Childhood Trauma Associated With Abnormal Resting-State Brain Network Connectivity in First-Episode Schizophrenia Patients

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Abstract

Childhood trauma is a central risk factor for schizophrenia. We explored the correlation between early traumatic experiences and the functional connectivity of resting-state networks. This fMRI study included 28 first-episode schizophrenia patients and 27 healthy controls. In first-episode schizophrenia patients, higher levels of childhood trauma associated with abnormal connections of resting-state networks, and these anomalies distributed among task-positive networks (i.e., ventral attention network, dorsal-ventral attention network and frontal-parietal network), and sensory networks (i.e., visual network and auditory network). These findings mentioned that childhood traumatic experiences may impact resting-state network connectivity in adulthood, mainly involving systems related to attention and execution control.

1. Background

Childhood trauma (CT), a severe form of stress, and a central risk factor for schizophrenia(SZ)[1]. A meta-analysis involving prospective and retrospective studies showed that early traumatic experiences were significantly related to increased risk of psychosis[2]. Other studies conducted in various countries have also revealed that abuse or neglect in childhood increase the risk of schizophrenia in later life[3–5], and in clinical high-risk population [6]. Read et al. proposed the Traumagenic Neurodevelopmental (TN) model based on the similarities of biochemical and neurological changes between schizophrenia patients and individuals exposed to childhood abuse in 2001, which heuristically postulated that the biochemical and neurological abnormalities could originate in traumatic experiences in childhood. As more evidence emerged from studies investigating the relationship between CT and dopaminergic system, neuroimaging alterations, and hypothalamic–pituitary–adrenal (HPA) axis, the revised TN model highlighted that CT could contribute to manifestations of schizophrenia via the heightened sensitivity to stress and reduced cognitive functioning[7]. Indeed, previous studies have pointed that CT can significantly impact stress responses[8, 9] and cognitive performances, including processing speed[10, 11], working memory[10, 12], attention[13] and social cognition[14], although findings in cognitive functioning sometimes contradict with one another. On the other hand, research in schizophrenia suggested that CT is related to poor insight and metacognitive ability, social function, family function [15–18].

Giving its role in stress reactivity and cognitive functioning[19], some related brain areas(i.e., amygdala and prefrontal cortex (PFC)) been extensively scrutinize in schizophrenia and other psychosis. Hoy et al. had initially reported the association between CT and brain morphology[20]. Their study showed that traumatic experience in childhood negatively predicted the volumes of right and total amygdala in first-episode schizophrenia(FES) patients. Similar results found in a larger sample[21]. Moreover, several functional MRI (fMRI) studies suggested that childhood adversity was also correlated with abnormal amygdala activation under emotional stimuli[22], while those findings in schizophrenia patient were discrepant, that both hyper and hypoactivation were both shown in this region[23]. Benedetti et al. first discovered that severer adverse childhood experience was associated with higher gray matter (GM) volume in some brain areas(i.e., anterior cingulate cortex(ACC) and PFC) in chronic SZ patients[24]. Sheffield et al. suggested that sexual abuse was negatively associated with GM volume in the left middle frontal gyrus in psychotic patients[25]. Cancel et al. found an association between emotional neglect with reduced GM volume in the right dorsal lateral prefrontal cortex (dlPFC) in same population, and which predicted the disorganization symptoms[26].

Subsequently, Cancel was inspired by the idea proposed by Friston that connectivity between brain regions offer more crucial information on aberrant brain function in psychosis[27], thereby setting off to investigate the correlation between CT and functional connectivity of the amygdala during an emotional valence task in SZ patients[28]. Benedetti et al. also reported the association between increased ACC activity during an emotional processing task and higher exposure to CT in chronic SZ patients[24]. Quide et al. demonstrated increased activation in the dorsal median prefrontal cortex (dmPFC) during a Theory-of-Mind task were associated with CT in schizophrenia patients[12]. This work indicated that sexual abuse and physical neglect occurred were associated with functional connectivity of the amygdala, prefrontal cortex region[28]. However, the role of the correlation between CT and brain resting-state networks（RSNs）in the pathogenesis of schizophrenia is still unclear. The dysfunction of RSNs is a typical neuroimaging characteristic of schizophrenia while comparing with healthy controls[29], which was mainly manifested in the ventral attention network(VAN), the default mode network(DMN), the frontal-parietal network(FPN) and so on, maybe the basis of abnormal behavioral characteristics[30]. Moreover, the abnormalities in network connectivity in schizophrenia are associated with psychotic symptoms[31], cognition[32] and social cognition impairment[33], treatment outcomes[34] and so on.

In summary, as a significant risk factor for schizophrenia, CT prominently impacts the function of the brain regions related to stress reactivity and cognitive functioning. Despite there are shreds of evidence showing the correlations between CT and structural or functional alterations in some brain areas, as well as in the pathophysiology of schizophrenia. Still, the functional abnormalities of RSNs didn't been well investigated. Therefore, we proposed to examine the correlation between CT and brain functional connectivity of RSNs in FES through a resting-state fMRI study. We first compared differences in CT history between FES and healthy control(HC)，then, among the FES group, we examine correlations between CT and demographic, cognition, clinical characteristics. Finally, we studied relationships between CT and brain network connectivity in resting state. In general, we used seed-based methods to test two patterns of functional connectivity, including seed-to-voxel maps for each RSN versus the whole brain and ROI-to-ROI maps for between-network connectivity.

2. Methods

2.1 Participants

This study approved by the Human Research Ethics committees of Tongji Hospital of Tongji University and Shanghai Mental Health Center (SMHC) in China, and all recruited participants ensured informd consent, data were collected from Feb. 2014 to Sept. 2018, statistical analysis conducted from Jun. 2019 to Jan. 2020.

Including 30 FES subjects were recruited from outpatients of the hospital, and 30 HC subjects matched for gender and age (n= 30) were recruited from the local community. Two senior associate chief physicians would determine whether individuals of FES were presence or absence of psychotic symptoms by the SCID (Structured Clinical Interview for Diagnostic) assessment form of DSM-IV(Diagnostic and Statistical Manual of Mental Disorders fourth edition) and ensured the first episode with a course of disease less than two years, had never taken antipsychotics or stopped antipsychotics for five half-life periods or more. Other inclusion criteria for both groups were as follows:(1) Han ethnicity, right-handed; (2) Wechsler Intelligence Scale(IQ) was >70. Exclusion criteria for all participants were as follows: (1) Inability to conduct the MRI examination;(2)Current neurological disorder and major somatic diseases; (3)History of severe head injuries; (4)Having received electro-convulsive therapy within six months; (5)long-term use of medication that could potentially affect cognitive function(i.e., anticholinergics, benzodiazepine). In this study, some FES subjects may have received a certain amount of antipsychotic drugs from the time of enrollment to the time of examination due to impulsivity and behavioral chaos, so antipsychotics drug doses at that time have been converted to olanzapine (OLZ) equivalent doses for further analysis.

2.2 Study materials

2.2.1 Demographics and clinical assessments

The Demographics and clinical data collected through two modules. Module one completed by researchers, including demographic survey forms, previous medical history tables, clinical symptom assessments, and cognitive assessments. Demographic survey forms include gender, age, race, marital status, hand habits, occupation, years of education, birth and current residence, family status, and general family relationships; previous medical history table contain the history of precious physical diseases and combined medications (non-antipsychotics), it mainly investigates the history of hospitalization and illnesses that can cause mental symptoms such as hyperthyroidism, encephalitis, head injury and so on. The following five clinical measures were used to evaluate clinical symptoms: PANSS(Positive and Negative Syndrome Scale); CGI (Clinical Global Impression Scale); GAF (Global Assessment Functio; MADRS (Montgomery-Åsberg Depression Rating Scale); And MCCB (MATRICS Consensus Cognitive Battery) for assessing cognitive functions.

Module two completed by the patients, including the Chinese version of CTQ (Childhood Trauma Questionnaire) and FACES Family Adaptability and Cohesion Scale . CTQ was a scale consisting of 28 self-assessed items used to assess children's traumatic experience, includes five sub-dimensions (i.e., emotional abuse and neglect, physical abuse and neglect, sexual abuse), CTQ had good reliability and validity in patients with mental disabilities, and its Cronbach alpha coefficient of Chinese version was 0.824[35]. FACES was translated into Chinese by Fei, composed of two sub-dimensions: family cohesion and family adaptability, 15 items per dimension, each item graded from 1 to 5 points. The Cronbach alpha coefficient of the total and subscales was > 0.6 in schizophrenic families[36].

2.2.2 Statistical Analysis

Demographics and clinical assessments comparisons between groups were conducted with the SPSS software (SPSS version22.0, http://www.spss.com.hk/statistics/) for all tests. Clinical assessments, CTQ, FACES Ⅱ, and other continuous variables were compared using a two-sample, two-tailed t-test (significance level of $P < 0.05$). Categorical variables (i.e., gender) between the two groups assessed using a $\chi 2$ test (significance level of $P < 0.05$). Next, we performed multivariate statistics across clinical measurement dimensions using the Pearson correlation test (significance level of $P < 0.05$) and Bonferroni correction.

2.3 MRI data Acquisition

SMHC conducted MRI scans using a Siemens 3.0T MAGNETOM Trio Tim MRI Scanner, and all subjects were equipped with foam ear tips to reduce noise, foam pads were placed between the subject's head and the coil to minimize subject's head movement, and required to lie down and keep awake but eyes closed and head still. A total of 240 Whole-brain T2*-weighted echo-planer images (EPI) was obtained with slice thickness 3 mm, TR 2000 ms, TE 30 ms, flip angle 77°, matrix 74 × 74, a field of view (FOV) 220*220 mm2, voxel size=3×3×3 and 50 layers continuous scan. A high-resolution T1-weighted anatomical scan (MPRAGE) also obtained from each participant; TR 2530ms, echo time (TE)=3.65 ms, flip angle=70°, slice thickness=1 mm, FOV=256×256 mm2, matrix=256×256 and number of layers=224 layers. All scans were visually inspected and reviewed by a radiologist to ensure that there were no evident gross abnormalities.

2.4 Preprocessing

Image preprocessing and analysis were performed using CONN(version 18b, http://www.nitrc.org/projects/conn) and SPM(version 12b; www.fil.ion.ucl.ac.uk/spm) toolbox, ran in Matlab 2013b (Mathworks Inc., Sherborn, MA, USA). After format conversion(DICOM to NIFTI), all functional data preprocessing according to a standard two-step normalize pipeline, including the following steps：(1) Removal of initial ten scans;(2) Slice-timing correction;(3) Realignment;(4) Outlier detection;(5) Normalization into Montreal Institute of Neurology (MNI) Space with resampled voxel to 3 mm * 3 mm * 3 mm volume; (6) Smooth with isotropic Gaussian kernel of 8 mm full-width half-maximum (FWHM); (7) Denoised to remove confounding variables including grey matter, white matter, and CSF BLOD signal noise;(8) Band-pass Filter in 0.01 to 0.08 Hz; (9) Linear detrending.

2.5 Functional Network Connectivity Analysis

After functional MRI preprocessing, blood oxygen level-dependent (BOLD) time series extracted from 264 areas by using a Power template[37], and a 6 mm sphere based on coordinates was used to define the Regions-of-interest (ROIs). Firstly, according to our hypothesis, previous studies described and verified ten brain subnetworks based on the Power template[38], including default mode network (DMN), ventral attention network(VAN), dorsal-ventral attention network (DAN), frontal-parietal network (FPN), cingulo-opercular network (CON), sensorimotor network (SMN), subcortical network (Subc), salience network (SAN), visual network (VIS) and auditory network(AUD). BOLD time courses of all voxels in the ROIs mentioned above were averaged. Secondly, according to the definitions made by previous researches, for the brain network area definitions above, we measured two types of network connectivity, including seed-to-voxel maps for each RSN versus whole brain and ROI-to-ROI maps for between-network connectivity[39].

Bivariate-regression analyses performed separately to measure the static correlation strength for seed regions between CTQ sub-dimension scores. The multiple comparison corrections approaches performed at a peak voxel threshold of $p \leq 0.001$ and FDR(false discovery rate) correction with p＜0.05 using both for seed-to-voxel and ROI-to-ROI analysis, the gender, age and dose of antipsychotics were included as covariate regressors.

3. Results

3.1 Demographics and Clinical Characteristics

Due to excessive motion(>3 mm or 3°), 2 FES, and 3 HC Subjects were excluded, the final sample for the current study included 27 HCs and 28 FESs. Detailed clinical and demographic data for two groups shown in Table 1. Compared to the control group, the FES group had lower education year ($t = -2.348$, $p = 0.023$), family cohesion ($t = -3.975$, $p \leq 0.001$), and adaptability scores (t

=-5.754, p ≤ 0.001), and no significant differences in age and gender among two groups. Significant differences shown in emotional abuse (t =4.253, p ≤ 0.001), sexual abuse (t =2.193, p ≤ 0.039), physical abuse (t =2.178, p = 0.033), physical neglect (t =2.129, p = 0.016) and total score (t =3.584, p = 0.001), but no significant difference was found in emotional neglect.

(Table 1, here)

3.2 CTQ and FACES Ⅱ-CV correlation with Clinical Characteristics

Among all subjects, a strong negative correlation shown between emotional abuse, emotional neglect, physical neglect and cohesion, adaptability scores of FACES Ⅱ (|r| = 0.524-0.720, p ≤ 0.003 after Bonferroni correction for multiple comparisons) (shown in Table 2.), physical abuse also showed significant negative correlation with adaptability score (r=-0.449, p ≤ 0.003 after Bonferroni correction for multiple comparisons). And physical abuse correlated negatively with family cohesion (r = -0.354, p ≤ 0.05), sexual abuse also correlated negatively with adaptability scores (r = -0.273, p ≤ 0.05).

(Table 2, here)

Results in table3 showed sporadic correlations between childhood trauma with clinical characteristics in FES patients, such as: (1) Total scores with speed of processing(r = -0.439, p ≤ 0.05); (2) Sexual abuse with positive(r = -0.485, p ≤ 0.05) and general psychotic symptom(r = -0.433, p ≤ 0.05) scores, speed of processing(r = -0.376, p ≤ 0.05) and social cognition(r = -0.378, p ≤ 0.05), MADRS scores(r = -0.377, p ≤ 0.05); (3); (4)Emotional neglect with positive(r = -0.380, p ≤ 0.05) and general scores(r = -0.409, p ≤ 0.05); (5)Physical neglect with positive(r = -0.438, p ≤ 0.05), negative(r = -0.424, p ≤ 0.05) and general scores(r = -0.389, p ≤ 0.05).

(Table 3, here)

3.3 Correlation of CTQ and Functional Connectivity within networks in Schizophrenia- ROI-to-ROI Analysis

The functional connectivity maps within RSNs and their relationships to childhood trauma presented in Table 4. CTQ total scores correlated with greater connectivity in DAN and AUD (p□0.050, FDR correction), and with reduced connectivity in DAN and VIS (p□ 0.050, FDR correction). Sexual abuse was correlated with greater connectivity in DAN and Subc (p=0.030, FDR correction) as well as in VIS and VAN (p=0.048, FDR correction), and reduced connectivity in VIS and DAN (p=0.020, FDR correction). Emotional neglect was correlated with greater connectivity in DAN with SMN (p=0.008, FDR correction) and AUD (p=0.010, FDR correction).

(Table 4, here)

3.4 Correlation of CTQ and Functional Connectivity between each network and the whole brain in Schizophrenia- Seed-to-voxel Analysis

The functional connectivity maps between each RSN and the whole brain and their relationships to childhood trauma were presented in Table 5 and Fig.1. CTQ total scores were correlated with greater connectivity in FPN and left Superior Frontal Gyrus (LSFG) (p=0.019, FDR correction). Physical abuse was associated with greater connectivity in FPN and left anterior Supramarginal Gyrus (LaSMG)(p□0.001, FDR correction), as well as left Postcentral Gyrus(LPCG)(p□0.001, FDR correction) and LSFG (p=0.009, FDR correction). Physical Neglect was correlated with reduced connectivity in FPN and right inferior Lateral Occipital Cortex(RiLOC) (p=0.015, FDR correction), as well as in Subc and left Middle Frontal Gyrus(LMFG) (p=0.042, FDR correction) and LSFG (p=0.042, FDR correction).

(Table 5, here)

(Figure 1, here)

4. Discussion

As the first study to explore the relationship between different types of early traumatic experiences and RSNs connectivity of schizophrenia in adulthood, our research mainly found that CT of schizophrenic patients correlated with abnormal connections

within RSNs and each RSN to the whole brain, and these anomalies distributed among task-positive networks and sensory networks. Trauma experiences were different between FESs and HCs, and play a particular role in the clinical symptoms of patients, the current study found sexual abuse, emotional and physical neglect correlated with some psychotic symptoms, and all results shown a positive correlation. These results consistent with previous research[40, 41], and a network-based study implemented by Isvoranu et al. also suggested that different types of traumatic experiences were related to positive and negative symptoms through general psychotic symptoms[42]. Previous studies reported that cognitive deficits of psychiatric patients who experienced CT are more obvious than those had no history of CT[43], and abnormal results related to CT had been found in both general cognition[44] and social cognition[45], this article also found sexual abuse was negatively associated with speed of processing and social cognition, but we didn't conduct a stratified analysis of the two types of patients because of insufficient sample size. It was worth mentioning that we found that family functions are significantly associated with CT, the family cohesion or adaptability were negatively related to most types of CT, and results are consistent with a previous study which concentrated on dissociative symptoms in adolescents, mentioned the possibility of coexistence between family dysfunction and early trauma frequency[46]. However, there were few studies in this direction, revealing causality requires the increase of the sample size for analyzing the subgroup of family functions.

Previous structural image studies had indicated that childhood abuse might lead to reaction-related neural circuit changes in individuals in the response of potential threat stimuli, high reactivity in some brain areas(i.e., amygdala and prefrontal cortex) were prominent features[21, 22, 26]. Lack of emotional conflict regulation may be a basis for the increased risk of psychosis of individuals suffering from early life traumas, subjects once exposed to traumas had a lower ability in regulating emotional conflicts, which was also related to the activities of DLPFC, amygdala, and ACC gyrus [47], these studies laid the foundation for impaired functional network connectivity related to CT. And we found that decreased connection of DAN and VIS, increased connection of DAN and AUS, FPN and LSFG was relative to the severity of Traumatic experiences. These findings were precisely to be a supplement of above researches from the aspect of RSNs, we speculate that RSN connection impairment of schizophrenia patients related to trauma experiences focused on patients' perceptual attention regulating related network. And results of the abnormal connection between the task-positive network(DAN) and the perception network(VIS, AUS) were consistent with a similar study on depression patients[48]. The DAN and FPN were involved in adjustment and control of attention, and FPN also associated with the executive of emotion. The previous task-fMRI study found that the abnormal activation of some brain regions of the attention network like the cuneus and cingulate cortex were related to the exposure of trauma[49].

In the sub-dimensions of childhood trauma, we discovered that sexual abuse was associated with abnormal connections between AN (DAN&VAN) and VIS with Subc, and emotion abuse was associated with abnormal relationships between DAN and AUD with SMN. These findings also mentioned that the impairment of AN was a core pathological characteristic of schizophrenia patients when associated with childhood trauma, consistent with results in related studies of depression and other psychosis[50]. And we found patients' sexual abuse was associated with psychotic and depression symptoms, processing speed, and social cognition. We speculated that the impairments of attention processing in schizophrenia patients were associated with patient's increased negative attention bias[51], nervousness and mood disorders[15], which may result to the abnormality of information transmission between networks or the overall brain network imbalance background. A task-fMRI study also found that women with a history of sexual abuse showed increased correlative activation of AN and decreased activation of FPN[52]. These results all suggested that sexual abuse was related to abnormal brain areas or networks involved in cognitive control. Except for findings in sexual and emotional trauma, this study also found increased connections of FPN and LaSG, LPG and LSFG represent the level of physical abuse, and decreased connections of FPN and RiLOC, Subc, and LMFG with LSFG represent the level of physical neglect. Previous results on physical trauma are inconsistent, and studies on mental illness have shown that it is mainly related to the abnormal function of the amygdala, vmPFC, hippocampus, and cingulate[28, 53]. The characteristics of the abnormal brain network of physical trauma concentrated on areas related to executive and emotional control functions, And these findings were consistent with the previous perspective on children's adversity and brain development, This suggested that Physical abuse considered to have effects on the function of the cortical circuits[54]. In contrast, physical neglect supposed to have a broader and more specific impact on brain development such as gray matter thickness[55].

We re-verified previous results of some independent brain regions from the level of the RSNs in this article. Our findings mainly consist of abnormalities involving attention and execution controlling networks, and impaired patterns of these networks may be

associated with clinical manifestations. The human brain needs to maintain normal functions of RSNs, including maintaining cognitive function of perception, attention, execution, and other functions. In previous studies, abnormalities in CT related brain regions, such as the prefrontal lobe and amygdala, were influential in multiple resting-state networks. For example, emotional processing and default mode network (DMN) included prefrontal lobe, anterior cingulate gyrus and other brain regions. Although DMN and SAN impairments in other networks were often mentioned in previous studies on schizophrenia, in which DMN was related to internal attention and self-reference of the patient, and SAN was related to the emotional regulation of the patient. However, in this study, we didn't found relations between abnormal of this network and childhood traumas. The mechanism of CT and brain function impairment is unclear, some researchers suggested that by affecting the balance of excitatory and inhibitory neurotransmitters of a single brain area or multiple functional networks[56], traumatic experiences may cause clinical symptoms and cognitive abnormalities of the patient. The dopaminergic related brain structure considered as a possible influencing mechanism. A study of 153 schizophrenic subjects had demonstrated a significant two-way interaction between the dopaminergic risk allelic load (RAL) in partial brain regions and childhood trauma[57]. Another study on the relation of childhood abuse and nerve growth found that subjects with abused experience have lower amygdala volume, and the positive correlation expected between their brain-derived neurotropic factor (BDNF) genetic expression and amygdala volume was decreasing[58], indicating that childhood abuse may damage the nerve protective effect of BDNF, these studies all suggested the direction of further research on neural mechanism.

In conclusion, this research has shown the link between CT in first-episode schizophrenia patients and functional connectivity of RSNs, but the results need further verification due to the small sample size and lack of follow-up. And for now, we can't fully illustrate the causal relationship between CT and RSNs, hypothesis suggested that it may be the childhood trauma that causes changes in the early development of the brain, especially during the stage when internal consistency was still weak[59]. Meanwhile, childhood trauma may also be related to factors such as neuroplasticity and connectivity, which may increase the risk of mental illness[60]. In future studies, we can further analyze the properties of brain resting-state networks, especially in the attention and frontal-parietal networks mentioned in this article, to explore the causes of network information transmission abnormal or imbalance. Then we can evaluate the effects of physical treatments such as transcranial magnetic stimulation or deep brain stimulation on patients with childhood trauma.

Declarations

Ethics approval and consent to participate

This study was approved by the ethical review committee of Tongji Hospital Affiliated to Tongji Hospital and Shanghai Mental Health Center (SMHC, Shanghai, China), and carried out in accordance with the Declaration of Helsinki. Written informed consent was received from all participants prior to inclusion.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

ZL conceived of the study. XYL, FL and ZL contributed to the design of the study. XYL and WJX contributed to the patient recruitment and data acquisition. XYL, FL, NH, NL, XFG, and ASQ contributed to the data interpretation and statistical analysis. XYL and WJX contributed to the drafting of the paper. FL and ZL revised the manuscript critically. All the authors read and approved the final manuscript.

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Availability of data and materials

The dataset(s) generated during the current study are not publically available due to ethical restrictions but are available from the corresponding author on reasonable request.

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Tables

Table 1. Demographic, cognition and clinical characteristicis of all Subjects()

	FES(n=28)	HC(n=27)	t/x^2 value	p value
Age (years)	23.46±7.16	26.15±5.10	-1.605	0.115
Gender (male (%))	15(53.57%)	13(48.15%)	0.162	0.688
Education (years)	12.43±2.82	14.04±2.21	-2.348	0.023*
Intelligence (WASI)	95.89±11.96	110.15±13.28	-4.185	0.000**
FACES Ⅱ-CV				
Cohesion	60.36±11.16	70.85±8.13	-3.975	0.000**
Adaptability	36.54±9.78	49.52±6.58	-5.754	0.000**
Total	96.89±20.36	120.37±13.65	-5.004	0.000**
CTQ				
Emotional Abuse	10.96±5.43	6.30±2.02	4.253	0.000**
Physical Abuse	7.89±4.50	5.63±3.04	2.178	0.033*
Sexual Abuse	7.18±3.73	5.44±2.12	2.193	0.039*
Emotional Neglect	11.82±4.89	10.52±2.61	2.109	0.222
Physical Neglect	10.21±3.50	8.15±2.55	2.129	0.016*
Total	57.82±15.87	45.81±7.75	3.584	0.001*
MCCB				
Speed of processing	52.89±7.80	n.a.	n.a.	n.a.
Attention/vigilance	49.57±10.25	n.a.	n.a.	n.a.
Working memory	43.86±8.42	n.a.	n.a.	n.a.
Verbal learning	45.82±9.46	n.a.	n.a.	n.a.
Visual learning	52.00±10.10	n.a.	n.a.	n.a.
Reasoning and problem solving	53.43±10.67	n.a.	n.a.	n.a.
Social cognition	36.10±7.53	n.a.	n.a.	n.a.
Overall composite	45.64±8.78	n.a.	n.a.	n.a.
PANSS				
Positive	24.52±8.30	n.a.	n.a.	n.a.
Negative	21.71±10.08	n.a.	n.a.	n.a.
General	46.39±12.01	n.a.	n.a.	n.a.
Total	92.63±26.72	n.a.	n.a.	n.a.
MADRS total	18.38±8.17	n.a.	n.a.	n.a.
GAF now	39.98±15.43	n.a.	n.a.	n.a.
CGI	5.36±0.99	n.a.	n.a.	n.a.

Dose of antipsychotics	6.89±5.38	n.a.	n.a.	n.a.

*p≤0.05. **p≤0.001.

mean value, s standard deviation, FES first-episode schizophrenia, HC healthy controls

Table 2. Correlation between CTQ and FACE of all Subjects

measures	CTQ					
	Emotional Abuse	Physical Abuse	Sexual Abuse	Emotional Neglect	Physical Neglect	Total
FACES Ⅱ-CV						
Cohesion	-.643**	-.354*	-.202	-.571**	-.524**	-.603**
Adaptability	-.720**	-.449**	-.329*	-.506**	-.552**	-.666**
Total	-.703**	-.414**	-.273*	-.557**	-.556**	-.655**

*p≤0.05. **p≤0.001.

Table 3. Correlation between CTQ、FACE and Clinical Characteristics of FES

measures	CTQ						FACES Ⅱ-CV		
	Emotional Abuse	Physical Abuse	Sexual Abuse	Emotional Neglect	Physical Neglect	Total	Cohesion	Adaptability	Total
Psychotic symptoms (PANSS)									
Positive	.049	.178	.485*	.380*	.438*	.276	-.097	-.155	-.128
Negative	-.003	.103	.370	.373	.424*	.253	-.127	-.179	-.155
General	.049	.152	.433*	.409*	.389*	.303	-.201	-.280	-.245
Total	.049	.178	.485*	.380*	.438*	.318	-.169	-.242	-.208
Cognitive symptoms (MCCB)									
Speed of processing	-.185	-.373	-.376*	.197	-.067	-.439*	-.182	-.070	.262
Attention/vigilance	.060	-.139	-.173	.243	-.038	-.151	-.071	-.101	.112
Working memory	.010	-.128	-.137	.105	.117	-.266	-.130	-.123	.227
Verbal learning	.056	-.228	-.242	.351	.047	-.277	-.262	-.223	.115
Visual learning	.048	-.207	-.247	.330	.000	-.247	-.187	-.113	.149
Reasoning and -problem solving	.076	-.265	-.338	.217	.163	-.071	-.154	-.117	-.140
Social cognition	-.009	-.132	-.378*	.046	-.229	-.157	.136	.243	.191
Overall composite	-.021	-.159	-.307	.184	.026	-.074	-.041	.066	.009
MADRS total	.075	.140	.377*	.044	.143	.208	-.108	-.258	-.183
GAF now	.101	.086	-.203	-.077	-.071	.011	-.271	-.210	-.249
CGI	.009	.109	.223	.182	-.012	.099	.139	.083	.116
Dose of antipsychotics	-.070	.070	.215	.085	.007	.044	-.018	.119	.048

*p≤0.05. *FES first-episode schizophrenia.*

Table 4. abnormal brain functional connectivity within networks associated with trauma in schizophrenia□ROI to ROI analysis□

Seed area	Area altered	MNI Coordinates			T value	*p*(FDR)	*p* uncorrected
		x	y	z			
CTQ total							
Dorsal Ventral Attention Network	↓Visual Network	37	-81	1	-2.73	□0.050	0.009
Dorsal Ventral Attention Network	↑ Auditory Network	-30	-27	12	2.64	□0.050	0.011
Emotional Abuse							
Nil							
Physical Abuse							
Nil							
Sexual Abuse							
Dorsal Ventral Attention Network	↓ Visual Network	37	-81	1	-3.22	0.020	0.002
Dorsal Ventral Attention Network	↑ Subcortical Network	9	-4	6	2.84	0.030	0.007
Visual Network	↑ Ventral Attention Network	-49	25	-1	2.65	0.048	0.011
Emotional Neglect							
Dorsal Ventral Attention Network	↑ Auditory Network	29	-5	54	3.53	0.008	□0.001
Dorsal Ventral Attention Network	↑ Sensorimotor Network	47	-30	49	3.24	0.010	0.002
Physical Neglect							
Nil							
FES first-episode schizophrenia, MNI montreal neurological institute.							

Table 5. Peaks of clusters showing significant BOLD signal change between trauma and brain functional connectivity in schizophrenia——seed-to-voxel analysis.

Networks	Area altered	MNI Coordinates			Cluster size (voxels)	T value	Cluster p(FDR)	Peak *p* uncorrected
		x	y	z				
CTQ total								
Frontal Parietal Network	↑L Superior Frontal Gyrus	-24	+21	+54	43	4.31	0.019	0.001
Emotional Abuse								
Nil								
Physical Abuse								
Frontal Parietal Network	↑L anterior Supramarginal Gyrus	-54	-33	+54	75	5.75	0.001	0.001
	↑L Postcentral Gyrus	-54	-33	+54	57	5.75	0.001	0.001
	↑L Superior Frontal Gyrus	-18	+21	+54	52	4.80	0.009	0.001
Sexual Abuse								
Nil								
Emotional Neglect								
Nil								
Physical Neglect								
Frontal Parietal Network	↓R inferior Lateral Occipital Cortex	+48	-72	+03	68	-4.69	0.015	0.001
Subcortical Network	↓L Middle Frontal Gyrus	-27	+30	+51	35	-4.45	0.042	0.001
	↓L Superior Frontal Gyrus	-27	+30	+51	13	-4.45	0.042	0.001

FES first-episode schizophrenia, MNI montreal neurological institute, L left, R right.

Figures

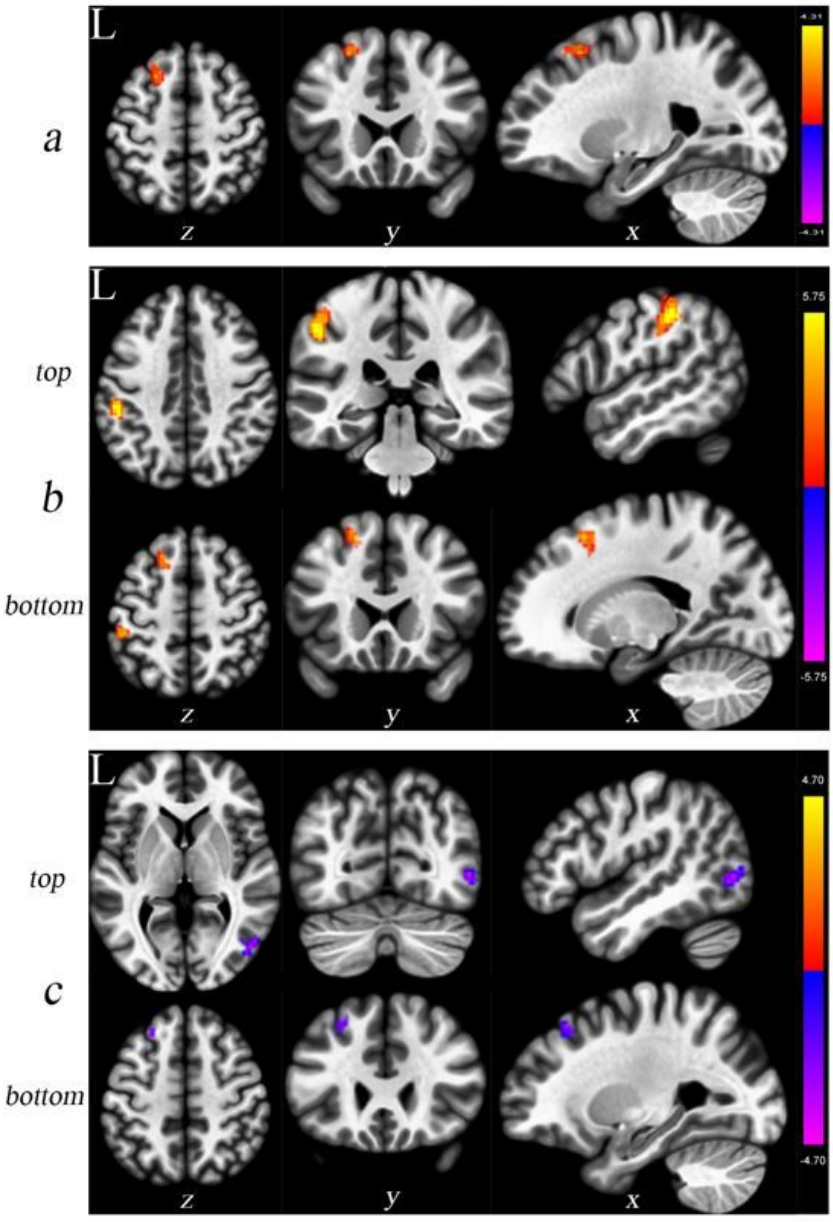

Figure 1

Correlation of trauma and Functional Connectivity between each network and the whole brain in participants with Schizophrenia (Seed-to-voxel Analysis) a. Correlation of CTQ total scores and functional connectivity. Seed region in FPN, peak voxel in the left superior frontal gyrus (-24, +21, +54); b. Correlation of physical abuse and functional connectivity. Top row Seed region in FPN, peak voxel in the left anterior supramarginal gyrus, and left postcentral gyrus (-54, -33, +54). Bottom row Seed region in FPN, peak voxel in the left superior frontal gyrus (-18, +21,+54); c. Correlation of physical neglect and functional connectivity. Top row Seed region in FPN, peak voxel in the right inferior lateral occipital cortex (+48, -72,+03). Bottom row Seed region in Subc, peak voxel in the left middle frontal gyrus and superior frontal gyrus(-27,+30,+51).