Aberrant static and dynamic functional connectivity of amygdala subregions in patients with major depressive disorder and childhood maltreatment

Qianyi Luo [a], Juran Chen [a], Yuhong Li [a], Zhiyao Wu [a], Xinyi Lin [a], Jiazheng Yao [a], Huiwen Yu [a], Huawang Wu [b,c,*], Hongjun Peng [a,c,*]

[a] *Department of Clinical Psychology, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou 510370, China*
[b] *Department of Radiology, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou 510370, China*
[c] *Guangdong Engineering Technology Research Center for Translational Medicine of Mental Disorders, Guangzhou 510370, China*

ARTICLE INFO

ABSTRACT

Major depressive disorder (MDD) with childhood maltreatment is a heterogeneous clinical phenotype of depression with prominent features of brain disconnectivity in areas linked to maltreatment-related emotion processing (e.g., the amygdala). However, static and dynamic alterations of functional connectivity in amygdala subregions have not been investigated in MDD with childhood maltreatment. Here, we explored whether amygdala subregions (i.e., medial amygdala [MeA] and lateral amygdala [LA]) exhibited static functional connectivity (sFC) and dynamic functional connectivity (dFC) disruption, and whether these disruptions were related to childhood maltreatment. We compared sFC and dFC patterns in MDD with childhood maltreatment (n = 48), MDD without childhood maltreatment (n = 30), healthy controls with childhood maltreatment (n = 57), and healthy controls without childhood maltreatment (n = 46). The bilateral MeA and LA were selected as the seeds in the FC analysis. The results revealed a functional connectivity disruption pattern in maltreated MDD patients, characterized by sFC and dFC abnormalities involving the MeA, LA, and theory of mind-related brain areas including the middle occipital area, middle frontal gyrus, superior medial frontal gyrus, angular gyrus, supplementary motor areas, middle temporal gyrus, middle cingulate gyrus, and calcarine gyrus. Significant correlations were detected between impaired dFC patterns and childhood maltreatment. Furthermore, the dFC disruption pattern served as a moderator in the relationship between sexual abuse and depression severity. Our findings revealed neurobiological features of childhood maltreatment, providing new evidence regarding vulnerability to psychiatric disorders.

1. Introduction

Childhood maltreatment, including experiences of abuse and neglect (Teicher et al. 2016), has a substantial societal burden (Gilbert et al. 2009). Childhood maltreatment causes both physical impairments (e.g., coronary heart disease (Llabre et al. 2017) and diabetes (Hughes et al. 2017)) and mental illness (e.g., major depressive disorder, MDD (Nelson et al. 2017)) among victims, throughout their lives. Previous studies have reported that MDD patients with cumulative adversity in childhood show stronger anti-treatment responses (Nikkheslat et al. 2020) and poorer social functioning (McLaughlin et al. 2020). Researchers have

proposed that MDD with childhood maltreatment should be considered as a heterogeneous clinical phenotype of depression (Misiak et al. 2017). Although there is a clear relationship between childhood maltreatment and depression, clarifying how childhood maltreatment increases the risk of MDD is of crucial importance. Fig. 1.

The amygdala has long been linked to motivation and emotion, acting as a core region for processing rewarding and fearful environmental stimuli. Emerging evidence indicates that childhood maltreatment leads to functional and structural alterations in the amygdala, affecting the circuits involved in emotional regulation (Regev et al. 2011), threat detection (Coccaro et al. 2007), and reward anticipation

(Liu et al. 2011). These alterations constitute susceptibility to depression, further contributing to the development of MDD (Alexopoulos 2005;Wurtman 2005). In the past decade, the amygdala was considered as a single homogeneous structure that functioned as a whole. However, animal and human studies have shown that the amygdala is composed of functionally and structurally heterogeneous nuclei (Amaral and Price 1984;Bzdok et al. 2013;LeDoux 2003;Roy et al. 2009). A groundbreaking study developed a connectivity-based parcellation framework to determine the subdivisions of the amygdala (i.e., medial amygdala [MeA] and lateral amygdala [LA]), revealing the architecture of subregional connectivity in the amygdala (Fan et al. 2016). The MeA has been proposed to function as a key node for socio-sexual behavior in humans (Li et al. 2017). Substantial evidence indicates that the MeA is recruited in parental care and the control of aggression (Sano et al. 2013;Wang et al. 2013). Evidence from lesion (LeDoux 2000) and electrophysiological recording studies (Quirk et al. 1995;Rogan et al. 1997;Romanski et al. 1993) indicates that the LA is a key region of plasticity underlying fear learning (Grosso et al. 2018). Specifically, hyperactivation of LA appears to facilitate fear expression, while the inactivation of LA causes the excessive inhibition of fear reactions (i.e., freezing response to high threat (Grosso et al. 2018;Schafe et al. 2005). Moreover, impaired functional connectivity (FC) in the LA may reflect increased sensitivity to fear-related stimuli from the surrounding environment. To date, no studies have investigated abnormal FC patterns in the amygdala at the subregional level in MDD patients with childhood maltreatment. The amygdala subregions facilitate the understanding of brain dysfunction from a single anatomical dimension to an integrated dimension that includes function, structure, connectivity, and other potential sources of information (Fan et al. 2016).

FC is a fundamental method for characterizing interregional brain activity, including static FC (sFC) and dynamic FC (dFC), according to different hypotheses regarding the temporal and spatial stationarity of functional interactions (Allen et al. 2014;Calhoun et al. 2014). sFC has been applied to investigate the temporal correlation of blood oxygen level-dependent signals among distinct brain regions on the basis of the assumption that intrinsic brain activity is stable across the time series (Biswal et al. 1995). The sFC approach could provide valuable information regarding normal and abnormal brain organization (Biswal et al. 1995). However, to achieve more comprehensive comprehension of large-scale network activity, the dFC approach should be considered and evaluated (Hutchison et al. 2013). dFC was developed to examine the altered interactions across brain regions over time, and to enable the characterization of the spontaneous variability and fluctuation of FC across multiple time windows (Hutchison et al. 2013). dFC approaches enable exploration of temporal-dynamic integration in the brain (Hutchison et al. 2013). Existing study suggested that dFC indexes alterations in neural activity patterns underlying critical aspects of emotion and behavior from a macroscopic perspective (Hutchison et al. 2013). A number of researchers have suggested that combining the sFC

and dFC approaches could provide more comprehensive understanding of the neuropathological alterations underlying MDD compared with the use of a single approach (Guo et al. 2012;Cui et al. 2020; Fu et al. 2019; Lewis et al. 2020;Liu et al. 2013; Liu et al., 2017;Wang et al. 2021;Xue et al. 2020). Considering the respective advantages of sFC and dFC, combined sFC and dFC analyses were adopted in the current study.

Previous studies have investigated anomalous sFC or dFC findings in cases of MDD with childhood maltreatment. For instance, one study confirmed the association between childhood maltreatment and abnormal amygdala-based functional networks in healthy adults using sFC analysis (Luo et al. 2022). In addition, Luo et al. linked the maltreatment history with altered sFC between the lingual and fusiform gyrus in MDD patients with childhood maltreatment, revealing that MDD patients with and without maltreatment are neurobiologically and clinically distinct (Luo et al. 2022). Moreover, another study reported that childhood abuse is positively correlated with increased sFC between the brainstem and amygdala among school-aged children, indicating overactivity of fear neurocircuitry in children with a history of abuse. Using dFC and large-scale network models of brain function, the relationship between early life maltreatment and aberrant brain activity was examined in young females (Cisler 2017). The studies mentioned above mainly focused on sFC alterations in MDD with childhood maltreatment, ignoring dFC alterations with underlying abundant neurobiological information. However, it remains unclear whether MDD with childhood maltreatment involves anomalous dFC function. Moreover, the differences between sFC and dFC patterns in MDD with childhood maltreatment are also unclear. Thus, studies combining static and dynamic approaches are urgently needed to explore abnormal sFC and dFC in MDD with childhood maltreatment.

In the current study, we explored sFC and dFC differences in MDD patients with childhood maltreatment, MDD patients without childhood maltreatment, healthy controls (HCs) with childhood maltreatment, and HCs without childhood maltreatment. We sought to examine the association between brain functional alterations, psychopathology, and childhood maltreatment, investigating whether these alterations reflect psychological effects of childhood maltreatment or etiological effects of MDD. Moreover, we aimed to identify the differences between sFC and dFC, further revealing the differential sFC and dFC patterns in MDD patients with childhood maltreatment. Informed by previous FC studies of MDD with childhood maltreatment (Fan et al. 2021; Hakamata et al. 2021; Luo et al. 2022; Wu et al. 2021), we hypothesized that (i) relative to MDD patients without childhood maltreatment, aberrant sFC and dFC patterns would be widely detected in the subregions of the amygdala in MDD patients with childhood maltreatment; (ii) compared with MDD patients without childhood maltreatment, abnormal dFC patterns would exist in MeA (related to socio-sexual behavior and adversity related to parental care) in MDD patients with childhood maltreatment; (iii) Between-group differences in sFC and dFC patterns would be exhibited in different brain regions; and (iv) sFC and dFC abnormalities would be
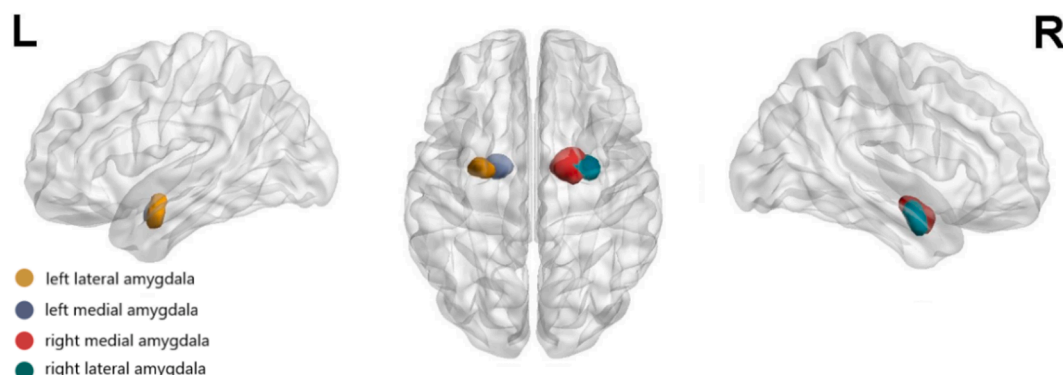

- left lateral amygdala
- left medial amygdala
- right medial amygdala
- right lateral amygdala

Fig. 1. The four subregions of the amygdala in the bilateral hemisphere.

associated with childhood maltreatment. To examine our hypothesis, we applied combined sFC and dFC analyses to investigate the association between abnormal FC patterns and the impacts of childhood maltreatment in MDD patients. These findings extend current understanding of the underlying neurobiological basis of MDD with childhood maltreatment, and could potentially be adopted as a diagnostic neuroimaging biomarker.

2. Methods

2.1. Participants

A total of 78 MDD patients and 103 HCs were included in the current study. Diagnoses of MDD were made by two psychiatrists using DSM-5 diagnostic criteria. Severity of depression and anxiety were assessed using the Hamilton Depressive Rating Scale (HAMD) (Helmreich et al. 2012) and Hamilton Anxiety Scale (HAMA) (Maier et al. 1988), respectively. Childhood maltreatment was evaluated using the childhood trauma questionnaire (CTQ) (Bernstein et al. 1994; Bernstein et al., 1997; Bernstein et al., 2003). The CTQ has been confirmed as a reliable tool for quantifying the psychological impact of childhood maltreatment on maltreated subjects before the age of sixteen (Bernstein et al. 2003; Bernstein et al., 1997; Bernstein et al., 1994). The CTQ is reported to exhibit a high level of criterion-related validity internationally (Bernstein et al. 1994; Bernstein et al., 1997; Bernstein et al., 2003). According to different types of childhood maltreatment, CTQ can be divided into five subscales: emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN), and physical neglect (PN). The cutoff points of CTQ subscales are as follows: EA score $\geq$ 13, PA score $\geq$ 10, SA score $\geq$ 8, EN score $\geq$ 15, and PN score $\geq$ 10. Classification of participants with or without a history of childhood maltreatment using the cutoff points for the CTQ subscale scores has been validated in multiple previous studies (Geng et al. 2014; Gong et al. 2017; Xu et al. 2011). Thus, we used the same criterion to identify whether the participants suffered from childhood maltreatment. Specifically, we used CTQ subscale scores to determine whether each participant had been exposed to childhood maltreatment, and the CTQ total score was used to evaluate the severity of maltreatment-related adversity (Bernstein et al. 1994; Popovic et al. 2020). In the current study, participants with an above-threshold score in any childhood maltreatment subtype were considered as having been exposed to childhood maltreatment (Bernstein et al. 1997; Fink et al. 1995).

According to the above criterion, each participant was classified as belonging to the MDD with childhood maltreatment group (n = 48), the MDD without childhood maltreatment group (n = 30), the HC with childhood maltreatment group (n = 57), or the HC without childhood maltreatment group (n = 46). Of note, the age-, gender-, and educational level-matched HC were also undergo screening test for latent mental problems before recruited. The exclusion criteria were as follows: (i) patients suffered from any other major psychiatric illness apart from depression (e.g., posttraumatic stress disorder, bipolar disorder, anxiety); (ii) patients received psychotropic medication or had undergone electroconvulsive therapy before; (iii) patients had contraindications for rs-fMRI. All participants were undergoing their first episode of MDD (for MDD patients), drug-naive (for MDD patients), and right-handed. We received written informed consent from each participant before enrollment. This study was approved by the ethics committees of the Affiliated Brain Hospital of Guangzhou Medical University.

2.2. MRI data acquisition

MRI data were collected at the radiology department, The Affiliated Brain Hospital of Guangzhou Medical University, China, with a 3.0 T Philips scanner. During the scanning, participants were required to keep the eyes closed, keep awake, remain motionless, and stay relax. The blood-oxygen-level-dependent (BOLD) signals were obtained within an

8 min scan with 240 time points. Resting state functional scans were conducted by using a gradient-echo echoplanar imaging sequence with the following parameters: 33 slices; repetition time = 2000 ms; echo time = 30 ms; flip angle = $90°$; field of view = 220×220 mm^2; slice thickness = 4 mm; inter slice gap = 0.6 mm; acquisition matrix = 64×64.

2.3. MRI data preprocessing

The rs-fMRI image preprocessing was conducted using Data Processing Assistant for Resting-State fMRI (DPABI V3.0) (Yan et al. 2016). For each subject, the first 10 volumes were removed to reach steady-state longitudinal magnetization. Subsequently, the remaining 230 volumes were performed slice-time correction and head motion correction. The head motion correction was performed using a six motions parameter (rigid body). The average value of framewise displacement (FD) from every time point for each subject were computed to result the mean FD (Jenkinson et al. 2002). Of note, the participants with mean FD <0.2 mm were included in the current study. Moreover, the images were spatially normalized into the standard Montreal Neurological Institute (MNI) space Echo-planar Imaging (*EPI*) template, and each voxel was then resampled to $3 \times 3 \times 3$ mm^3. After the spatially normalization, the images were smoothed using a 4-mm full-width at half maximum (FWHM) Gaussian kernel. In order to reduce the influence of the physiological artifacts, the rigid-body 6 model, the white matter signal, and the cerebrospinal fluid signal were treated as nuisance covariates to regressed out. Finally, the processed images were filtered with a temporal band-pass filter between 0.01 Hz − 0.08 Hz.

2.4. Definition of regions of interest

Derived from the Brainnetome atlas (Fan et al. 2016), four subregions of the amygdala including bilateral LA and bilateral MeA were selected as regions of interest (ROIs) in the seed-based dFC analyses.

2.5. Static functional connectivity analysis

The static FC analyses were performed using the DPABI software. The four subregions of the amygdala were defined as seed when calculating the static FC. First, we extracted the time series within the selected seed. Subsequently, we conducted the voxel-wise correlation analyses between the amygdala subregions seed and the other brain regions to acquire static FC maps. Finally, the z transformation was applied to the resulted static FC maps to improve the normality of the data distribution.

2.6. Dynamic functional connectivity analysis

With the Hamming sliding-window method, dFC of amygdala were calculated using the temporal dynamic analysis toolkits integrated into DPABI software (DPABI, version 4.5) (Yan et al. 2016). As reported, a longer window length might affect the characterization of the temporal variability dynamics while a shorter window length might heighten the risk of introducing spurious fluctuations when observing dFC (Shunkai et al. 2021). Evidence have revealed that window length of 50 TRs is appropriate to maintain the balance between achieving FC reliable calculations and capturing high-speed FC time-varying alterations (Cui et al. 2020; Liao et al. 2019; Liu et al. 2021). Hence, the time series was segmented into 50 TR windows with a size of 100 s. A sliding window with a step size of 1 TR was applied, resulting in 181 consecutive windows across the entire scan. Furthermore, dFC with window lengths of 30 TRs and 70 TRs were also calculated to evaluate the impact of different window length on dFC (Liao et al. 2014). The correlation maps for each sliding window were generated by calculating the temporal correlation coefficients between the time series of the amygdala subregion and all the other voxels. Thus, 181 sliding window correlation maps

were resulted for each subject. We then obtained dFC maps by calculating standard deviation maps for 181 sliding windows. The dFC maps represent the temporal variance of FC in each amygdala subregion and characterize the fluctuations of FC. We then performed a z-transformation of the resulted dFC maps. The dFC maps were further smoothed with a 4 mm FWHM Gaussian kernel. To further examine the reliability of our findings, we reperormed our calculations of dFC pattern with sliding window length of 30 TRs and 70 TRs respectively (Liao et al. 2014).

2.7. Statistical analysis

The statistical analyses in the current study could be divided into the following five modules:

(i) Behavioral analysis: between-group differences in the demographic data (i.e. age, gender, educational level), clinical characteristics (i.e. HAMD score and HAMA score) and childhood maltreatment severity (i.e. total score and subscale score of CTQ) were analyzed using the method of t test, χ^2 test, and one-way analyses of variance (ANOVA) in SPSS software version 19.0 (IBM Corp., Armonk, NY, USA).

(ii) Identification of the within-group dFC variability distribution: one-sample t-test was conducted to characterize the within-group dFC variability distribution of each amygdala subregion in MDD patients with childhood maltreatment, MDD patients without childhood maltreatment, and healthy subjects ($p < 0.05$, uncorrected).

(iii) Analysis of group difference in dFC and sFC. Two-way ANOVA with Bonferroni adjusted post hoc tests was applied to further investigated the dFC and sFC differences between MDD with childhood maltreatment group, MDD without childhood maltreatment group, healthy controls with childhood maltreatment group, and healthy controls without childhood maltreatment group. With the two-way ANOVA analysis, we could examined whether altered FC pattern in maltreated MDD patients could be attributed to the psychological effects of childhood maltreatment or to the etiological effects of MDD. Specifically, we can distinguish the different effect on aberrant FC, including etiological effect, traumatic effect, and interaction effect (affected by MDD plus childhood maltreatment).

We computed the etiological effect, traumatic effect, and interaction effect on dFC and sFC of each amygdala subregions, respectively. Bonferroni adjusted post hoc tests was subsequently adopted for the multiple comparisons. Of note, before calculating the dFC group differences with two-way ANOVA analysis, we generated the union mask of one-sample t test results of four groups. Correspondingly, two-way ANOVA of dFC was conducted within the resulted subregion dFC mask. Demographic characteristics were considered as nuisance covariates in the analyses (FDR corrected, $p_{adj} < 0.05/12 = 0.004$, corrected).

(iv) Correlation analyses: the dFC values of the clusters with significant group differences in two-way ANOVA were extracted. Then, partial correlation analysis with the Benjamini-Hochberg correction was conducted to analyze the associations between the dFC values and the childhood maltreatment severity (CTQ total and subscale scores). The demographic factors were treated as nuisance covariates. The whole datasets (i.e., MDD with childhood maltreatment, MDD without childhood maltreatment, healthy subjects) were used in the current correlation analyses.

(v) Moderation analysis: Moderator analysis was subsequently applied to unpack the issue that whether abnormal dFC patterns affect the relationship between childhood maltreatment and the depression severity. Moderator analysis was performed with PROCESS 3.3 toolbox (https://processmacro.org/index.html) for

SPSS software. Hierarchical moderated regression analysis was conducted to evaluate the effects of independent variable (childhood maltreatment) on the dependent variable (depression severity) and the effect of moderating variable (abnormal dFC variability) in the model. Before conducting the moderated regression analysis, values of the independent variable and moderator variable were both mean centered (Holmbeck 1997). During the moderated regression analysis, childhood maltreatment (characterized by CTQ total score and its subscale score) and abnormal dFC variability were first entered in Step1. Then, their interaction (childhood maltreatment × abnormal dFC variability) was subsequently entered in Step2. When the interaction was significant, depiction of the moderating effect of M (abnormal dFC variability) by plotting the simple relationship between X (childhood maltreatment, characterized by CTQ total score and its subscale score) and Y (HAMD score) for different values of M (mean ± 1 SD). Conventional 5 % (two-tailed) was accepted as statistical significance.

3. Results

3.1. Demographics and clinical characteristics

Demographic characteristics are shown in Table 1. In maltreated MDD patients, 48 participants met the criteria for more than one element of childhood maltreatment. No significant differences were found in age, gender, educational level, or mean FD in the MDD with childhood maltreatment, MDD without childhood maltreatment, HC with childhood maltreatment, or HC without childhood maltreatment groups (all $p > 0.05$). HAMD and HAMA scores did not differ between MDD patients with and without childhood maltreatment (all $p > 0.05$). In addition, significant differences were observed in CTQ total scores, EA, PA, SA, EN, and PN among four groups (all $p < 0.05$).

3.2. Amygdala subregions seed-based static functional connectivity

As shown in Table 2 and Fig. 2, significant sFC differences were only detected between the right LA seed and right calcarine gyrus, indicating a traumatic effect on abnormal sFC. Bonferroni adjusted post hoc tests were subsequently adopted in multiple comparisons. Decreased sFC between the right LA seed and the right calcarine gyrus was observed in MDD patients with childhood maltreatment, relative to MDD patients without childhood maltreatment ($p = 0.003$). Analogously, HCs with childhood maltreatment exhibited decreased sFC between the right LA seed and the right calcarine gyrus compared with HC without childhood maltreatment ($p = 0.009$).

3.3. Within-group dFC patterns of amygdala subregions

dFC patterns of each amygdala subregion in the MDD with childhood maltreatment, MDD without childhood maltreatment, HC with childhood maltreatment, and HC without childhood maltreatment groups are shown in Fig. S1. dFC spatial maps show the results of one-sample t tests ($p < 0.05$, uncorrected for visual inspection). Among the four groups, dFC of the amygdala subregions was mainly distributed in the postcentral gyrus, middle frontal gyrus (MFG), superior frontal gyrus, middle temporal gyrus (MTG), superior temporal gyrus, occipital lobe, precuneus, and limbic lobe.

3.4. Between-group dFC patterns of amygdala subregions

We could distinguish the etiological effects of MDD, traumatic effect, and interaction effect of MDD plus childhood maltreatment on aberrant dFC though two-way ANOVA analysis. Significant differences exhibited in the following pair brain regions (Table 2, Fig. 3 and Fig. 4):

Table 1

Demographic and clinical characteristics of MDD with childhood maltreatment, MDD without childhood maltreatment, and HC with childhood maltreatment, HC without childhood maltreatment groups.

	MDD with childhood maltreatment (n = 48)	MDD without childhood maltreatment (n = 30)	HC with childhood maltreatment (n = 57)	HC without childhood maltreatment (n = 46)	$F/t/\chi^2$	p
Age	28.1 ± 6.524	29.07 ± 7.913	26.82 ± 7.033	27.28 ± 6.065	0.824	0.482
Gender (male/female)	25/23	11/19	27/30	17/29	2.436	0.119
Educational level	12.92 ± 3.319	13.73 ± 3.35	14.14 ± 2.799	14.54 ± 2.335	2.671	0.051
HAMD score	29.46 ± 8.543	29.73 ± 5.458	–	–	0.081	0.97
HAMA score	24.09 ± 6.687	6.7 ± 4.276	–	–	3.91	0.052
Onset age	27.8 ± 4.23	28.3 ± 5.66	–	–	0.673	0.529
Illness duration	0.46 ± 0.23	0.55 ± 0.16	–	–	2.732	0.069
Mean FD (mm)	0.462 ± 0.214	0.559 ± 0.183	0.532 ± 0.119	0.521 ± 0.124	0.069	0.893
CTQ score	55.33 ± 12.575	29.7 ± 4.535	43.6 ± 8.252	31.26 ± 4.234	85.943	<0.001
Emotional abuse	11.02 ± 4.987	5.73 ± 1.461	7.81 ± 3.17	6.13 ± 1.47	23.49	<0.001
Physical abuse	8.06 ± 4.503	5.57 ± 1.165	6.6 ± 2.137	5.41 ± 0.777	9.17	<0.001
Sexual abuse	6.02 ± 2.686	5.2 ± 0.407	5.67 ± 1.286	5.3 ± 0.662	2.271	0.042
Emotional neglect	18.04 ± 3.984	7.43 ± 2.921	13.51 ± 4.822	8.22 ± 2.43	72.382	<0.001
Physical neglect	12.19 ± 3.486	5.77 ± 1.04	10.02 ± 2.781	6.2 ± 1.24	65.192	<0.001

Table 2

Two-way ANOVA of amygdala seed based dynamic and static functional connectivity.

	Seed	Effect	Brain region	Cluster size	x	y	z	F
Dynamic	left medial amygdala	traumatic effect	left middle occipital area	17	−48	−69	0	−4.8276
			right middle frontal gyrus	16	42	57	3	4.33
		interaction effect	left superior medial frontal gyrus	11	0	66	12	27.2794
			left angular gyrus	11	−45	−63	27	20.2398
	right medial amygdala	traumatic effect	right middle frontal gyrus	12	39	42	33	4.5342
		etiological effect	right supplementary motor areas	12	3	24	54	4.3162
		interaction effect	left middle temporal gyrus	10	−45	−60	18	19.3422
	left lateral amygdala	etiological effect	right middle cingulate gyrus	16	6	−48	36	4.2578
Static	right lateral amygdala	traumatic effect	right calcarine gyrus	70	9	−57	12	−4.4811

(i) left MeA – left middle occipital area (MOA), left MeA – right MFG (effect of maltreatment); (ii) left MeA – left superior medial frontal gyrus (SMFG), left MeA – left angular gyrus (AG) (interaction effect); (iii) right MeA – right MFG (effect of maltreatment); (iv) right MeA – right SMA (etiological effects of MDD); right MeA – left MTG (interaction effect); (v) left LA – right middle cingulate gyrus (MCG) (etiological effects of MDD); No significant difference was observed in the dFC analysis with the right LA selected as seed. Bonferroni adjusted post hoc tests was subsequently adopted for the multiple comparisons ($p_{adj} < 0.05/12 = 0.004$, corrected).

(ii) left MeA seed based dFC analysis: relative to MDD without childhood maltreatment, decreased dFC were observed in MDD with childhood maltreatment in the left MeA – left MOA, left MeA – left SMFG; Conversely, increased dFC were found in the left MeA – right MFG in MDD with childhood maltreatment, compared to MDD without childhood maltreatment. Moreover, relative to HC without childhood maltreatment group, HC with childhood maltreatment group showed increased dFC in left MeA – right MFG, left MeA – left AG.

(iii) right MeA seed based dFC analysis: compared to MDD without childhood maltreatment group, MDD with childhood maltreatment group showed higher dFC in right MeA – right MFG while lower dFC was observed in right MeA – left MTG. Compared with HC without childhood maltreatment group, higher dFC between right MeA and left MTG exhibited in HC with childhood maltreatment group.

(iv) left LA seed based dFC analysis: the results revealed no significant difference between MDD with and without childhood maltreatment as well as HC with and without childhood maltreatment.

3.5. Correlation analyses

We used the dataset of MDD patients for partial correlation analysis. Benjamini-Hochman correction was applied to avoid reporting false positive results. As shown in Table 3 and Fig. 5, dFC between left MeA and left MOA was negatively correlated with emotional neglect (r = −0.358, $p_{adj} = 0.012$). dFC between left MeA and right MFG was positively correlated with emotional neglect (r = 0.315, $p_{adj} = 0.0343$). dFC between left MeA and left SMFG was negatively correlated with emotional neglect (r = −0.451, $p_{adj} < 0.001$), physical neglect (r = −0.315, $p_{adj} = 0.0343$), and CTQ total score (r = −0.350, $p_{adj} = 0.0192$). dFC between right MeA and right MFG was positively correlated with emotional neglect (r = 0.313, $p_{adj} = 0.0343$) and physical neglect (r = 0.300, $p_{adj} = 0.0384$). dFC between right MeA and left middle temporal gyrus was negatively correlated with emotional neglect (r = −0.402, $p_{adj} < 0.001$), physical neglect (r = −0.301, $p_{adj} = 0.0373$), and CTQ total score (r = −0.404, $p_{adj} < 0.001$).

3.6. Moderation analysis

Multiple linear regression analysis was performed to determine whether abnormal dFC moderated the relationship between childhood maltreatment and MDD severity Baron and Kenny (1986). Table 4 shows the moderation model in detail. For predicting the severity of MDD, the step 1 predictor was significant ($R^2 = 0.041$, $p = 0.025$). The step 2 predictor (interactions) also reached significance ($R^2 = 0.091$, $p = 0.002$). Specifically, the interaction of sexual maltreatment and abnormal dFC between right MeA and right SMA predicted the severity of MDD (B = 0.239; $p = 0.002$). The results of a simple slope test using the Johnson-Neyman approach are shown in Fig. 6.
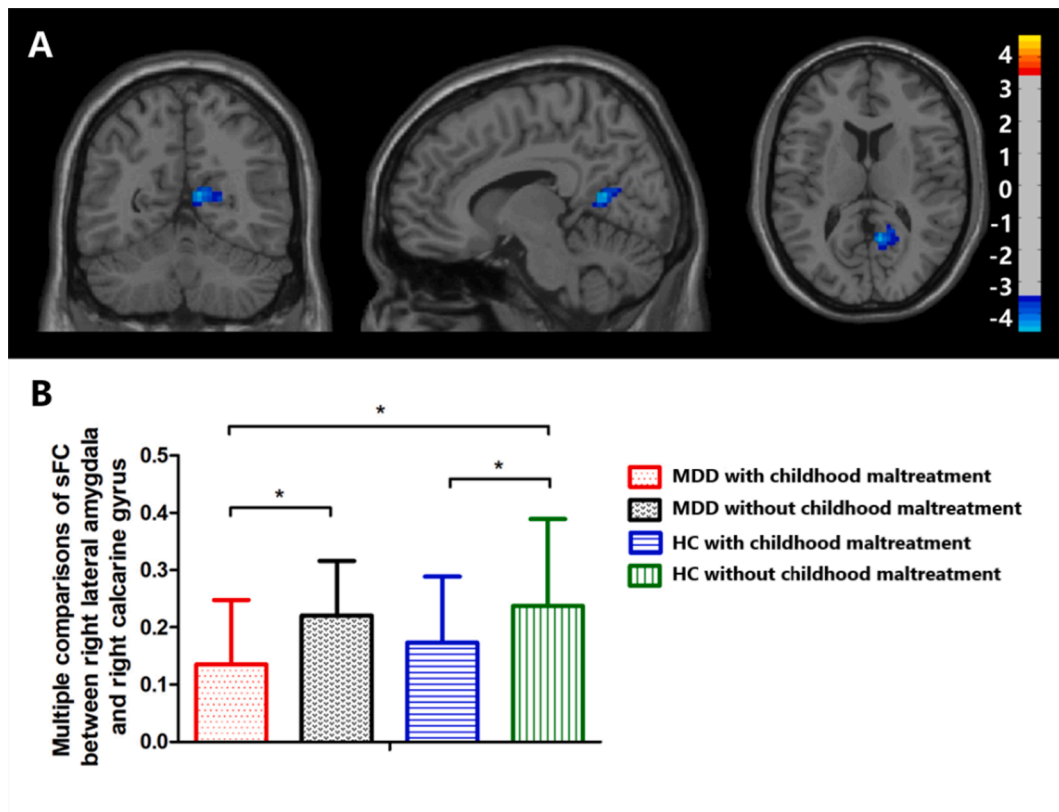
Fig. 2. Significant sFC differences between the four groups for amygdala seed. Fig. 3A show decreased sFC between right lateral amygdala seed and right calcarine gyrus. Fig. 3B displayed the multiple comparisons of sFC between right lateral amygdala seed and right calcarine gyrus. MDD: major depressive disorder; HC: healthy control.

3.7. Validation

To examine the reliability of our findings, we repeated the calculation of dFC patterns using sliding window lengths of 30 TRs and 70 TRs. Most of the results remained consistent in the validation analyses. With a window length of 70 TRs, MDD patients with childhood maltreatment exhibited higher dFC in right MeA – right MFG, and lower dFC in left MeA – left SMFG, right MeA – left MTG, and right LA – left MFG compared with MDD patients without childhood maltreatment. With a window length of 30 TRs, MDD patients with childhood maltreatment consistently exhibited decreased dFC in right MeA – right MFG, right LA – left MTG, and right LA – left precuneus. Detailed information is provided in *Supplementary Materials*.

4. Discussion

In the current study, we combined the sFC and dFC approaches to investigate aberrant FC patterns in MDD patients with childhood maltreatment, MDD patients without childhood maltreatment, HCs with childhood maltreatment, and HCs without childhood maltreatment. Compared with MDD patients without childhood maltreatment, aberrant FC patterns of MDD patients with childhood maltreatment were characterized by: (i) decreased sFC between right LA and right calcarine gyrus, (ii) decreased dFC in left MeA – left MOA, left MeA – left SMFG, (iii) increased dFC in left MeA – right MFG, (iv) increased dFC in right MeA – right MFG, and (v) decreased dFC in right MeA – left MTG. Compared with HCs without childhood maltreatment, HCs with childhood maltreatment also exhibited unique FC patterns: (i) decreased sFC between the right LA seed and right calcarine gyrus, (ii) increased dFC in left MeA – right MFG, left MeA – left AG, and (iii) increased dFC between right MeA and left MTG. Significant correlations were detected between the aberrant dFC patterns and CTQ total and subscale scores (reflecting

the negative effects of childhood maltreatment). Importantly, the abnormal dFC pattern between right MeA and right SMA was a moderator in the relationship between sexual abuse history and the depression severity. Collectively, our findings distinguished a maltreatment-related FC pattern and an MDD etiology-related FC pattern. Additionally, we contrasted the sFC and dFC patterns in MDD with childhood maltreatment, further characterizing the unique FC pattern in MDD with maltreatment. The enduring effect of childhood maltreatment was highlighted in MDD patients, indicating that childhood maltreatment cause aberrant interregional brain activity. Below, we distinguish subregion-specific anomalous connectivity in MDD with childhood maltreatment and discuss the anomalous sFC and dFC patterns in the amygdala subregions.

4.1. Anomalous sFC of the right lateral amygdala in MDD patients with childhood maltreatment

In the current study, decreased sFC was observed between the right LA and right calcarine gyrus, revealing an effect of childhood maltreatment on altered FC patterns. The disrupted neural communication described above could be linked to the role of the right LA in freezing responses to high threat (LeDoux 2000). Pathological investigations have reported that serious damage to the LA inhibits fear conditioning (LeDoux 2000). MDD patients with childhood maltreatment frequently exhibit affective inhibition and fear suppression. We speculate that threat-related adversity in childhood may lead to disruption of communication in LA, which may be a susceptibility factor predisposing individuals to depression. Susceptibility might develop through alterations in neuroplasticity (Uys et al. 2006). However, the neural basis underlying childhood maltreatment and enhanced vulnerability to depression has not been explored in depth. In accord with the current findings, Feldker and colleagues suggested that increased LA
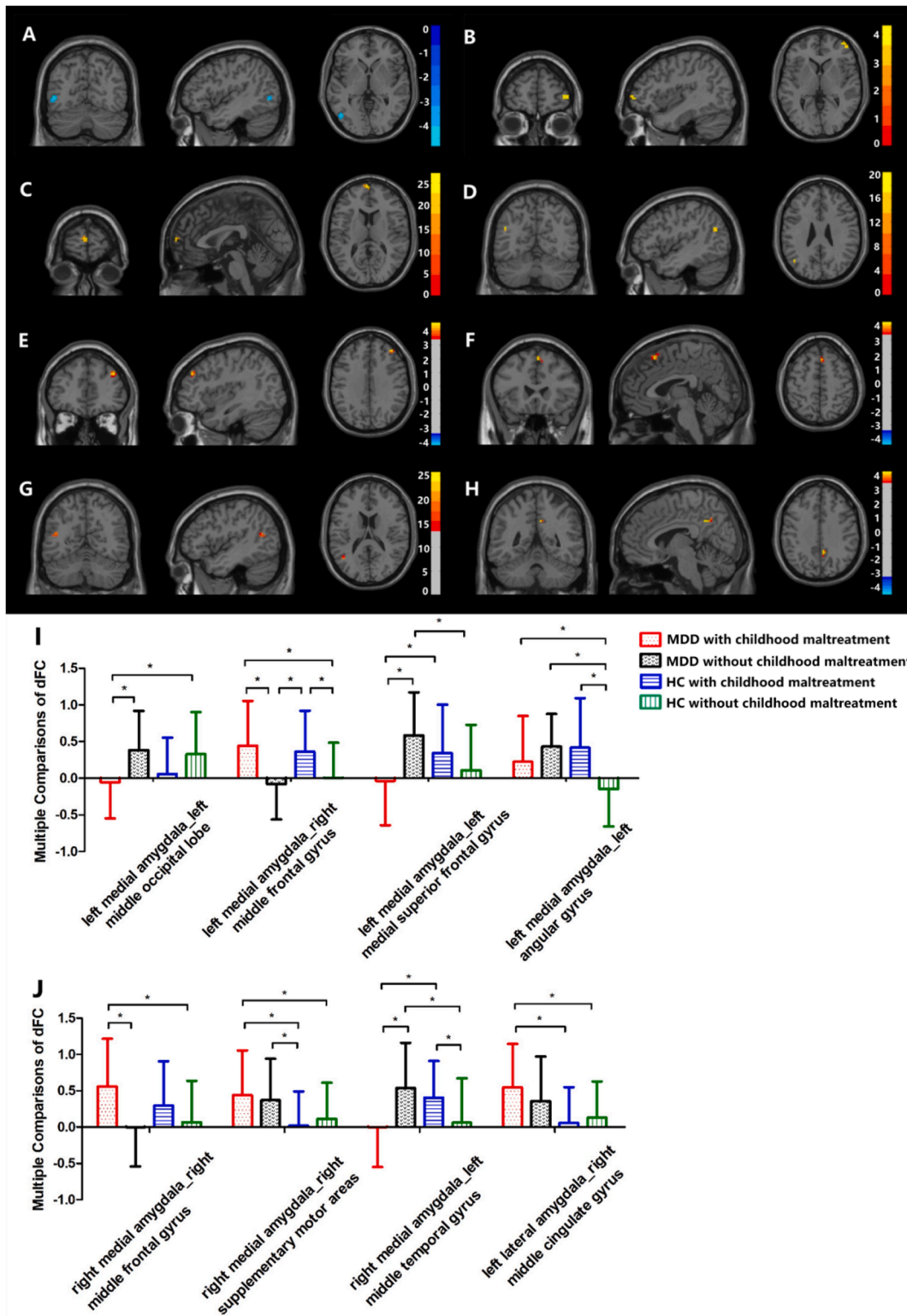
Fig. 3. **Significant dFC differences among MDD with childhood maltreatment, MDD without childhood maltreatment, HC with childhood maltreatment, and HC without childhood maltreatment.** Fig. 4A shows decreased dFC between left medial amygdala and left middle occipital area; Fig. 3B ~ D display increased dFC between left medial amygdala and right middle frontal gyrus, left superior medial frontal gyrus, left angular gyrus, respectively. Fig. 3E ~ G present increased dFC between right medial amygdala and right middle frontal gyrus, right supplementary motor areas, respectively. Fig. 3H shows increased dFC between left lateral amygdala and right middle cingulate gyrus. Fig. 3I ~ J show multiple comparisons of dFC. MDD: major depressive disorder; HC: healthy control.
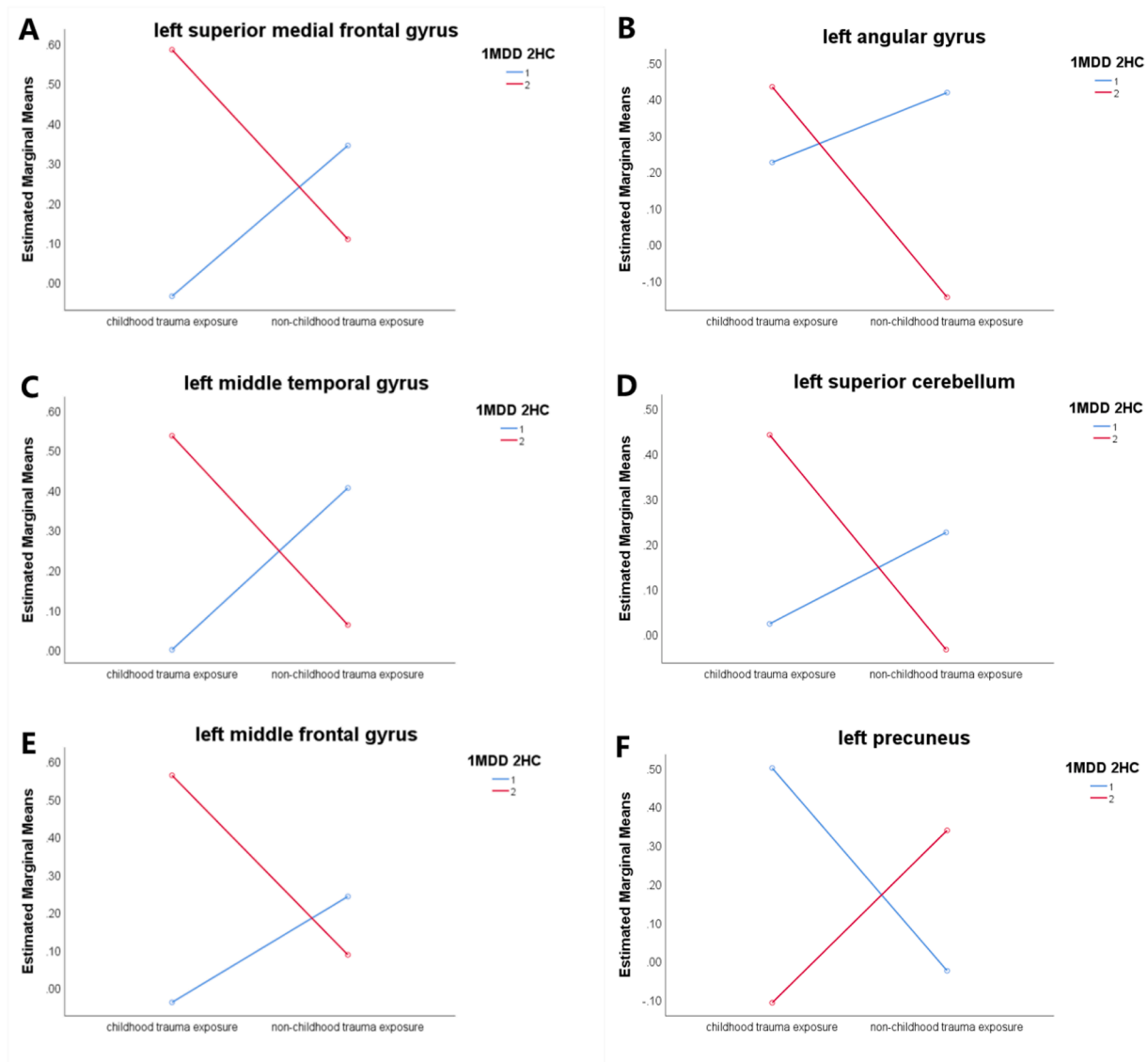
Fig. 4. Additive effects of MDD and childhood maltreatment on dFC pattern. MDD: major depressive disorder; HC: healthy control.

Table 3
Correlation analyses of CTQ and the dFC variability in MDD patients.

Seed	Effect	brain region	emotional abuse	physical abuse	sexual abuse	emotional neglect	physical neglect	CTQ total score
Left medial amygdala	traumatic effect	left middle occipital area	−0.151	−0.074	−0.13	−0.358*	−0.201	−0.271
		right middle frontal gyrus	0.183	0.113	0.198	0.315*	0.207	0.284
	interaction effect	left superior medial frontal gyrus	−0.182	−0.123	−0.07	−0.451**	−0.315*	−0.350*
		left angular gyrus	−0.09	−0.157	−0.174	−0.139	−0.097	−0.166
Right medial amygdala	traumatic effect	right middle frontal gyrus	0.19	0.001	0.168	0.313*	0.300*	0.279
	etiological effect	right supplementary motor areas	−0.078	0.059	−0.002	−0.059	0.022	−0.026
	interaction effect	left middle temporal gyrus	−0.266	−0.237	−0.258	−0.402**	−0.301*	−0.404**
Left lateral amygdala	etiological effect	right middle cingulate gyrus	0.145	−0.117	−0.066	0.198	0.125	0.116

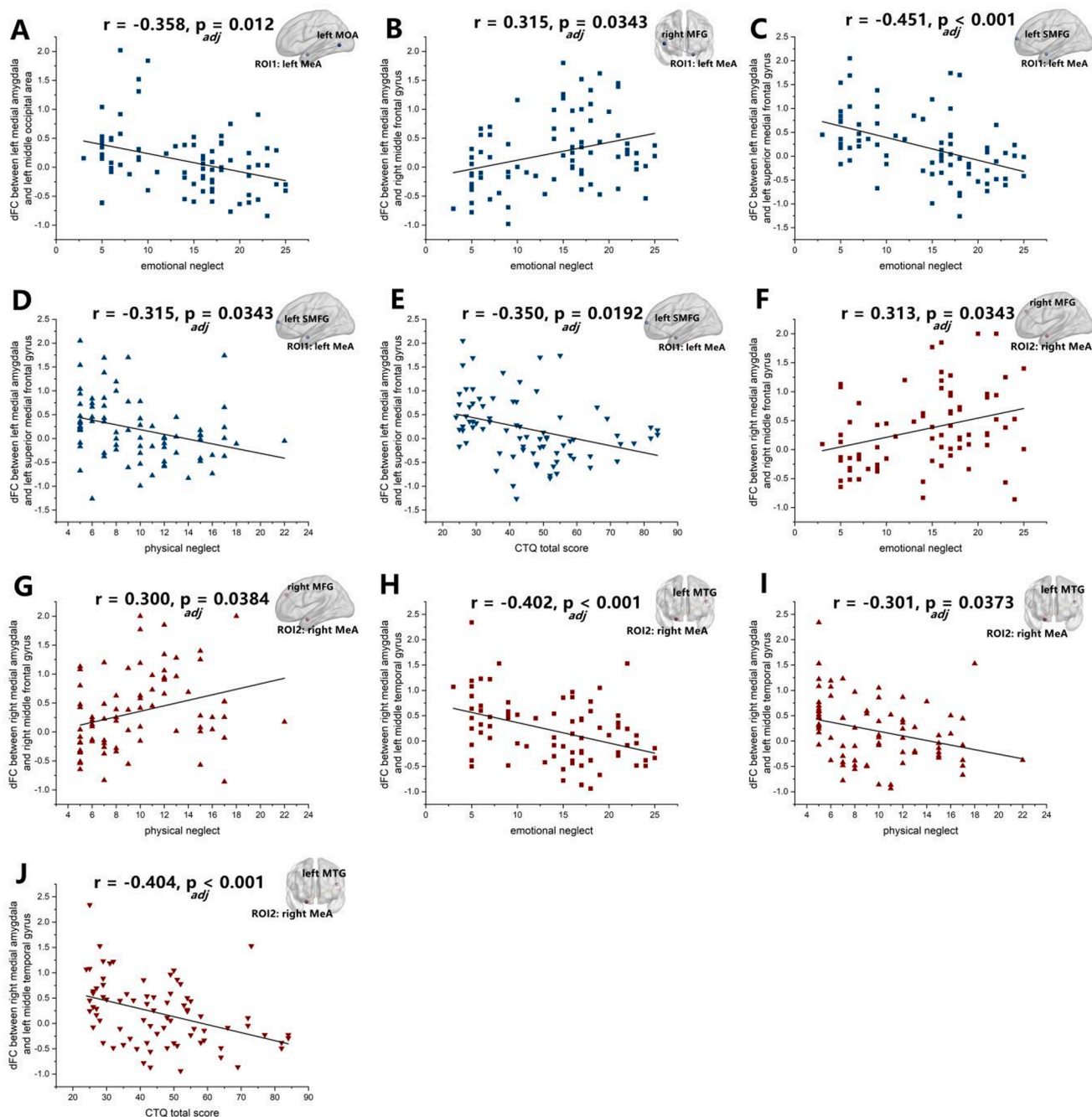* $p_{adj} < 0.05$.
** $p_{adj} < 0.01$.

Fig. 5. The correlation analyses between dFC pattern and CTQ total score in MDD patients.

activation is associated with affective disorder and maltreatment-related disorders (Feldker et al. 2017). Teicher et al. reported that childhood maltreatment can cause brain morphological, structural, and functional alterations during development in childhood (Teicher and Samson 2013). Brain developmental abnormalities in childhood may include the aberrant sFC in right LA detected in the current study. Our finding of decreased sFC might offer a better explanation of the pathological mechanism underlying MDD with childhood maltreatment and a nuanced perspective regarding the disrupted brain communications in MDD with childhood maltreatment.

4.2. Anomalous dFC of the amygdala subregion in MDD with childhood maltreatment

It has been well established that theory of mind (ToM) deficits are common in MDD with childhood maltreatment. ToM refers to the ability of an individual to make inferences about the beliefs, desires and intentions of the self and others, and to comprehend that others have a mind that is distinct from one's own (Premack and Woodruff 1978). Investigations into the neural mechanisms underlying ToM have implicated a number of brain regions (including MOA (Caillaud et al. 2020), MFG (Völlm et al. 2006), SMFG (Kandylaki et al. 2015), AG (Kandylaki et al. 2015), SMA (Weng et al. 2022), MTG (Boccadoro et al. 2019), and MCG (O'Neill et al. 2015)) related to attention, executive functions, complex perceptual recognition, imitation, and emotion processing-
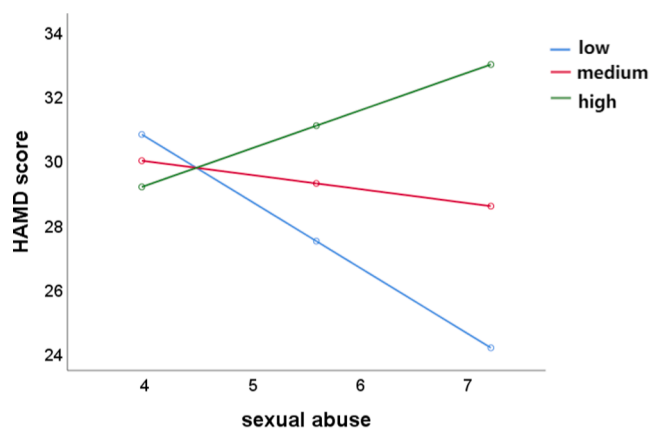
Table 4
dFC variability of right medial amygdala seed – right supplementary motor areas as a moderator in the relationship between sexual abuse and the depression severity.

Predictor variable	R^2	F	B	t
Step 1				
Sexual abuse	0.041*	3.775*	−0.022	−0.3
dFC between right medial amygdala and right supplementary motor areas			0.201	2.732*
Step 2				
Sexual abuse	0.091**	5.931**	−0.094	−1.247
dFC between right medial amygdala and right supplementary motor areas			0.238	3.28**
Sexual abuse × dFC of right medial amygdala – right Supplementary motor areas			0.239	3.141**

* $p < 0.05$.
** $p < 0.01$.

Fig. 6. Abnormal dFC between right medial amygdala and right supplementary motor areas is moderating the relationship between sexual abuse and the depression severity. HAMD: Hamilton Depressive Rating Scale.

recognition (Carrington and Bailey 2009;Korkmaz 2011). Compared with MDD patients without childhood maltreatment, the dFC in MDD patients with childhood maltreatment exhibited pathologically heightened activity in ToM-related brain areas in the current study. Specifically, altered dFC was detected in MDD patients with childhood maltreatment between bilateral MeA and multiple areas, involving left MOA, left SMFG, right MFG, and left MTG. A previous study has confirmed our findings from a multivariate pattern analysis perspective. Pang et al. suggested that childhood maltreatment has an enduring effect on FC modulation within the ToM network, which may be preserved in adulthood (Pang et al. 2022). However, the current finding regarding maltreatment-related dFC abnormalities in MDD patients with childhood maltreatment could be interpreted from other perspectives. Evidence from murine models has revealed a key role of MeA in processing socio-sexual behavior, particularly taking charge of aggression control (Sano et al. 2013;Wang et al. 2013). Nordman et al. suggested that potentiation of the MeA pathway heightens individual aggression levels. Overall, the current dFC results suggest that abnormalities in MeA and impairments in ToM processing might play critical roles in identifying neural features for the diagnosis and treatment of MDD patients with childhood maltreatment.

4.3. Clinical correlation and moderation of the relationship between dFC abnormalities and childhood maltreatment

As expected, a negative correlation between dFC abnormalities in bilateral MeA and child neglect history was confirmed. In accord with our finding, Puetz and colleagues investigated the neural patterns underlying child neglect, reporting that the effects of neglect experiences could lead to more dispersed effects relative to child abuse (Puetz et al. 2020). We observed that dFC variability served as a moderator in the relationship between sexual abuse and MDD severity, further highlighting the long-term influence on the psychological well-being. The impacts of child neglect and abuse should not to be underestimated, involving a lifelong burden for victims.

The current findings should be interpreted in consideration of the following limitations. First, because childhood maltreatment was evaluated retrospectively using the CTQ, the results might have been influenced by the the mood of the subjects and/or the inherent subjectivity of the evaluation. Second, because our investigation was cross-sectional, we could not determine causality in the current study. Third, because of our relatively small sample size, it was not possible to group the patients by childhood maltreatment subtype. Future investigations should investigate the impact of single subtypes of childhood maltreatment, such as neglect or abuse. Additionally, the robustness of the impaired FC patterns in MDD patients with childhood maltreatment needs further validation with a lager sample size. Fourth, more psychological and behavioral measures (e.g., MATRICS Consensus Cognitive Battery) should be included in the further study to explore the impact of childhood maltreatment on psychological functions in depressed patients. Finally, task-based fMRI data were not acquired in our study. Thus, some caution is warranted when interpreting the behavioral and functional significance of ToM-related FC abnormalities.

Investigations of sFC and dFC patterns can significantly advance current understanding of functional neural organization in patients and healthy participants. Our findings confirmed an inextricable relationship between impaired FC patterns and childhood maltreatment. The effects of childhood maltreatment were significant in both sFC and dFC abnormalities. Our findings revealed an aberrant FC pattern in MDD patients with childhood maltreatment, characterized by sFC and dFC abnormalities involving the MeA, LA, and ToM-related brain areas. Our findings revealed the neurobiological features of childhood maltreatment and provided new clues regarding vulnerability to psychiatric disorders.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103270.

References

Alexopoulos, G.S., 2005. Depression in the elderly. Lancet 365, 1961–1970. https://doi.org/10.1016/S0140-6736(05)66665-2.

Allen, E.A., Damaraju, E., Plis, S.M., Erhardt, E.B., Eichele, T., Calhoun, V.D., 2014. Tracking whole-brain connectivity dynamics in the resting state. Cereb Cortex 24, 663–676. https://doi.org/10.1093/cercor/bhs352.

Amaral, D.G., Price, J.L., 1984. Amygdalo-cortical projections in the monkey (Macaca fascicularis). J Comp Neurol 230, 465–496. https://doi.org/10.1002/cne.902300402.

Baron, R.M., Kenny, D.A., 1986. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 51, 1173–1182. https://doi.org/10.1037//0022-3514.51.6.1173.

Bernstein, D.P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E., Ruggiero, J., 1994. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry 151, 1132–1136. https://doi.org/10.1176/ajp.151.8.1132.

Bernstein, D.P., Ahluvalia, T., Pogge, D., Handelsman, L., 1997. Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. J Am Acad Child Adolesc Psychiatry 36, 340–348. https://doi.org/10.1097/00004583-199703000-00012.

Bernstein, D.P., Stein, J.A., Newcomb, M.D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., Zule, W., 2003. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl 27, 169–190. https://doi.org/10.1016/s0145-2134(02)00541-0.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 34, 537–541. https://doi.org/10.1002/mrm.1910340409.

Boccadoro, S., Cracco, E., Hudson, A.R., Bardi, L., Nijhof, A.D., Wiersema, J.R., Brass, M., Mueller, S.C., 2019. Defining the neural correlates of spontaneous theory of mind (ToM): An fMRI multi-study investigation. Neuroimage 203, 116193. https://doi.org/10.1016/j.neuroimage.2019.116193.

Bzdok, D., Laird, A.R., Zilles, K., Fox, P.T., Eickhoff, S.B., 2013. An investigation of the structural, connectional, and functional subspecialization in the human amygdala. Hum Brain Mapp 34, 3247–3266. https://doi.org/10.1002/hbm.22138.

Caillaud, M., Bejanin, A., Laisney, M., Gagnepain, P., Gaubert, M., Viard, A., Clochon, P., de La Sayette, V., Allain, P., Eustache, F., Desranges, B., 2020. Influence of emotional complexity on the neural substrates of affective theory of mind. Hum Brain Mapp 41, 139–149. https://doi.org/10.1002/hbm.24794.

Calhoun, V.D., Miller, R., Pearlson, G., Adali, T., 2014. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron 84, 262–274. https://doi.org/10.1016/j.neuron.2014.10.015.

Carrington, S.J., Bailey, A.J., 2009. Are there theory of mind regions in the brain? A review of the neuroimaging literature. Hum Brain Mapp 30, 2313–2335. https://doi.org/10.1002/hbm.20671.

Cisler, J.M., 2017. Childhood Trauma and Functional Connectivity between Amygdala and Medial Prefrontal Cortex: A Dynamic Functional Connectivity and Large-Scale Network Perspective. Front Syst Neurosci 11, 29. https://doi.org/10.3389/fnsys.2017.00029.

Coccaro, E.F., McCloskey, M.S., Fitzgerald, D.A., Phan, K.L., 2007. Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. Biol Psychiatry 62, 168–178. https://doi.org/10.1016/j.biopsych.2006.08.024.

Cui, Q., Pang, Y., Lu, F., Tang, Q., Han, S., Shen, Q., Wang, Y., Xie, A., Huang, J., Li, D., Lei, T., He, Z., Chen, H., 2020b. Dynamic changes of amplitude of low-frequency fluctuations in patients with generalized anxiety disorder. Hum Brain Mapp 41, 1667–1676. https://doi.org/10.1002/hbm.24902.

Cui, G., Wang, Y., Wang, X., Zheng, L., Li, L., Li, P., Zhang, L., Guo, Y., Chen, Y., Sun, Z., Meng, X., 2020a. Static and dynamic functional connectivity of the prefrontal cortex during resting-state predicts self-serving bias in depression. Behav Brain Res 379, 112335. https://doi.org/10.1016/j.bbr.2019.112335.

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A. R., Fox, P.T., Eickhoff, S.B., Yu, C., Jiang, T., 2016. The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture. Cereb Cortex 26, 3508–3526. https://doi.org/10.1093/cercor/bhw157.

Fan, J., Liu, W., Xia, J., Li, S., Gao, F., Zhu, J., Han, Y., Zhou, H., Liao, H., Yi, J., Tan, C., Zhu, X., 2021. Childhood trauma is associated with elevated anhedonia and altered core reward circuitry in major depression patients and controls. Hum Brain Mapp 42, 286–297. https://doi.org/10.1002/hbm.25222.

Feldker, K., Heitmann, C.Y., Neumeister, P., Tupak, S.V., Schrammen, E., Moeck, R., Zwitserlood, P., Bruchmann, M., Straube, T., 2017. Transdiagnostic brain responses to disorder-related threat across four psychiatric disorders. Psychol Med 47, 730–743. https://doi.org/10.1017/S0033291716002634.

Fink, L.A., Bernstein, D., Handelsman, L., Foote, J., Lovejoy, M., 1995. Initial reliability and validity of the childhood trauma interview: a new multidimensional measure of childhood interpersonal trauma. Am J Psychiatry 152, 1329–1335. https://doi.org/10.1176/ajp.152.9.1329.

Fu, Z., Caprihan, A., Chen, J., Du, Y., Adair, J.C., Sui, J., Rosenberg, G.A., Calhoun, V.D., 2019. Altered static and dynamic functional network connectivity in Alzheimer's disease and subcortical ischemic vascular disease: shared and specific brain connectivity abnormalities. Hum Brain Mapp 40, 3203–3221. https://doi.org/10.1002/hbm.24591.

Geng, H., Ye, D.Q., Shi, Y.Y., Xu, Z., Pu, M.J., Li, Z.Y., Li, X.L., Li, Y., Zhang, Z.J., 2014. Influence of genetic polymorphisms involved in the hypothalamic-pituitary-adrenal axis and their interactions with environmental factors on antidepressant response. CNS Neurosci Ther 20, 237–243. https://doi.org/10.1111/cns.12201.

Gilbert, R., Widom, C.S., Browne, K., Fergusson, D., Webb, E., Janson, S., 2009. Burden and consequences of child maltreatment in high-income countries. Lancet 373, 68–81. https://doi.org/10.1016/S0140-6736(08)61706-7.

Gong, J.B., Wang, Y., Lui, S., Cheung, E., Chan, R., 2017. Childhood trauma is not a confounder of the overlap between autistic and schizotypal traits: A study in a non-clinical adult sample. Psychiatry Res 257, 111–117. https://doi.org/10.1016/j.psychres.2017.07.035.

Grosso, A., Santoni, G., Manassero, E., Renna, A., Sacchetti, B., 2018. A neuronal basis for fear discrimination in the lateral amygdala. Nat Commun 9, 1214. https://doi.org/10.1038/s41467-018-03682-2.

Guo, W.B., Liu, F., Xue, Z.M., Xu, X.J., Wu, R.R., Ma, C.Q., Wooderson, S.C., Tan, C.L., Sun, X.L., Chen, J.D., Liu, Z.N., Xiao, C.Q., Chen, H.F., Zhao, J.P., 2012. Alterations of the amplitude of low-frequency fluctuations in treatment-resistant and treatment-response depression: a resting-state fMRI study. Prog Neuropsychopharmacol Biol Psychiatry 37, 153–160. https://doi.org/10.1016/j.pnpbp.2012.01.011.

Hakamata, Y., Mizukami, S., Izawa, S., Moriguchi, Y., Hori, H., Matsumoto, N., Hanakawa, T., Inoue, Y., Tagaya, H., 2021. Childhood trauma affects autobiographical memory deficits through basal cortisol and prefrontal-extrastriate functional connectivity. Psychoneuroendocrinology 127, 105172. https://doi.org/10.1016/j.psyneuen.2021.105172.

Helmreich, I., Wagner, S., Mergl, R., Allgaier, A.K., Hautzinger, M., Henkel, V., Hegerl, U., Tadic, A., 2012. Sensitivity to changes during antidepressant treatment: a comparison of unidimensional subscales of the Inventory of Depressive Symptomatology (IDS-C) and the Hamilton Depression Rating Scale (HAMD) in patients with mild major, minor or subsyndromal depression. Eur Arch Psychiatry Clin Neurosci 262, 291–304. https://doi.org/10.1007/s00406-011-0263-x.

Holmbeck, G.N., 1997. Toward terminological, conceptual, and statistical clarity in the study of mediators and moderators: examples from the child-clinical and pediatric psychology literatures. J Consult Clin Psychol 65, 599–610. https://doi.org/10.1037//0022-006x.65.4.599.

Hughes, K., Bellis, M.A., Hardcastle, K.A., Sethi, D., Butchart, A., Mikton, C., Jones, L., Dunne, M.P., 2017. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. e366 Lancet Public Health 2, e356. https://doi.org/10.1016/S2468-2667(17)30118-4.

Hutchison, R.M., Womelsdorf, T., Allen, E.A., Bandettini, P.A., Calhoun, V.D., Corbetta, M., Della, P.S., Duyn, J.H., Glover, G.H., Gonzalez-Castillo, J., Handwerker, D.A., Keilholz, S., Kiviniemi, V., Leopold, D.A., de Pasquale, F., Sporns, O., Walter, M., Chang, C., 2013. Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage 80, 360–378. https://doi.org/10.1016/j.neuroimage.2013.05.079.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825–841. https://doi.org/10.1016/s1053-8119(02)91132-8.

Kandylaki, K.D., Nagels, A., Tune, S., Wiese, R., Bornkessel-Schlesewsky, I., Kircher, T., 2015. Processing of false belief passages during natural story comprehension: An fMRI study. Hum Brain Mapp 36, 4231–4246. https://doi.org/10.1002/hbm.22907.

Korkmaz, B. 2011. Theory of mind and neurodevelopmental disorders of childhood. *Pediatr Res* 69, 101R-108R. 10.1203/PDR.0b013e318212c177.

LeDoux, J.E., 2000. Emotion circuits in the brain. Annu Rev Neurosci 23, 155–184. https://doi.org/10.1146/annurev.neuro.23.1.155.

LeDoux, J., 2003. The emotional brain, fear, and the amygdala. Cell Mol Neurobiol 23, 727–738. https://doi.org/10.1023/a:1025048802629.

Lewis, N., Lu, H., Liu, P., Hou, X., Damaraju, E., Iraji, A., Calhoun, V., 2020. Static and dynamic functional connectivity analysis of cerebrovascular reactivity: An fMRI study. Brain Behav 10, e1516.

Li, Y., Mathis, A., Grewe, B.F., Osterhout, J.A., Ahanonu, B., Schnitzer, M.J., Murthy, V. N., Dulac, C., 2017. Neuronal Representation of Social Information in the Medial Amygdala of Awake Behaving Mice. Cell 171, 1176–1190. https://doi.org/10.1016/j.cell.2017.10.015.

Liao, W., Wu, G.R., Xu, Q., Ji, G.J., Zhang, Z., Zang, Y.F., Lu, G., 2014. DynamicBC: a MATLAB toolbox for dynamic brain connectome analysis. Brain Connect 4, 780–790. https://doi.org/10.1089/brain.2014.0253.

Liao, W., Li, J., Ji, G.J., Wu, G.R., Long, Z., Xu, Q., Duan, X., Cui, Q., Biswal, B.B., Chen, H., 2019. Endless Fluctuations: Temporal Dynamics of the Amplitude of Low Frequency Fluctuations. IEEE Trans Med Imaging 38, 2523–2532. https://doi.org/10.1109/TMI.2019.2904555.

Liu, J., Bu, X., Hu, X., Li, H., Cao, L., Gao, Y., Liang, K., Zhang, L., Lu, L., Hu, X., Wang, Y., Gong, Q., Huang, X., 2021. Temporal variability of regional intrinsic neural activity in drug-naive patients with obsessive-compulsive disorder. Hum Brain Mapp 42, 3792–3803. https://doi.org/10.1002/hbm.25465.

Liu, F., Guo, W., Liu, L., Long, Z., Ma, C., Xue, Z., Wang, Y., Li, J., Hu, M., Zhang, J., Du, H., Zeng, L., Liu, Z., Wooderson, S.C., Tan, C., Zhao, J., Chen, H., 2013. Abnormal amplitude low-frequency oscillations in medication-naive, first-episode patients with major depressive disorder: a resting-state fMRI study. J Affect Disord 146, 401–406. https://doi.org/10.1016/j.jad.2012.10.001.

Liu, X., Hairston, J., Schrier, M., Fan, J., 2011. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev 35, 1219–1236. https://doi.org/10.1016/j.neubiorev.2010.12.012.

Liu, F., Wang, Y., Li, M., Wang, W., Li, R., Zhang, Z., Lu, G., Chen, H., 2017. Dynamic functional network connectivity in idiopathic generalized epilepsy with generalized tonic-clonic seizure. Hum Brain Mapp 38, 957–973. https://doi.org/10.1002/hbm.23430.

Llabre, M.M., Schneiderman, N., Gallo, L.C., Arguelles, W., Daviglus, M.L., Gonzalez, F. N., Isasi, C.R., Perreira, K.M., Penedo, F.J., 2017. Childhood Trauma and Adult Risk Factors and Disease in Hispanics/Latinos in the US: Results From the Hispanic

Community Health Study/Study of Latinos (HCHS/SOL) Sociocultural Ancillary Study. Psychosom Med 79, 172–180. https://doi.org/10.1097/PSY.0000000000000394.

Luo, Q., Chen, J., Li, Y., Wu, Z., Lin, X., Yao, J., Yu, H., Peng, H., Wu, H., 2022b. Altered regional brain activity and functional connectivity patterns in major depressive disorder: A function of childhood trauma or diagnosis? J Psychiatr Res 147, 237–247. https://doi.org/10.1016/j.jpsychires.2022.01.038.

Luo, L., Yang, T., Zheng, X., Zhang, X., Gao, S., Li, Y., Stamatakis, E.A., Sahakian, B., Becker, B., Lin, Q., Kendrick, K.M., 2022a. Altered centromedial amygdala functional connectivity in adults is associated with childhood emotional abuse and predicts levels of depression and anxiety. J Affect Disord 303, 148–154. https://doi.org/10.1016/j.jad.2022.02.023.

Maier, W., Buller, R., Philipp, M., Heuser, I., 1988. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affect Disord 14, 61–68. https://doi.org/10.1016/0165-0327(88)90072-9.

McLaughlin, K.A., Colich, N.L., Rodman, A.M., Weissman, D.G., 2020. Mechanisms linking childhood trauma exposure and psychopathology: a transdiagnostic model of risk and resilience. BMC Med 18, 96. https://doi.org/10.1186/s12916-020-01561-6.

Misiak, B., Krefft, M., Bielawski, T., Moustafa, A.A., Sasiadek, M.M., Frydecka, D., 2017. Toward a unified theory of childhood trauma and psychosis: A comprehensive review of epidemiological, clinical, neuropsychological and biological findings. Neurosci Biobehav Rev 75, 393–406. https://doi.org/10.1016/j.neubiorev.2017.02.015.

Nelson, J., Klumparendt, A., Doebler, P., Ehring, T., 2017. Childhood maltreatment and characteristics of adult depression: meta-analysis. Br J Psychiatry 210, 96–104. https://doi.org/10.1192/bjp.bp.115.180752.

Nikkheslat, N., McLaughlin, A.P., Hastings, C., Zajkowska, Z., Nettis, M.A., Mariani, N., Enache, D., Lombardo, G., Pointon, L., Cowen, P.J., Cavanagh, J., Harrison, N.A., Bullmore, E.T., Pariante, C.M., Mondelli, V., 2020. Childhood trauma, HPA axis activity and antidepressant response in patients with depression. Brain Behav Immun 87, 229–237. https://doi.org/10.1016/j.bbi.2019.11.024.

O'Neill, A., D'Souza, A., Samson, A.C., Carballedo, A., Kerskens, C., Frodl, T., 2015. Dysregulation between emotion and theory of mind networks in borderline personality disorder. Psychiatry Res 231, 25–32. https://doi.org/10.1016/j.pscychresns.2014.11.002.

Pang, Y., Zhao, S., Li, Z., Li, N., Yu, J., Zhang, R., Lu, F., Chen, H., Wu, F., Zheng, W., Gao, J., Yang, Y., Wu, H., Wang, J., 2022. Enduring effect of abuse: Childhood maltreatment links to altered theory of mind network among adults. Hum Brain Mapp. https://doi.org/10.1002/hbm.25787.

Popovic, D., Ruef, A., Dwyer, D.B., Antonucci, L.A., Eder, J., Sanfelici, R., Kambeitz-Ilankovic, L., Oztuerk, O.F., Dong, M.S., Paul, R., Paolini, M., Hedderich, D., Haidl, T., Kambeitz, J., Ruhrmann, S., Chisholm, K., Schultze-Lutter, F., Falkai, P., Pergola, G., Blasi, G., Bertolino, A., Lencer, R., Dannlowski, U., Upthegrove, R., Salokangas, R., Pantelis, C., Meisenzahl, E., Wood, S.J., Brambilla, P., Borgwardt, S., Koutsouleris, N., 2020. Traces of Trauma: A Multivariate Pattern Analysis of Childhood Trauma, Brain Structure, and Clinical Phenotypes. Biol Psychiatry 88, 829–842. https://doi.org/10.1016/j.biopsych.2020.05.020.

Premack, D., Woodruff, G., 1978. Chimpanzee problem-solving: a test for comprehension. Science 202, 532–535. https://doi.org/10.1126/science.705342.

Puetz, V.B., Viding, E., Gerin, M.I., Pingault, J.B., Sethi, A., Knodt, A.R., Radtke, S.R., Brigidi, B.D., Hariri, A.R., McCrory, E., 2020. Investigating patterns of neural response associated with childhood neglect. Psychol Med 50, 1398–1407. https://doi.org/10.1017/S003329171900134X.

Quirk, G.J., Repa, C., LeDoux, J.E., 1995. Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. Neuron 15, 1029–1039. https://doi.org/10.1016/0896-6273(95)90092-6.

Regev, L., Neufeld-Cohen, A., Tsoory, M., Kuperman, Y., Getselter, D., Gil, S., Chen, A., 2011. Prolonged and site-specific over-expression of corticotropin-releasing factor reveals differential roles for extended amygdala nuclei in emotional regulation. Mol Psychiatry 16, 714–728. https://doi.org/10.1038/mp.2010.64.

Rogan, M.T., Staubli, U.V., LeDoux, J.E., 1997. Fear conditioning induces associative long-term potentiation in the amygdala. Nature 390, 604–607. https://doi.org/10.1038/37601.

Romanski, L.M., Clugnet, M.C., Bordi, F., LeDoux, J.E., 1993. Somatosensory and auditory convergence in the lateral nucleus of the amygdala. Behav Neurosci 107, 444–450. https://doi.org/10.1037//0735-7044.107.3.444.

Roy, A.K., Shehzad, Z., Margulies, D.S., Kelly, A.M., Uddin, L.Q., Gotimer, K., Biswal, B. B., Castellanos, F.X., Milham, M.P., 2009. Functional connectivity of the human amygdala using resting state fMRI. Neuroimage 45, 614–626. https://doi.org/10.1016/j.neuroimage.2008.11.030.

Sano, K., Tsuda, M.C., Musatov, S., Sakamoto, T., Ogawa, S., 2013. Differential effects of site-specific knockdown of estrogen receptor alpha in the medial amygdala, medial pre-optic area, and ventromedial nucleus of the hypothalamus on sexual and aggressive behavior of male mice. Eur J Neurosci 37, 1308–1319. https://doi.org/10.1111/ejn.12131.

Schafe, G.E., Doyere, V., LeDoux, J.E., 2005. Tracking the fear engram: the lateral amygdala is an essential locus of fear memory storage. J Neurosci 25, 10010–10014. https://doi.org/10.1523/JNEUROSCI.3307-05.2005.

Shunkai, L., Su, T., Zhong, S., Chen, G., Zhang, Y., Zhao, H., Chen, P., Tang, G., Qi, Z., He, J., Zhu, Y., Lv, S., Song, Z., Miao, H., Hu, Y., Jia, Y., Wang, Y., 2021. Abnormal dynamic functional connectivity of hippocampal subregions associated with working memory impairment in melancholic depression. Psychol Med 1–13. https://doi.org/10.1017/S0033291721004906.

Teicher, M.H., Samson, J.A., 2013. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am J Psychiatry 170, 1114–1133. https://doi.org/10.1176/appi.ajp.2013.12070957.

Teicher, M.H., Samson, J.A., Anderson, C.M., Ohashi, K., 2016. The effects of childhood maltreatment on brain structure, function and connectivity. Nat Rev Neurosci 17, 652–666. https://doi.org/10.1038/nrn.2016.111.

Uys, J.D., Marais, L., Faure, J., Prevoo, D., Swart, P., Mohammed, A.H., Stein, D.J., Daniels, W.M., 2006. Developmental trauma is associated with behavioral hyperarousal, altered HPA axis activity, and decreased hippocampal neurotrophin expression in the adult rat. Ann N Y Acad Sci 1071, 542–546. https://doi.org/10.1196/annals.1364.060.

Völlm, B.A., Taylor, A.N., Richardson, P., Corcoran, R., Stirling, J., McKie, S., Deakin, J. F., Elliott, R., 2006. Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. Neuroimage 29, 90–98. https://doi.org/10.1016/j.neuroimage.2005.07.022.

Wang, Y., He, Z., Zhao, C., Li, L., 2013. Medial amygdala lesions modify aggressive behavior and immediate early gene expression in oxytocin and vasopressin neurons during intermale exposure. Behav Brain Res 245, 42–49. https://doi.org/10.1016/j.bbr.2013.02.002.

Wang, C., Wang, Y., Lau, W., Wei, X., Feng, X., Zhang, C., Liu, Y., Huang, R., Zhang, R., 2021. Anomalous static and dynamic functional connectivity of amygdala subregions in individuals with high trait anxiety. Depress Anxiety 38, 860–873. https://doi.org/10.1002/da.23195.

Weng, Y., Lin, J., Ahorsu, D.K., Tsang, H., 2022. Neuropathways of Theory of Mind in Schizophrenia: A Systematic Review and Meta-Analysis. Neurosci Biobehav Rev 104625. https://doi.org/10.1016/j.neubiorev.2022.104625.

Wu, H., Wu, C., Wu, F., Zhan, Q., Peng, H., Wang, J., Zhao, J., Ning, Y., Zheng, Y., She, S., 2021. Covariation between Childhood-Trauma Related Resting-State Functional Connectivity and Affective Temperaments is Impaired in Individuals with Major Depressive Disorder. Neuroscience 453, 102–112. https://doi.org/10.1016/j.neuroscience.2020.08.002.

Wurtman, R.J., 2005. Genes, stress, and depression. Metabolism 54, 16–19. https://doi.org/10.1016/j.metabol.2005.01.007.

Xu, Z., Zhang, Z., Shi, Y., Pu, M., Yuan, Y., Zhang, X., Li, L., 2011. Influence and interaction of genetic polymorphisms in catecholamine neurotransmitter systems and early life stress on antidepressant drug response. J Affect Disord 133, 165–173. https://doi.org/10.1016/j.jad.2011.04.011.

Xue, K., Liang, S., Yang, B., Zhu, D., Xie, Y., Qin, W., Liu, F., Zhang, Y., Yu, C., 2020. Local dynamic spontaneous brain activity changes in first-episode, treatment-naive patients with major depressive disorder and their associated gene expression profiles. Psychol Med 1–10. https://doi.org/10.1017/S0033291720003876.

Yan, C.G., Wang, X.D., Zuo, X.N., Zang, Y.F., 2016. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. Neuroinformatics 14, 339–351. https://doi.org/10.1007/s12021-016-9299-4.