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Decreased functional coupling within default mode network in major depressive disorder with childhood trauma

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ABSTRACT

Objective: Childhood trauma (CT) has been supported to be a high-risk factor for major depressive disorder (MDD), but the neural mechanism linking CT and depression remains unclear. The aim of this study is to deepen our understanding of this issue by establishing the neuroimaging correlations between CT and depression.
Methods: A sample of 123 MDD patients (91 with moderate-to-severe CT and 32 with no or low CT) and 79 healthy controls (HC, 33 with moderate-to-severe CT and 46 with no or low CT) participated. All participants completed assessments of depression level, anxiety, recent perceived stress, and resting-state functional MRI scan.
Results: Participants with moderate-to-severe CT showed elevated depression level and trait anxiety, and reduced spontaneous neural activity in left inferior temporal gyrus (ITG). Abnormalities of seed-based functional connectivity (FC) of left ITG – bilateral precuneus/posterior cingulate cortex (PCC), left middle temporal gyrus (MTG), left medial orbitofrontal cortex (mOFC), and bilateral medial prefrontal cortex (mPFC)/anterior cingulate cortex (ACC) were observed. CT was associated with decreased FCs in MDD, but with increased FCs in HC. The total altered FCs of left ITG – bilateral precuneus/PCC and left mOFC mediated relationship between CT and depression in MDD, and total altered FCs and trait anxiety have a significant chain mediation effect in the association between CT and depression in HC.
Conclusion: These findings highlight the changes of default mode network (DMN) functions and trait anxiety as targets of CT. The decreased functional coupling within DMN may be involved in the mechanism of MDD following CT.

1. Introduction

Childhood trauma (CT) is one of the strongest risk factors for MDD in adulthood. Previous studies have tried to understand the potential mechanism(s) of CT affecting depression from psychosocial and neurobiological dimensions. However, this issue has not been clarified so far. It is believed that CT exposure has been observed to increase the susceptibility to the effect of current stressors in the development of symptoms of depression (Harkness et al., 2006), contributing to the vulnerability to stress-induced depression (Heim and Binder, 2012). For example, CT experiences could increase one's trait anxiety (Mancini et al., 1995; Reiser et al., 2014; Uchida et al., 2018), which has been suggested as a vulnerability characteristic and risk factor of depression (Bishop and Forster, 2013; Kok et al., 2016). Neuroendocrine research also suggested that prolonged or excessive responses of the hypothalamic-pituitary-adrenal axis (HPA axis) caused by CT during a time of high neuronal plasticity can affect neurodevelopment, leading to alterations in brain function, structure, and network architecture (Teicher and Samson, 2016), thereby increasing the vulnerability of depression.

With the development of neuroimaging technology, several evidences have documented the association between CT and alterations of

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brain function and structure (Teicher and Samson, 2016) both in MDD and healthy individuals, indicating that brain alterations may play an important role between CT and MDD (Ohashia et al., 2017). In MDD patients, CT is related to alterations in various brain regions, such as the prefrontal cortex (PFC) and orbitofrontal cortex (OFC) (Dannlowski et al., 2012b; Frodl et al., 2010), amygdala (Grant et al., 2011; Tottenham et al., 2010), hippocampus, and striatum (Hanson et al., 2015) etc. In healthy individuals, CT exposure was also associated with alterations of brain functions and structure, involving in anterior cingulate cortex (ACC) (Cohen et al., 2006; Dannlowski et al., 2012b), the medial prefrontal cortex (mPFC) (van Harmelen et al., 2010), caudate nucleus (Cohen et al., 2006), as well as insula (Baker et al., 2013). It is noted that inconsistent brain regions were found in different studies, which may be due to different methods and populations. For example, some studies only compared MDD patients with CT and HC, which could not clarify whether these brain alterations were related to CT exposure or the MDD diagnosis itself. Although some studies have directly compared HC with CT and HC without CT, it is difficult to determine the roles of these altered brain functions in links of CT to depression. In addition, most of previous studies defined regions of interest (ROIs) according to priori hypotheses to explore the alterations of brain function and structure following CT (e.g., hippocampus, striatum). Although reliable results could be obtained using this method, it also ignores the associations between CT and brain abnormalities in other areas. These findings from previous studies also demonstrated that the links between CT and brain alterations might be different in MDD and healthy individuals (Saleh et al., 2017). These population-specific findings may provide clues related to the underlying mechanism of the CT-related depression vulnerability. The expected results may help us understand how CT is related to MDD by specific neurological alterations from the population-specific perspective. Therefore, it is still a very significant issue to understand the underlying mechanism of CT affecting depression from the perspective of neurophysiology.

In recent years, resting-state functional magnetic resonance imaging (rs-fMRI) was widely used for identifying the underlying pathophysiology mechanisms of neuropsychiatric diseases. The Amplitude of Low Frequency Fluctuation (ALFF) was considered as a useful marker of rs-fMRI, which can reflect regional autonomous neuronal activity (Zang et al., 2007) and has been successfully applied to detect potential neural markers in various mental disorders (Cao et al., 2016; Xu et al., 2015). Meanwhile, regional signal alterations of ALFF were associated with long distant functional connectivity (FC) abnormalities and ALFF analysis has been shown to be an effective approach to define and detect seeds in resting-state functional connectivity (rs-FC) investigations (Li et al., 2015; Liu et al., 2017, 2018; Zang et al., 2007). The rs-FC has been increasingly utilized to investigate the characteristics of resting-state networks and suggested as a reliable method to evaluate the coordination and interaction of neural activity between anatomically distributed but functionally related brain regions (Fox and Raichle, 2007).

Taken together, the current study was designed to explore whether the associations between CT and alterations of brain functions were different among MDD and healthy individuals, and how these alterations of brain functions link CT and MDD. To investigate this issue, both MDD patients and HC (with moderate-to-severe CT and with no or low CT) were included. Levels of depression, anxiety were assessed, and ALFF and rs-FC were calculated to evaluate brain function. Firstly, the effects of CT on depressive symptomatology were established. Then, CT-related ALFF and rs-FC alterations were detected. Finally, the correlations between brain function alterations and depressive symptomatology were established, and the mediation effects of these alterations on the relationship between CT and depression were examined to identify the pattern of associations among CT, altered FC, and depression.

2. Methods and materials

2.1. Participants

Participants included 123 MDD patients and 69 HC in the present study. MDD patients were recruited from the psychological clinic at Second Xiangya Hospital of Central South University, Changsha, China. Diagnosis was established by two experienced psychiatrists using Structured Clinical Interview for DSM-IV-TR Axis I (SCID-I). Exclusion criteria for patients was: diagnosis of other axis I psychiatric disorders and a history of major medical or neurological problems. HC were recruited from local colleges and communities in Changsha. Exclusion criteria were history of any psychiatric disorders and any major medical or neurological problems. All participants were right-handed, 18–35 years old, and had at least 9 years of education. The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (grant no. 2016013). All participants agreed to participate, and written informed consents were obtained.

2.2. Clinical assessments and group classification

Sociodemographic and clinical characteristics of all participants were collected. The handedness was confirmed by the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). Beck Depression Inventory (BDI) (Beck et al., 1961), Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), and the State-Trait Anxiety Inventory (STAI) (Spielberger, 1983) were used to assess depression and anxiety levels. The Perceived Stress Scale (PSS) (Reis et al., 2010) was used to assess their recent perceived stress, which was used to control for the potential confounding effects caused by more recent stressors on the impacts of childhood stress (Grosse et al., 2016). The age-adjusted scores of subtests (information, similarity, arithmetic, and digit span) of the Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-RC) (Gong, 1992) were used for controlling participants' intelligence levels.

Childhood trauma was assessed using the Chinese version of Childhood Trauma Questionnaire (CTQ) (Zhao et al., 2005), which is a reliable and valid self-reporting instrument, containing 28 items and can yield five factors which evaluate five aspects of CT exposure: physical neglect (PN), physical abuse (PA), emotional neglect (EN), emotional abuse (EA), and sexual abuse (SA). The cut-off scores of each subscale for moderate-to-severe trauma are: PN $\geq$ 10, PA $\geq$ 10, EN $\geq$ 15, EA $\geq$ 13 and SA $\geq$ 8. Subjects who score higher than the threshold (moderate-to-severe) of a subscale were treated as exposure to corresponding CT (Bernstein and Fink, 1998). According to criteria for the CT dichotomous group classification used in previous studies (Chaney et al., 2014; Dannlowski et al., 2012a; Moog et al., 2018), participants who reported having a moderate-to-severe CT on at least one subscale were classified into moderate-to-severe CT group, and those reporting no or low exposure to all five types of CT were classified into no or low CT group. In this study, participants were classified into four group: MDD patients with moderate-to-severe CT, MDD patients with no or low CT, HC with moderate-to-severe CT and HC with no or low CT.

2.3. Functional MRI processing

2.3.1. MRI acquisition

The MRI was conducted on a Siemens Skyra 3.0T magnetic resonance scanner at the Second Xiangya Hospital of Central South University. Subjects were asked to lie on the scanner, foam pads were used to fix head in order to minimize head motion. The scanning sessions and the parameters were as follows: (1) three-dimensional T1-weighted, magnetization-prepared rapid gradient echo (MPRAGE) sagittal images: repetition time (TR) = 1900 ms; echo time (TE) = 2.01 ms; slices = 176; slice thickness = 1 mm; voxel size = 1.0 × 1.0 × 1.0 mm; flip angle = 9°; inversion time = 900 ms; field of view (FOV) = 256 mm; matrix = 256 × 256. (2) resting-state fMRI series using the echoplanar imaging

sequence: TR = 2500 ms; TE = 25 ms; axial slices = 39; slice thickness/gap = 3.5/0 mm; voxel size = 3.8 × 3.8 × 3.5 mm, 200 vol; flip angle = 90°; FOV = 240 mm; matrix = 64 × 64. During the scanning, subjects were informed to keep eyes close but remain awake.

2.3.2. MRI preprocessing

MRI data preprocessing were performed using the Data Processing Assistant for Resting-State fMRI (DPARSF V5.2) (Chao-Gan and Yu-Feng, 2010). The preprocessing procedures were as follows: (1) convert raw DICOM data to NIfTI format; (2) the first 10 vol were discarded to allow the magnetization to reach equilibrium and the participants to adapt to scanning noise; (3) slice-timing correction and realignment of head motion. Participants who demonstrated a maximum displacement greater than 2-mm or more than 2-degree of angular rotation were excluded from this study; (4) T1-weighted images of each participant were co-registered to the mean functional images; (5) functional images normalized to the standard Montreal Neurological Institute (MNI) space using the transformation (co-registered T1 to standard MNI) parameters and resampled to 3 × 3 × 3 mm; (6) spatial smoothing with a 6 mm full-width half maximum Gaussian filter; (7) linear detrending was performed to remove low-frequency drift; (8) regressing out of nuisance covariates including WM signal, CSF signal as well as Friston-24 head motion parameters; (9) temporal bandpass filtering at 0.01–0.08 Hz was performed to reduce physiological high-frequency noise.

2.3.3. ALFF and FC calculations

After preprocessing, the filtered time series was transformed into the frequency domain with a fast Fourier transform (FFT), and the power spectrum was obtained. To obtain ALFF value, the power spectrum was square-rooted and averaged across 0.01–0.08 Hz at each voxel, the obtained square root was referred to as the ALFF (Zang et al., 2007). In order to standardize ALFF value across participants, the ALFF of each voxel was divided by the global mean of ALFF values for each participant (Zang et al., 2007). Based on the results of ALFF analysis, seed-based whole-brain FC analysis was performed. The seed region was defined by generating a 6-mm radius centering on the peak voxel of regions of ALFF alterations related to CT. Then, the average time series data from seed regions were extracted and seed-based whole-brain FC maps for all participants were subsequently generated by computing pearson correlations (r scores) between the time course of the average signal in the seed region and all other brain voxels. Finally, Fisher's r to z transform was performed to convert the correlation coefficients to normally distributed z scores for further statistical analysis. In addition, the frame-wise displacement (FD) by Jenkinson et al. (2002) was calculated due to its consideration of voxel-wise differences in motion in its derivation. According to recommendation (Yan et al., 2013), a "scrubbing routine" was used to censor any frame with an FD > 0.2 mm from the following seed-based FC calculation. Meanwhile, the mean FD was further controlled as a covariate in the group-level imaging statistical analysis.

2.4. Statistical analysis

Demographic and clinical characteristics were compared with chi-square tests, two-sample t-tests and one-way ANOVAs among four groups. The effects of CT on depression and anxiety levels, as well as ALFF and rs-FC, were analyzed by 2 (diagnosis: MDD/HC) × 2 (CT: moderate-to-severe/no or low) ANCOVAs with age, gender, intelligence score as covariates. The recent stress level was additionally controlled when investigating the effects involving CT. For ALFF and rs-FC analyses, mean FD was also controlled. Statistical analyses were conducted with SPSS 26.0 software for behavioral data, and SPM12 for images analysis. A bayesian *Probabilistic Threshold-free Cluster Enhancement* (pTFCE) method (Spisak et al., 2019) and whole brain false discover rate (FDR) correction were used for all contrasts (main effect of CT, main effect of diagnosis, and interactive effect of CT-by-diagnosis) to reduce false positives with a significance threshold of $p < 0.05$.

For all regions survived after multiple comparison corrections, mean ALFF and FC estimates of each subject in regions of main effect of CT and interactive effect of CT-by-diagnosis were extracted to respectively assess their relationship with CT and depressive symptomatology by applying partial correlation analyses (controlling for age, gender, intelligence score, and PSS). FDR analysis was performed for the multiple comparison correction using MATLAB, with adjusted p value (FDR q-value) < 0.05 considered statistically significant. If correlations were established, the mediation models were constructed using Haye's bootstrapping method (PROCESS macro based on SPSS; model 4 and 6, utilizing 5000 bootstrap samples to estimate the 95% confidence interval) (Preacher and Hayes, 2004) to test the role of ALFF and FC alterations on the relationships between CT and depressive symptomatology in both groups, controlling for age, gender, intelligence score, and PSS. In addition, if two altered FCs were found to be associated with one depressive symptomatology component, and high correlations were also found between FCs, potential problem of multicollinearity should be considered. To address this issue, a principal components analysis (PCA) (Fan et al., 2021; Herringa et al., 2013) was applied to transfer high-correlated variables to two independent (uncorrelated) components by summing (total or shared FC) and subtracting (differential FCs) the two FCs.

3. Results

3.1. Demographical and clinical variables

Table 1 provides demographical and clinical characteristics among four groups.

3.2. Diagnosis and CT effects on clinical variables

The main effects of CT on depression level and trait anxiety were observed, indicating that subjects with moderate-to-severe CT, independent of diagnosis, demonstrated higher depression level and trait anxiety than subjects with no or low CT. Main effects of diagnosis were also observed. No significant effects of CT-by-diagnosis interactions were detected (see Table 2).

3.3. Diagnosis and CT effects on ALFF and FC

There was significant main effect of CT on ALFF. Independent of MDD diagnosis, participants with moderate-to-severe CT indicated decreased ALFF value in the left inferior temporal gyrus (ITG) (MNI peak voxel: -39, −18, −30, BA20, cluster size = 39, $F = 37.51$, $p = 0.014$, FDR corrected, TFCE enhancement, Fig. 1a) compared with those who have no or low CT. The main effects of diagnosis were also observed (see **Supplementary Materials**). Based on the ALFF result, the seed region was constructed for left ITG as a sphere with radius of 6 mm centered on the peak voxel (MNI coordinate: -39, −18, −30), to conduct subsequent rs-FC analysis.

Significant effects of MDD diagnosis-by-CT interactions on rs-FC were observed in bilateral precuneus/posterior cingulate cortex (PCC), left middle temporal gyrus (MTG), left medial orbitofrontal cortex (mOFC) as well as bilateral medial prefrontal cortex (mPFC), extending to anterior cingulate cortex (ACC) ($p < 0.05$, FDR corrected, TFCE enhancement, see Table 3, Fig. 1b). Further simple effects analyses revealed that MDD with moderate-to-severe CT showed reduced rs-FCs compared with MDD with no or low CT. On the contrary, relative to participants with no or low CT, participants with moderate-to-severe CT demonstrated increased FCs in HC. The main effects of diagnosis were also observed (see Table 3). No significant main effects of CT on FCs were detected.

Table 1
Demographical and clinical characteristics among four groups.

Characteristics	MDD		HC		$F/t/\chi^2$	p	Post-hoc tests (Bonferroni corrected)
	Moderate-to-severe CT (G1; n = 91)	No or low CT (G2; n = 32)	Moderate-to-severe CT (G3; n = 33)	No or low CT (G4; n = 46)			
Age (years)	22.41(4.01)	22.63 (4.03)	20.73 (3.42)	22.39 (4.11)	1.77	0.154	–
Gender (female %)	51 (56.04)	21 (65.63)	17 (51.52)	24 (52.17)	1.75	0.627	–
Intelligence score[a]	42.13 (6.48)	42.97 (6.24)	43.36 (4.67)	43.65 (6.03)	0.77	0.512	–
Duration (month)	10.98 (13.26)	8.81 (14.02)	–	–	0.78	0.437	–
Age onset	20.78 (4.31)	21.47 (3.84)	–	–	−0.80	0.427	–
Medication (yes/no)[b]	29/62	10/22	–	–	–	–	–
HAMD	20.23 (5.75)	19.55 (5.25)	–	–	0.59	0.555	–
BDI	31.34 (8.92)	27.69 (8.44)	7.18 (3.62)	4.70 (4.37)	183.85	<0.001	G1&G2>G3&G4
STAI_S	59.61 (10.70)	56.63 (9.02)	38.12 (8.50)	36.17 (9.76)	78.99	<0.001	G1&G2>G3&G4
STAI_T	63.43 (8.20)	59.84 (6.50)	42.70 (8.45)	37.63 (8.46)	131.80	<0.001	G1&G2>G3>G4
PSS	26.90 (5.05)	27.81 (8.55)	15.79 (6.58)	12.96 (5.09)	77.04	<0.001	G1&G2>G3&G4
CTQ_total	54.90 (11.61)	33.84 (4.47)	47.76 (8.38)	32.61 (3.73)	85.34	<0.001	G1>G3>G2&G4
Physical neglect	11.14 (3.20)	6.63 (1.45)	9.91 (2.66)	6.91 (1.49)	40.82	<0.001	G1&G3>G2&G4
Physical abuse	8.33 (3.84)	5.47 (0.98)	6.85 (2.43)	5.50 (1.09)	14.05	<0.001	G1>G2&G4
Emotional neglect	17.45 (4.20)	9.56 (3.13)	14.36 (4.08)	8.59 (2.65)	73.26	<0.001	G1>G3>G2&G4
Emotional abuse	11.69 (4.21)	6.91 (2.04)	9.45 (3.11)	6.37 (1.76)	33.48	<0.001	G1>G3>G2&G4
Sexual abuse	6.29 (2.98)	5.28 (0.63)	7.09 (3.21)	5.24 (0.52)	5.14	0.002	G3>G2&G4
FD	0.05 (0.03)	0.04 (0.02)	0.05 (0.03)	0.05 (0.02)	1.26	0.289	–

Notes: Means with standard deviations in parentheses. $F/t/\chi^2$: variables of age, intelligence score, CTQ assessments, BDI, STAI, PSS and FD were tested by one-way ANOVA as indicated by F; Categorical data was tested by chi-square test as indicated by χ^2; variables such as illness duration, age onset and HAMD were tested by two-sample t-test as indicated by t. [a] Intelligence score: age adjusted scores of subtests of the short form of the WAIS-RC (including Information, Similarity, Arithmetic and Digit span), which is only used for controlling the participants' intelligence level, rather than an estimation of IQ. [b] Medication: number of patients taking psychopharmacology yes/no. "No" means that the patients were medication-naïve, or they did not take any antipsychotic medicine at least for one month prior to the day when they were enrolled. "Yes" mean they were using medicine when enrolled (14 selective serotonin reuptake inhibitor; 3 serotonin and norepinephrine reuptake inhibitor; 1 tricyclic, 4 atypical antipsychotics).
Abbreviations: MDD, major depressive disorder; HC, healthy controls; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; STAI_S, Spielberger State-Trait Anxiety Inventory_State Form; STAI_T, Spielberger State-Trait Anxiety Inventory_Trait Form; PSS, Perceived Stress Scale; CTQ. Childhood Trauma Questionnaire; FD, Frame Displacement.

Table 2
Diagnosis and childhood trauma effect on anxiety and depression.

Characteristics	MDD		HC		Effect of diagnosis		Effect of CT		Effect of diagnosis × CT	
	Moderate-to-severe CT	No or low CT	Moderate-to-severe CT	No or low CT						
	(n = 91)	(n = 32)	(n = 33)	(n = 46)	*F (P)*	*Eta²*	*F (P)*	*Eta²*	*F (P)*	*Eta²*
BDI	31.34 (8.92)	27.69 (8.44)	7.18 (3.62)	4.70 (4.37)	466.88 (<.001)	0.71	6.91 (0.009)	0.03	3.64 (0.058)	–
STAI_S	59.61 (10.70)	56.63 (9.02)	38.12 (8.50)	36.17 (9.76)	186.70 (<.001)	0.49	1.88 (0.172)	–	1.40 (0.238)	–
STAI_T	63.43 (8.20)	59.84 (6.50)	42.70 (8.45)	37.63 (8.46)	296.60 (<.001)	0.60	11.98 (0.001)	0.06	0.30 (0.586)	–

Notes: Means with standard deviations in parentheses. Age, gender, and intelligence score were taken as covariates. The recent stress level was additionally controlled when investigating the effects involving CT.
Abbreviations: MDD, major depressive disorder; HC, healthy controls; CT, Childhood Trauma; BDI, Beck Depression Inventory; STAI_S, Spielberger State-Trait Anxiety Inventory_State Form; STAI_T, Spielberger State-Trait Anxiety Inventory_Trait Form.

3.4. Correlation and mediation analyses

The results of correlation and mediation analyses were presented in Table 4 and Figs. 2 and 3. In MDD group, the correlations of two FCs (left ITG – bilateral precuneus/PCC and left ITG – left mOFC) with CT and depression level were established (see Table 4 and Supplementary Table S1). Due to the two altered FCs were significantly correlated with BDI, and the two FCs were highly correlated ($r = 0.78$, $p < 0.001$), we calculated two independent measures: the sum of the FCs and the differences between FCs ($r = -0.19$, $p = 0.837$) to avoid the potential multicollinearity. The results of mediation analyses (see Fig. 3a) showed that the partial mediation effect of total altered FCs on the relationship between CT and depression in MDD (indirect effect: $\beta = 0.04$, bootstrapped 95% CI = 0.0045 to 0.0868; direct effect: $\beta = 0.18$, bootstrapped 95% CI = 0.0237 to 0.2090) but not differential FC, (indirect effect: $\beta = 0.0044$, bootstrapped 95% CI = −0.0120 to 0.0287) after controlling for age, gender, intelligence score, and PSS. For the specific types of CT, the total altered FC showed significant indirect effects on the relationship between EN and depression level ($\beta = 0.08$, bootstrapped 95% CI = 0.0196 to 0.1641), representing total mediation effect.

In HC, results showed that both altered left ITG – bilateral precuneus/PCC connectivity and left ITG – left mOFC connectivity were significantly correlated with trait anxiety, and the STAI_T and BDI score showed high correlations ($r = 0.83$, $p < 0.001$). Same method was conducted to avoid the potential multicollinearity. The mediation analyses results showed that total altered FC and trait anxiety have a significant chain mediation effect in the relationship between CT and depression ($\beta = 0.04$, bootstrapped 95% CI = 0.0049 to 0.1020) (see Fig. 3c), after controlling for age, gender, intelligence score, PSS, and other types of CT.

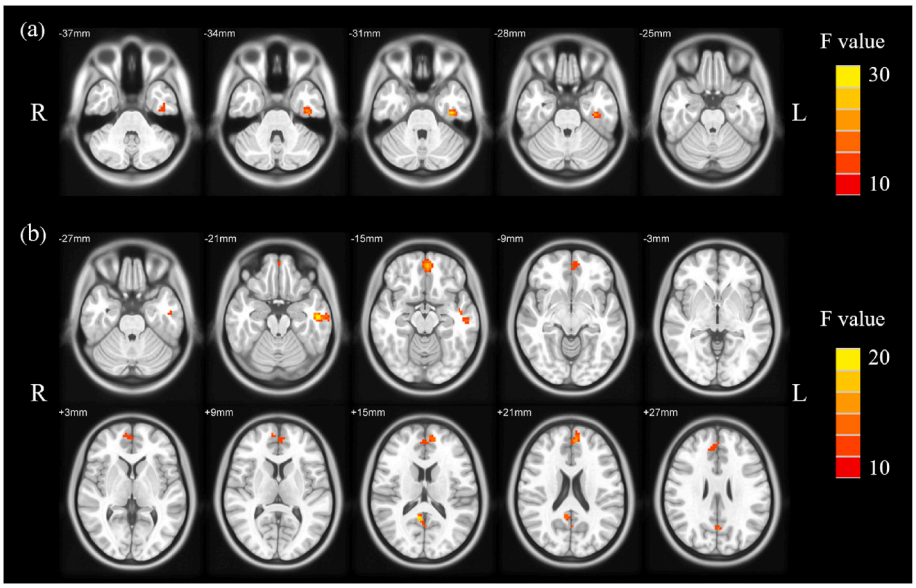

Fig. 1. Statistic maps showing effects of CT on ALFF and FCs. (a) Brain regions showing main effect of CT on ALFF value, controlling for age, gender, intelligence score, PSS, and FD (FDR corrected $p < 0.05$, TFCE). (b) Brain regions showing effects of MDD diagnosis-by-CT interactions on left ITG-seed FCs, controlling for age, gender, intelligence score, PSS, and FD (FDR corrected $p < 0.05$, TFCE).

4. Discussion

In the present study, the effects of CT on depression and the pattern of associations among CT, brain function alterations, and depression were investigated. The main findings of this study are as follows: (1) participants with moderate-to-severe CT had elevated depression and trait anxiety levels compared with participants with no or low CT; (2) CT was linked to abnormalities in spontaneous neural activity and rs-FC within DMN; (3) In HC, CT was associated with increased total FC of left ITG – bilateral precuneus/PCC and left ITG – mOFC, involving in a compensation response for CT exposure. Total altered FC and trait anxiety have a chain mediation effect in the relationship between CT and depression in HC (CT→total altered FC→trait anxiety→depression); (4) In MDD patients, CT was related to decreased total FC, which may represent a decompensation processing. Total altered FC mediated the relationship between CT and depression in MDD (CT→total altered FC→depression). These findings suggest the alterations of FC within DMN and trait anxiety as targets of CT, and support CT-related decreased functional coupling within DMN may be manifested as important mechanisms of CT leading to MDD.

Behavioral results of current study showed significant main effects of CT on depression and trait anxiety. These results indicated that, in addition to greater depression level, higher trait anxiety was also observed in participants with moderate-to-severe CT compared with participants with no or low CT. Previous studies had demonstrated that CT could increase trait anxiety in clinical (Mancini et al., 1995) and non-clinical samples (Reiser et al., 2014; Uchida et al., 2018), and has been supported as a vulnerability characteristic and risk factor associated with the development of stress-induced depression (Bishop and Forster, 2013; Kok et al., 2016). Subsequent imaging revealed that CT related to decreased ALFF in left ITG in both MDD and HC. The ITG is considered as an aera involving in cognitive processes and recognizing and interpreting information about body image (Monteleone et al., 2019) and has reciprocal connections with the amygdala and orbitofrontal cortex, which are linked to affective processing and expression (Rolls and Stringer, 2009). Our findings further support several structural (Monteleone et al., 2019; Teicher et al., 2014) and functional MRI studies (Du et al., 2016; Gold et al., 2016) that CT is associated with abnormalities in ITG, which may indicate potential neural marker of CT exposure.

The results of rs-FC showed the effects of CT-by-MDD diagnosis interactions on FCs of left ITG to bilateral precuneus/PCC, left MTG, left mOFC as well as bilateral mPFC/ACC. Subsequent correlation and mediation analyses highlight the crucial role of total altered FC (including FCs of left ITG – bilateral precuneus/PCC and left ITG – mOFC) in the relationship between CT and depression. The alterations of total FC relate to abnormal processing for self-reference and affective information (see Supplementary Materials for detail). An interesting finding is that CT-related FC alterations are reversed in MDD and HC. CT experiences can be constructed as threats to survival, body integrity or sense of self (McLaughlin et al., 2014). The prevailing view is that CT has deleterious effect on neurodevelopment, especially during a period of high neuronal plasticity, and psychopathology is a direct consequence. However, it seems unlikely that evolutionary forces have not selected for brains that are resistant to the damaging effects of CT (Teicher et al., 2016). The alternative view assumed that the brain is modified by early stress in a potentially adaptive way (Teicher, 2002; Teicher et al., 2003). Exposure to substantial levels of CT promotes the brain along alternative developmental pathways to promote reproduction and survival (Teicher and Samson, 2016), it makes sense to reported these brain alterations as potential adaptive responses. These two views are not mutually exclusive. In fact, not all individuals who experienced CT result in psychopathology. Some CT exposed individuals characterized as abnormalities in stress-susceptible brain regions or pathways but not overt psychopathology, suggesting that these neurobiological consequences in individuals without psychopathology may represent a kind of adaptation. In the present study, the increased rs-FC in HC with moderate-to-severe CT may represent a compensatory change (or adaptive modifications) to resist the damaging effects of CT exposure. However, these adaptive modifications may be weakened or obscured in MDD with moderate-to-severe CT, representing a decompensation process of brain function. The decompensated FCs (CT-related decreased coupling) in MDD observed in current study present the key difference in CT-related brain functional changes that distinguish MDD from HC, which may play an important role in the mechanism of CT leading to MDD. To our knowledge, altered connectivity within DMN has previously been noted in MDD patients (Greicius et al., 2007; Sheline et al., 2010; Yu et al., 2019), even in individuals at high familial risk for depression (Posner et al., 2016), suggesting the importance of DMN connectivity in MDD. The present study indicated that FC alterations within DMN are

Table 3
Diagnosis and childhood trauma effects on functional connectivity.

Brain region	BA	Cluster size	MNI coordinate			*F* scores
			x	y	z	
Seed: Left inferior temporal gyrus						
Diag Main effect						
Decreased FC						
Bilateral thalamus	NA	107	−3	−24	0	15.67
Right cerebellum/ right inferior occipital gyrus	18/19	2104	36	−69	−36	26.12
Right angular gyrus, superior and middle occipital gyrus	7/19	65	33	−63	30	13.56
Right angular gyrus, middle temporal gyrus	39	215	57	−69	27	17.67
Right inferior temporal gyrus	20	52	54	−24	−36	13.41
Right orbitofrontal cortex	11/47	55	27	30	−15	16.21
Left middle and inferior occipital gyrus	18	209	−27	−102	−9	21.73
Left temporal gyrus/ occipital gyrus/ parietal gyrus and angular gyrus	19/21/22/ 37/39/40	1041	−63	−57	−9	19.35
CT Main effect						
NA						
Diag × CT interactive effect						
Left middle temporal gyrus	20	68	−51	−18	−21	18.02
Bilateral precuneus and posterior cingulate cortex	17/23/30	50	9	−51	18	17.49
Left medial orbitofrontal cortex	11	66	−3	51	−15	15.64
Bilateral medial prefrontal cortex, extending to anterior cingulate cortex	10/32	113	9	42	30	14.91

Notes: the significance level for these brain regions was set at FDR corrected $p < 0.05$ after TFCE enhancement; age, gender, intelligence score, and FD were taken as covariates.
Abbreviations: ITG, Inferior temporal gyrus; BA, Broadmann area; x, y, z, coordinates of peak locations in the Montreal Neurological Institute space (MNI); NA, No applicable.

Table 4
Correlations between altered FCs and clinical variables in MDD and HC.

	BDI	STAI_S	STAI_T
MDD			
Left ITG-left MTG	−0.21	−0.17	−0.07
Left ITG-bilateral precuneus/PCC	−0.30**	−0.11	−0.16
Left ITG-left mOFC	−0.25*	−0.10	−0.06
Left ITG-bilateral mPFC/ACC	−0.23*	−0.21*	−0.11
HC			
Left ITG-left MTG	0.08	0.06	0.23
Left ITG- bilateral precuneus/PCC	0.07	0.17	0.38**
Left ITG-left mOFC	0.21	0.22	0.33**
Left ITG-bilateral mPFC/ACC	0.13	0.02	0.21

Notes: Significance level for partial correlations was set as FDR $q < 0.05$. *Significant at FDR $q < 0.05$, ** significant at FDR $q < 0.01$, controlling for age, gender, intelligence score, and PSS.
Abbreviations: MDD, Major depressive disorder; HC, Healthy controls; FC, Functional connectivity; BDI, Beck Depression Inventory; STAI_S, Spielberger State-Trait Anxiety Inventory_State Form; STAI_T, Spielberger State-Trait Anxiety Inventory_Trait Form; ITG, Inferior temporal gyrus; MTG, Middle temporal gyrus; PCC, Posterior cingulate cortex; mOFC, medial orbitofrontal cortex; mPFC, medial prefrontal cortex; ACC, Anterior cingulate cortex.

associated with CT exposure in MDD patients, implying the neural mechanism of MDD following CT may be related to DMN dysfunction. Nonetheless, further prospective studies should be performed to determine causality. Our findings were also supported by Wang et al. and reported that MDD with CT are associated with reduced FCs of some DMN regions (eg., mPFC) compared with MDD without CT, suggesting these disruptions neural system may be related to cognitive bias (Wang et al., 2014). Furthermore, we also found the main effects of MDD diagnosis on spontaneous neural activity and rs-FC, which were consistent with previous findings (see Supplementary Materials).

Combined with correlation and mediation analyses (Table 4, Fig. 2), our results may suggest that a specific pathological pathway of the impact of CT in development of MDD. Our mediation analyses revealed that the total rs-FCs (left ITG – bilateral precuneus/PCC and left ITG – mOFC) and trait anxiety have significant chain mediation effect on the relationship between CT and depression level in HC. This finding help link the neural alterations companied with CT to the behavioral targets. CT has been supported to increase trait anxiety in various samples (Mancini et al., 1995; Reiser et al., 2014; Uchida et al., 2018). In line with our findings, a recent neuroimaging study found that the mean strength of the self-reference network (SRN, which shares some similarities with the DMN in brain regions and the processing function of self-reference, mainly including PCC and vmPFC (Wei et al., 2021)) positively correlated with CTQ and STAI scores and mediated the relationship between CT and anxiety in healthy young adults (Tian et al., 2021). This result highlights the CT experience-dependent functional plasticity of SN in predicting adult anxiety. As a vulnerability factor of depression (Bishop and Forster, 2013; Kok et al., 2016), trait anxiety refers to a personality trait, which makes individuals prone to increase state anxiety when facing threats. Evidences showed that depression frequently develops secondary to the initial appearance of anxiety (Moriarity et al., 2018; Starr et al., 2016). The mediation role of trait anxiety on the relationship between CT and depression symptoms was also be reported in community sample (Uchida et al., 2018). The results of current study revealed the pathway of CT to trait anxiety and showed that CT exposure was associated with increased total FCs within DMN, which links to the development of anxiety trait, hyper responsiveness to threatening stimuli, and attentional biases towards to threats and aversiveness (Weger and Sandi, 2018), thereby contributing to specific vulnerability of depression in HC. It may suggest that the psychological and social intervention for reducing trait anxiety may decrease the risk of depression following CT. The significant mediation effects of trait anxiety between CT and depression were also observed in MDD, which further support the importance of trait anxiety. However, in MDD, due

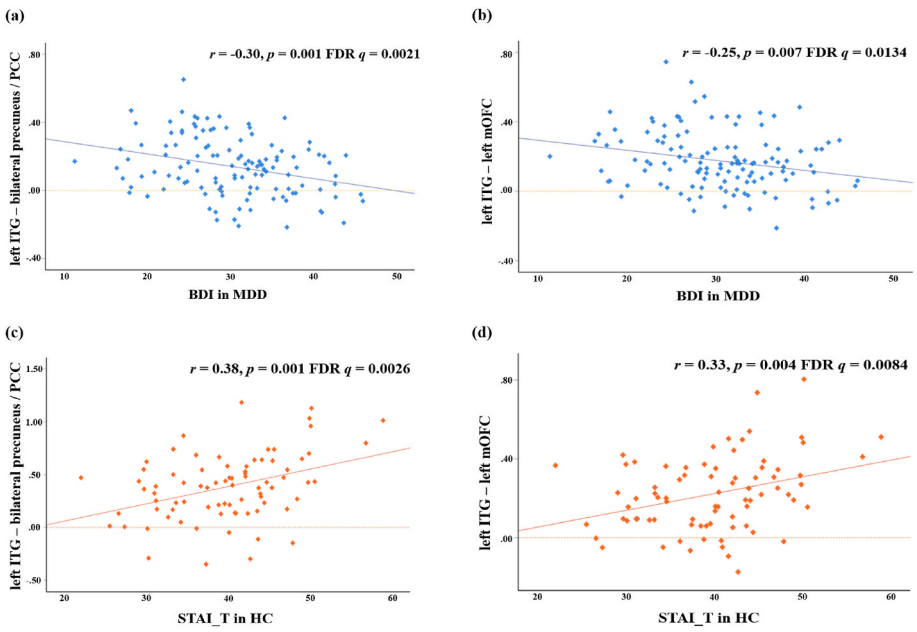

Fig. 2. Results of partial correlation analyses. BDI scores were significantly correlated with the altered FCs of (a) left ITG - bilateral precuneus/PCC, and (b) left ITG - left mOFC in MDD group. STAI_T scores were significantly correlated with the altered FCs of (c) left ITG - bilateral precuneus/PCC and (d) left ITG - left mOFC.
Abbreviations: MDD, Major depressive disorder; HC, Healthy controls; BDI, Beck Depression Inventory; STAI_T, Spielberger State-Trait Anxiety Inventory_Trait Form; ITG, Inferior temporal gyrus; PCC, Posterior cingulate cortex; mOFC, medial orbitofrontal cortex.

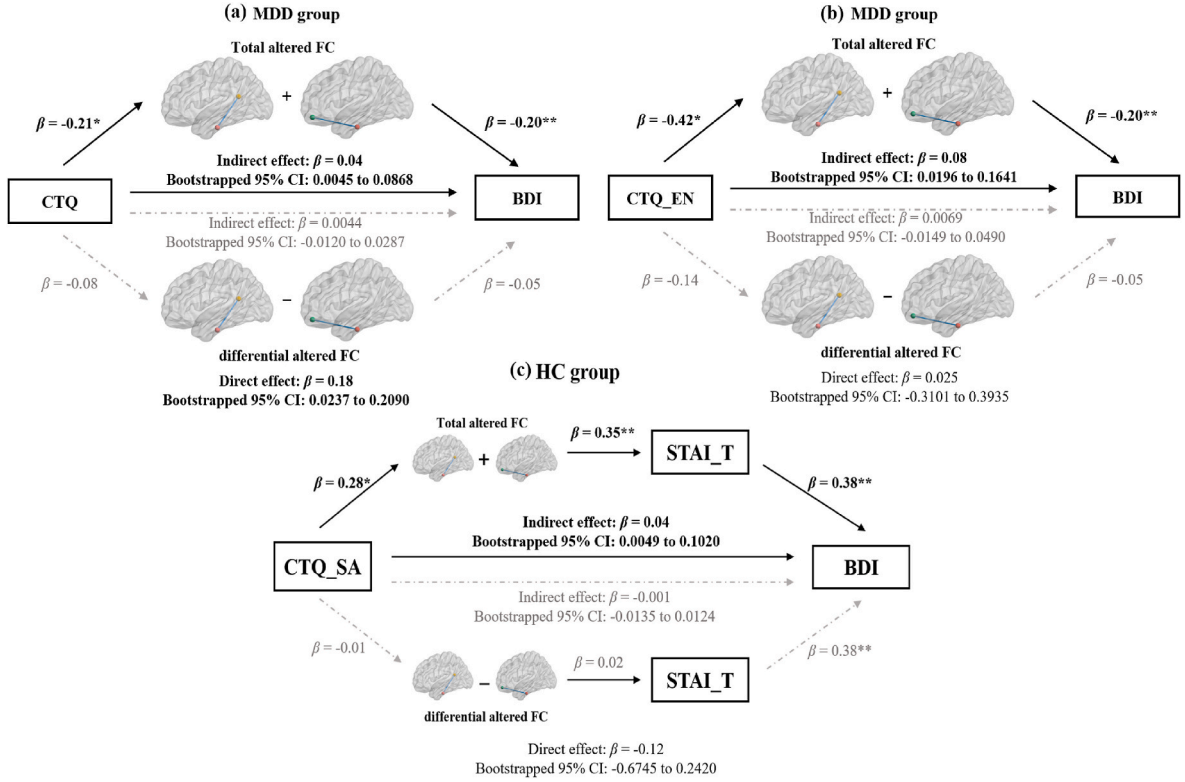

Fig. 3. Results of mediation analyses. Total altered FCs (between the left ITG and bilateral precuneus/PCC and between left ITG and left mOFC) significantly mediated (a) the relationship between CT and depression levels, as well as (b) the relationship between emotional neglect and depression level in MDD; (c) Total altered FCs and trait anxiety have a significant chain mediation effect on the relationship between sexual abuse and depression level in HC.
Abbreviations: MDD, Major depressive disorder; HC, Healthy controls; BDI, Beck Depression Inventory; STAI_T, Spielberger State-Trait Anxiety Inventory_Trait Form; ITG, Inferior temporal gyrus; PCC, Posterior cingulate cortex; mOFC, medial orbitofrontal cortex; CTQ, Childhood trauma questionnaire; EN, Emotional neglect; SA, Sexual abuse; *β*, standardized coefficient; CI, confidence interval.

to the decompensation process of CT related rs-FCs, the simple mediation effect CT on depression was detected. It is noted that the decompensation of total altered FC (decreased coupling) may present the key difference in CT-related brain functional changes that distinguish MDD from HC, which suggests that MDD patients with CT are associated with disruption in a neural system, involving in negative biases for self-reference and affective information processing. Thus, the correction for these negative biases is beneficial. In fact, MDD patients with CT experiences showed a poorer medication response than those without CT exposure. Previous studies suggested that for MDD patients with CT,

psychotherapy was more effective than pharmacotherapy (Klein et al., 2009; Nemeroff et al., 2003), which may be related to the effectiveness of psychotherapy for the correction of negative bias.

Taken together, the current study raises the possibility that alterations of FCs within DMN and trait anxiety as targets of CT, and highlight the decompensated FC within DMN may be involved in the mechanism of CT leading to MDD. Nevertheless, we cannot explain why some people with CT exist decompensation processing while others not, suggesting some additional risk or protective factors may interact with CT exposure to determine who will develop MDD, such as stress resilience, and family environment. Resilience has been suggested that can drive individuals to successfully adapt, cope with traumatic experiences and reduce the negative effect of risky exposure (Davydov et al., 2010). Previous studies have shown that resilience moderated the relationship between CT and depressive symptoms among adolescents (Ding et al., 2017) and adults (Wingo et al., 2010; Youssef et al., 2017), and the interaction of CT with resilience might predict MDD (Kwon et al., 2019). In addition, positive family environment is also a critical factor, which could protect children from traumatic experiences (Bush et al., 2020). Meanwhile, positive aspects of the family environment may contribute to resilience even in the face of CT exposure (Bradley et al., 2013). This needs to be further clarified. Thus, more factors should be considered to further clarify why some individuals with CT experiences might experience decompensation of brain function and further develop MDD while others do not. Moreover, in recent years, studies focused on intergenerational effects of trauma have produced additional insights. From a novel and powerful perspective of intergenerational psychiatry, the deleterious effects of CT not only affect people exposed to CT, but also affect the neurodevelopment of their children (Duarte et al., 2020). This should be pay more attention in future studies.

Several limitations should be noted with respect to our results. First, the current study is a cross-section design, which limits the determination of causality. Future research would especially benefit from longitudinal design to clarify how CT affects the onset of depression. Second, the retrospective assessment of CT using CTQ may be subject to recall biases and influenced by the current mood state of participants. Future prospective study may be able to overcome this issue, or combine self-reported questionnaires with face-to-face interviews to reduce information biases as possible. Third, the current study included medicated patients and the potential effect of antidepressants medications on resting-state brain function is still unclear. The main results involving CT of our study were not affected after removing the effect of medication (see Supplementary Tables S2 and S3). Nevertheless, the data from drug-naive MDD patients may be valuable to analyze in future studies.

5. Conclusions

In conclusion, our findings demonstrate that the changes of DMN functions and trait anxiety as targets of CT. Mediation analyses suggest an important role for total altered FCs of ITG – precuneus/PCC and mOFC within DMN in understanding connections between CT and depression, highlighting the key role of decreased functional coupling in CT to MDD. These findings may have implication for neural mechanism of CT leading to MDD, and provide clinical suggestions that the need to investigate psychotherapies for MDD with CT experiences, as well as early preventions targeting reduction of trait anxiety for high risky individuals with CT exposure.

CRediT authorship contribution statement

Xiang Wang: Data curation, Formal analysis, Writing - original draft. **Qian Liu:** Data curation, Writing - review & editing. **Jie Fan:** Data curation, Writing - review & editing. **Feng Gao:** Data curation, Writing - review & editing. **Jie Xia:** Data curation. **Xingze Liu:** Data curation. **Hongyu Du:** Data curation. **Haiyan Liao:** Data curation. **Changlian Tan:** Conceptualization, Supervision. **Xiongzhao Zhu:** Conceptualization, Supervision.

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Data availability statement

The data that support the findings of the study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declaration of competing interest

The authors declared no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.07.051.

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