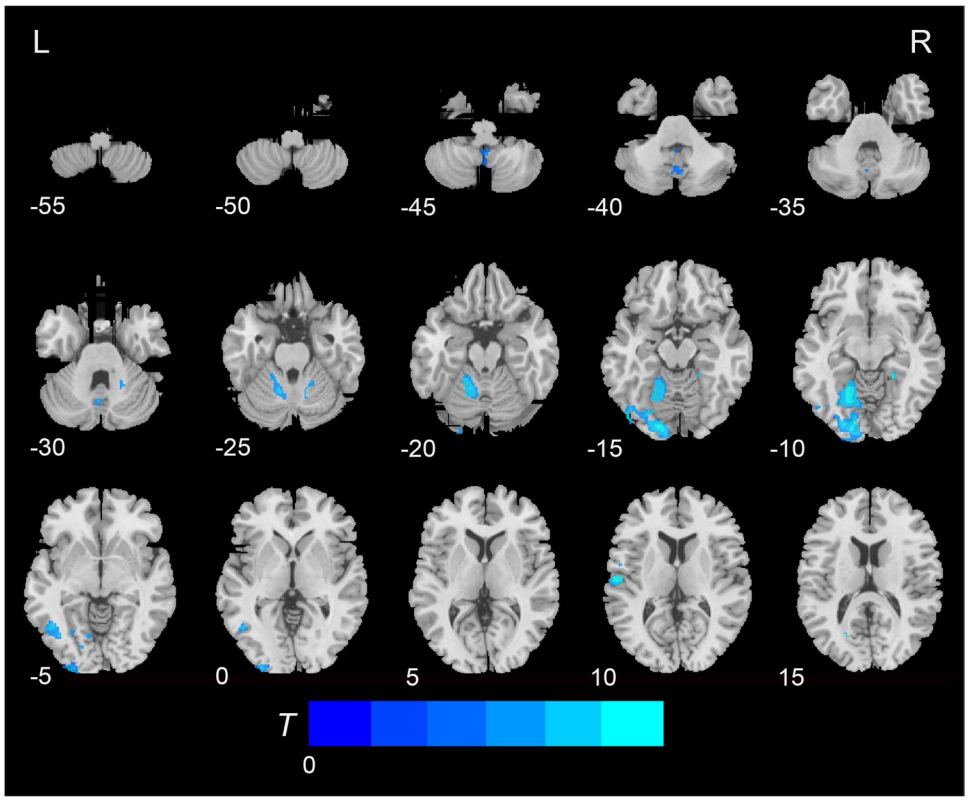

Fig. 3 Brain regions with significantly reduced GMV in schizophrenic patients compared to control subjects. Statistically significant differences in GMV were defined as $p < 0.005$, TFCE corrected after correcting for age, gender, education, illness duration and the total intracranial volume. Blue color indicates that GMV is lower in the schizophrenic patient group than in the healthy control group

GMV in brain regions that showed significant group differences. Performing the same analysis between the FEC performance and GMV in schizophrenia, we found a significant positive correlation between shift point and GMV in the left culmen of CAL ($r = 0.483$, $P < 0.05$, FWE-TFCE-corrected; Fig. 4B). These results are summarized in Table 3. No relationships were observed between GMV and shift point or slop in the control group.

Correlations between FEC performance and clinical variables are showed in Fig. 5. As shown in Fig. 5, there was a significant negative correlation between a slope and the PANSS negative factor. However, the value of the correlation coefficients was very low ($r = -0.349$), indicating a weak correlation between them. Moreover, the result is not significant with Bonferroni correction for multiple testing, for which a P value less than 0.0042 (0.05/12) is considered

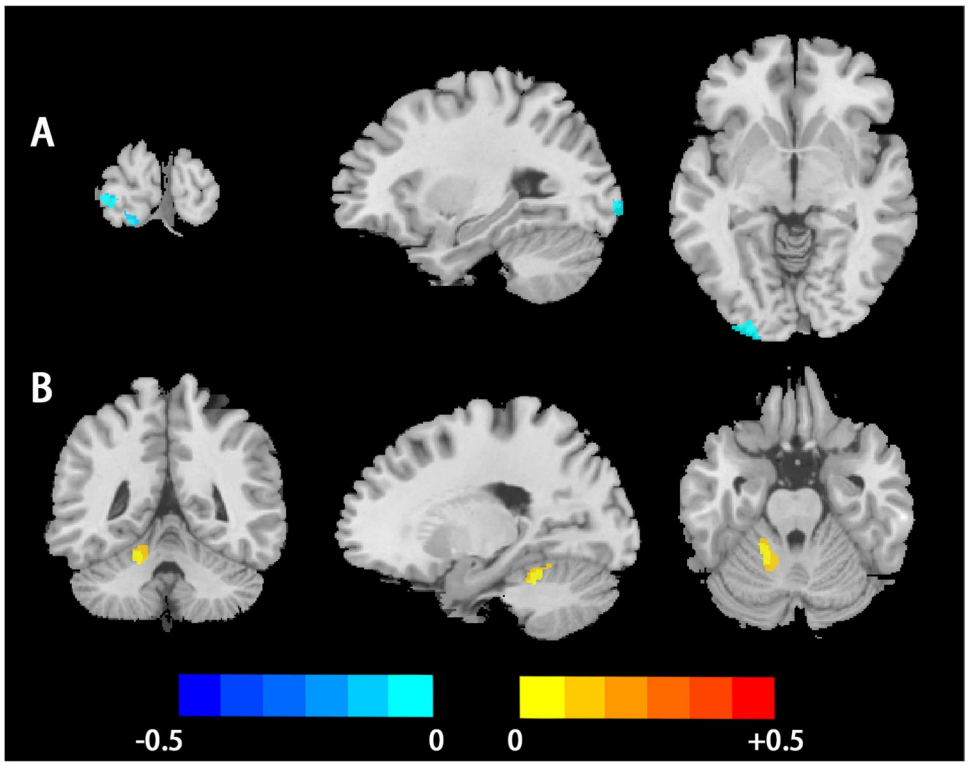

Fig. 4 The correlation analysis showed the PANSS negative factor negatively correlated with GMV in the left MOG (A), and the shift point positively correlated with GMV in the left CAL (culmen) in schizophrenic patients. Significant correlations were defined as $P < 0.05$, TFCE and FWE corrected after correcting for age, gender, education, and illness duration. The warm color indicates a positive correlation, and the cold color represents a negative correlation

Table 3 Significant correlations between PANSS, FEC performance and GMV in schizophrenic patients

	Correlation coefficient r	Anatomical region	MNI coordinate			Cluster size
			X	Y	Z	
PANSS						
Negative factor	- 0.480	Left MOG	-28.5	-96	-4.5	312
FEC						
Shift point	0.483	Left CAL (Culmen)	-19.5	-46.5	-24	362

Coordinates for the peak voxels are displayed. $P < 0.05$, corrected by TFCE and FWE after correcting for age, gender, education, and illness duration

significant. No significant correlations were found between slope and the PANSS total score, positive factor, disorganized/concrete factor, excited factor and depressed factor, respectively. Additionally, no significant correlations were observed between shift point with the PANSS total score or any component subscale.

Discussion

Facial emotion perception is considered a key component of social cognition (Olderbak et al., 2019) and has been previously observed to be abnormal in schizophrenia (Gao et al., 2021). However, it is not well investigated whether facial emotion perception deficit in schizophrenic patients is accompanied by GMV abnormalities in first-episode schizophrenia. In this study, the patients with first-episode schizophrenia exhibited significant deficits in FEP. These facial emotion perception impairments appear along alterations in regional GMV. Our study suggested that alterations in regional GMV might be associated with facial emotion perception deficit in first-episode schizophrenia.

The present study investigated the facial emotion perception of schizophrenia, and demonstrated a different response pattern in the happy–angry emotional continuum. When facial expressions initially presented happy (positive) and then gradually shifted to angry (negative), the schizophrenic patients compared with the controls, tended to categorize ambiguous expressions as happy, which demonstrated that patients with schizophrenia had an over-optimistic response bias towards angry or their insensitivity to the increasing intensity of facial expression. Consistent with our findings, there is a growing body of evidence to suggest that patients with schizophrenia have a positive bias for neutral cues in

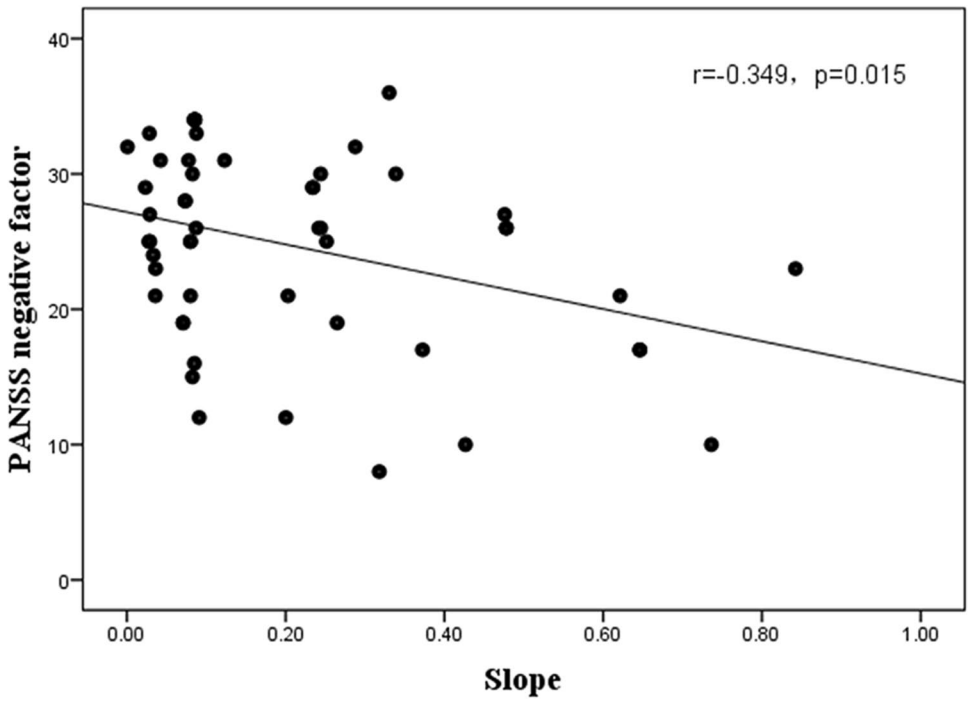

Fig. 5 Correlation between slope and PANSS negative factor in patients with schizophrenia. Partial correlation analysis revealed the negative correlation between the slope and negative factor

facial expressions (Huang et al., 2011; Kohler et al., 2003; van Dijke et al., 2016). The reason for this response bias, to some degree, might be interpreted as the result of the deficit of mislabeling ambiguous expressions as angry. Indeed, this was demonstrated in a number of studies that showed that the deficits on the perception of negative facial expressions were greater compared with that of positive facial expressions (Leppänen et al., 2006; Martin et al., 2005; Tseng et al., 2013; van Dijke et al., 2016). In addition, the reason why schizophrenia patients were less sensitive towards the increasing intensity of facial expressions could be partly due to the consequence of trying to avoid identifying angry facial expression. As such, the avoidance of threat-related signals such as angry may allow patients to cope with the unpleasant sensation related to socially threatening stimulus in individuals with schizophrenia. This is consistent with the observation from a "vigilance-avoidance" style of processing threat-related signal in cognitive models of anxiety (Forscher & Li, 2012; Fox et al., 2012).

In the present study, DARTEL-based VBM was used to evaluate the change of GMV in schizophrenic patients, showing a significant GMV reduction in the STG, MOG, parahippocampa gyrus, posterior cingulate, the culmen of CAL, cerebellar tonsil, and the declive of CPL. Our findings were largely consistent with previous VBM studies (Banaj et al., 2018; de Castro-Manglano et al., 2011; Greenstein et al., 2011; Moberget et al., 2017), while others reported GMV reduction in different regions (Fujiwara et al., 2007; Hirao et al., 2008). Although the GMV change in frontal lobe, which is often reported in schizophrenic patients, was not detected with a highly conservative threshold significance, it was found at a relatively lower threshold. While a considerable heterogeneity, such as illness duration, medication effects and methodological differences, has been confounded in the results of VBM studies, our current findings, together with those in most of the previous VBM studies, provide strong evidence for GMV abnormalities in the pathophysiology of schizophrenia, even at an incipient stage of disease, suggesting that the abnormalities in GMV may play a fundamental role in the global nature of the clinical, cognitive, and social symptoms(Banaj et al., 2018; Delvecchio et al., 2017; Kim et al., 2017; Minatogawa-Chang et al., 2009; Rigucci et al., 2013; Yamada et al., 2007).

Previous studies exploring the relationship between GMV and PANSS in schizophrenia have reported inconsistent results. An early study (Neckelmann et al., 2006) showed a negative correlation of the GMV with hallucinations in the left STG, left thalamus, and left and right cerebellum in chronic schizophrenia. In addition, Rigucci et al (2013) reported that the reduced GMV in the left cerebellum was associated with the disorganized/cognitive PANSS factor. A more recent study (Kim et al., 2017) showed a negative correlation of the GMV with the positive scales of the PANSS in STG and gyrus rectus and a negative correlation between negative scales and the GMV of STG and anterior cingulate cortex in chronic patients with schizophrenia. However, Rigucci et al (2013) did not detect a significant association between negative symptoms and cortical GMV in first-episode schizophrenia. The findings of this study showed that the GMV decrease in the left MOG was

negatively associated with PANSS negative factor in first-episode schizophrenia. Taken together, these studies suggest that GMV abnormalities in different brain regions may account for different symptoms of schizophrenia in the early stages of illness.

Commonly the cerebellum is thought of as a structure in fine motor control and coordination of the body. However, converging evidence suggests that the cerebellum is also involved in social and higher cognitive functions. The potential implication of the cerebellum has been involved in the "cognitive dysmetria" of schizophrenia proposed by Andreasen (Andreasen et al., 1999). Since the cognitive dysmetria model was proposed, converging evidence has provided strong support for cerebellar pathology and dysfunction. Such structural abnormalities contribute to impairments in cognitive processes, including facial recognition (Andreasen et al., 1996; Andreasen & Pierson, 2008) and contribute to sensorimotor dysfunction (Apthorp et al., 2018; Moussa-Tooks et al., 2018). Abnormalities in connectivity within the cerebellum or between the cerebellum and other brain regions could result in an impairment in sequencing and coordinating sensorimotor and mental processes (Andreasen et al., 1999). In particular, compelling evidence suggests that sensorimotor simulation is conductive to accurately and efficiently recognizing the facial expressions (Borgomaneri et al., 2020; Wood et al., 2016). Thus, it is notable that cerebellar anomalies may play a vital role in the deficit of FEP in schizophrenia, while this finding should be interpreted cautiously. In addition, previous studies have suggested volumetric alterations in prefrontal–thalamic–cerebellar grey matter networks may lead to executive dysfunction in schizophrenia (Rusch et al., 2007; Segarra et al., 2008). Besides, GMV alterations in the cerebellum have been reported to play an important role in such domains as neurological soft signs, posture, or equilibrium in schizophrenia (Picard et al., 2008). Substantial research evidence suggests that executive functions may be associated with FEP in first-episode patients with schizophrenia (Yang et al., 2015), which could be explained by the fact that schizophrenia patients with dysfunctions of FEP, have to mobilize more cognitive strategies in order to complete the recognition. In particular, our result suggests that GMV in the culmen of CAL is associated with FEP in schizophrenia, which indicates that the GMV alterations in the cerebellum may contribute to the impairments in FEP in patients.

After reviewing relevant studies examining the relationship between facial emotion perception and PANSS in schizophrenia, a heterogeneous picture emerges. The current study revealed that FEP impairment correlated with the PANSS negative factor, despite in a weak manner, consistent with other studies (Chan et al., 2010; Chen et al., 2012; Herbener et al., 2005; Kitoko et al., 2019; Kohler et al., 2003; Leszczyńska, 2015; She et al., 2017). However, some studies reported that poor performance on FEP correlated with PANSS total score, and the severity of the delusion/hallucination and cognitive symptom dimension (Arguedas et al., 2006; Bosnjak Kuharic et al., 2019; Bozikas et al., 2004; Tseng et al., 2013). The inconsistent findings of these studies may be due to the heterogeneity in the FEP assessment methods and clinical characteristics (age, gender, or intelligence quotient, etc.), and interpatient differences greatly affected by the course of the disease, antipsychotic drug use, and other factors. Taken together, these results suggest that impaired FEP may reflect structural abnormalities or dysfunction of the brain underlying severity of symptoms in schizophrenia.

Some limitations of the current study should be considered. To begin with, we acknowledge a major limitation of the present study is the small sample size derived from one center, although it is comparable to most imaging studies in FES to date. Larger samples available at multiple centers have to be analyzed in the future to confirm our findings. Moreover, our study ignored the effect of contextual information on FEP. Given the increasing evidence that patients with schizophrenia fail to integrate social contextual information into real-world situations, it is necessary to refine our paradigm by using social dyadic interaction, such as eye gazing (Caruana et al., 2020; Green et al., 2008) or conversation (Garrod & Pickering, 2004), to clarify the uncertainty of our findings. Furthermore, it is worth noting that the standard deviations of the slopes were large, indicating that per-participant difference in slopes is large for the measure. Besides, we adopted only the happy-angry emotion continuum, making it difficult to demonstrate whether the schizophrenia patients have general or specific differential response patterns in emotion processing. In addition, while the findings of correlations between FEP and GMV alterations are encouraging, it should be noted that they must be interpreted cautiously, as the associations achieved only marginal statistical significance, raising the possibility of false discovery and p-hacking. Last but not least, we excluded the patients who were unable to participate in the study or unwilling to cooperate due to impulsivity or severe symptoms, so the aforementioned limitations should be taken into consideration when the findings are interpreted.

Conclusion

In summary, with fewer confounders, our findings indicate that patients with first-episode schizophrenia showed GMV reductions in multiple brain regions, suggesting the involvement of GMV abnormalities in the pathophysiology of schizophrenia. The patients with schizophrenia showed a differential response pattern from controls, tending to categorize ambiguous expressions as happy, and possessing

an over-optimistic response bias towards angry when facial expressions gradually shifted from happy to angry. Moreover, the GMV reduction in the culmen of CAL was associated with the impaired FEP, shedding a new light on the contribution of cerebellum to the FEP deficits in schizophrenia.

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Author contributions Concept and design: X.Z., J.Y., Y.D., Y.S.; Acquisition, analysis, and interpretation of data: Y.L., X.Z., C.H., L.C., F.R., Q.Z., J,J., Y,L.; Drafting of the manuscript: X.Z.; Critical revision of the manuscript: Y.D., Y,S.; Statistical analysis: X.Z.; The authors read and approved the final manuscript.

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Data availability The de-identified datasets generated used in the study are available from the corresponding author on reasonable request.

Declarations

Ethical approval All research procedures were approved by the Medical Research Ethics Committee of Nanjing Brain Hospital, and were conducted in accordance with the 1964 Helsinki declaration and its later amendments.

Informed consent Written informed consent of the schizophrenic patients were obtained from his/her legally authorized representative and the controls provided written informed consent himself/herself after totally understanding the purpose of our study.

Conflicts of interest Xiaoxin Zhao, Jingjing Yao, Yiding Lv, Xinyue Zhang, Chongyang Han, Lijun Chen, Fangfang Ren, Qun Zhou, Zhuma Jin, Yuan Li, Yasong Du and Yuxiu Sui declare that they have no conflicts of interest.

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