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RESEARCH ARTICLE

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Distinct stress-related medial prefrontal cortex activation in women with depression with and without childhood maltreatment

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Abstract

Background: Emerging evidence has highlighted the moderating effect of childhood maltreatment (CM) in shaping neurobiological abnormalities in major depressive disorder (MDD). However, whether neural mechanisms underlying stress sensitivity in MDD are affected by the history of CM is unclear.

Methods: Two hundred and thirteen medication-free female participants were recruited for a functional magnetic resonance imaging study assessing the effects of psychosocial stress on neural responses. The Montreal Imaging Stress Task was administrated to 44 female MDD patients with CM (MDD/CM), 32 female MDD patients without CM (MDD/noCM), 43 female healthy controls (HCs) with CM (HC/CM), and 94 female HCs without CM (HC/noCM). A *CM (CM, noCM) × diagnosis (MDD, HC)* whole-brain voxel-wise analysis was run to assess putative group differences in neural stress responses.

Results: A significant *CM × Diagnosis* interaction emerged in the medial prefrontal cortex (mPFC). Bonferroni-corrected simple effects analysis clarified that (1) the MDD/CM group had less mPFC deactivation than the HC/CM group, (2) the MDD/noCM group exhibited greater mPFC deactivation than the HC/noCM group, and (3) the MDD/CM group exhibited less mPFC deactivation relative to the MDD/noCM group. In addition, the mPFC-seed psychophysiological interaction analysis revealed that individuals in the CM groups had significantly greater stress-related mPFC-left superior frontal gyrus and mPFC-right posterior cerebellum connectivity relative to the noCM groups.

Conclusions: Findings highlight distinct neural abnormalities in MDD depending on prior CM history, particularly potentiated stress-related mPFC recruitment among MDD individuals reporting CM. Moreover, CM history was generally associated with the disruption in functional connectivity centered on the mPFC.

KEYWORDS

adverse childhood experience, functional neuroimaging, major depressive disorder

1 | INTRODUCTION

Major depressive disorder (MDD) is a highly heterogeneous psychiatric disorder. MDD patients with and without a history of childhood maltreatment (CM) exhibit distinct clinical courses, including different onset times, severity, comorbidity, and treatment response (Teicher & Samson, 2013). Mounting neuroimaging evidence suggests that CM is associated with abnormalities in brain development within neural circuits critically implicated in threat detection (Hein et al., 2020; White et al., 2019), emotion regulation (Jenness et al., 2021; McLaughlin et al., 2015), reward anticipation (Dillon et al., 2009; Hein et al., 2020), and cognitive control (Bruce et al., 2013; Jankowski et al., 2017) (for review, see Teicher et al. (2016)). In addition, initial findings indicate that individuals with MDD and a history of CM exhibited smaller hippocampal volume (Colle et al., 2017; Gerritsen et al., 2015; Yuan et al., 2020) and weaker functional connectivity within the prefrontal-limbic-thalamic-cerebellar circuit relative to individuals with MDD but noCM (Wang et al., 2014). Notably, several studies found that abnormalities seen in MDD in terms of hippocampal atrophy (Opel et al., 2014) and reduced fractional anisotropy across various white matter tracts were abolished when regressing out the effects of CM (Meinert et al., 2019), suggesting some neural alterations underlying MDD could be the consequence of CM, rather than MDD. In this context, neural abnormalities in MDD may be further shaped by past CM.

Increased stress sensitivity has emerged as an important intermediate phenotype of MDD (Berghorst & Pizzagalli, 2010), therefore investigating the potential role of CM on stress sensitivity is of high significance. Prior neuroimaging findings revealed that MDD patients exhibited altered neural stress response in limbic-striatal-prefrontal regions (Admon et al., 2015; Holsen et al., 2011; Ming et al., 2017). Moreover, neuroimaging studies in healthy individuals reported that CM is associated with increased stress-induced activation in the amygdala (Grimm et al., 2014; Seo et al., 2019), hippocampus (Grimm et al., 2014; Seo et al., 2019), anterior cingulate cortex (Grimm et al., 2014), dorsal medial prefrontal cortex (mPFC; van Harmelen et al., 2014), cerebellum (Seo et al., 2019), medial temporal lobe (Seo et al., 2019), insula (Zhong et al., 2020), precuneus (Zhong et al., 2020), and decreased stress-induced activation in the ventromedial and dorsolateral prefrontal cortex (Purcell et al., 2021), as well as increased stress-induced amygdala-hippocampus connectivity (Fan et al., 2015). Although these findings are not always consistent, they suggest that CM may impact neural stress responses in neural circuitries partly overlapping with regions consistently implicated in MDD (e.g., amygdala, hippocampus, and prefrontal cortex). However, it is still unclear whether differences exist in stress circuitry between individuals with MDD with *versus* without a history of CM. This important question can only be addressed by specifically comparing maltreated/non-maltreated MDD individuals to the corresponding maltreated/non-maltreated healthy individuals.

Toward this aim, we evaluated neural activation during a psychosocial stressor in maltreated and non-maltreated healthy controls (HCs) and first-episode unmedicated MDD patients. The Montreal Imaging Stress Task (Dedovic et al., 2005), a reliable and widely-used psychosocial stressor, was administrated to induce psychosocial stress. Whole-brain analyses using a 2 × 2 factorial design were run, with the between-subject factors of *CM* and *Diagnosis*. In light of the overlapping stress-related neural circuits (i.e., limbic-prefrontal regions) implicated in MDD and CM, we hypothesized that the abnormal stress-related neural activation of MDD with past CM versus HC with CM could differ from the abnormal stress-related neural activation of MDD without a history of CM *versus* HC without CM, particularly in limbic-prefrontal regions.

2 | METHODS AND MATERIALS

2.1 | Participants

Participants with an MDD diagnosis ($N = 77$) were recruited from the outpatient department of the Second Xiangya Hospital affiliated with Central South University. Healthy participants ($N = 143$) were recruited from two colleges and the community through advertisements and posters. All participants were unmedicated. Two psychiatrists conducted psychiatric evaluations using the structured clinical interview for DSM-IV-TR axis I disorders-patient edition. Patients meeting DSM-IV-TR Axis I disorders criteria for their first episode were recruited, with exclusion criteria for potential confounding effects of antidepressant medications, multiple episodes, and comorbidities. Only females were included in light of abundant evidence of sex differences in stress responses at both the behavioral and neural levels (Goldfarb et al., 2019; Seo et al., 2017; Wang et al., 2007). See Supporting Information Methods for detailed eligibility criteria. All participants were aware of the study's purpose and provided informed written consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Second Xiangya Hospital of Central South University.

Six HC subjects and one patient with MDD were excluded because of excessive head motion (see Supporting Information Methods for detailed exclusion criteria), leaving 76 female MDD patients and 137 female HCs available for analyses.

2.2 | Assessment of CM

The childhood trauma questionnaire (CTQ) was used to assess CM (Bernstein et al., 1998; He et al., 2019). The CTQ consists of five subscales: emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect; with five items per scale rated on a 5-point Likert scale. Individuals were classified as experiencing CM when they met the respective moderate-to-severe cutoff score on at least one subscale according to Bernstein et al., (1998) (emotional abuse ≥12; physical abuse ≥10; sexual abuse ≥8; emotional neglect ≥15; and physical neglect ≥10). Forty-three of the 137 HCs were classified as HCs with CM ("HC/CM"), whereas the remaining 94 reported

noCM ("HC/noCM"); 44 of 76 MDD patients were classified as MDD with CM ("MDD/CM"), and the remaining individuals reported noCM ("MDD/noCM").

2.3 | Montreal Imaging Stress Task

The Montreal Imaging Stress Task (MIST), which involves uncontrollability and social evaluative threat, was administrated to induce acute psychosocial stress (Dedovic et al., 2005). Briefly, the MIST was conducted using a block design with three 7-min imaging runs. Each run consisted of three conditions: a rest condition (30 s) without task requirement; a control condition (90 s) in which participants answered arithmetic questions without a time limit; and a stress condition (90 s) in which subjects had to answer arithmetic questions with a time limit and a visible performance bar. Each condition was presented twice in each run. See Supporting Information Methods and Figure 1 for details. The contrast of interest for functional magnetic resonance imaging (fMRI) analyses was the stress condition minus the control condition.

2.4 | Stress response measurement

Self-reported subjective stress ratings and cortisol concentrations (through saliva) were collected across the MIST to evaluate stress responses. Subjective stress responses were indexed by subtracting the pre-MIST stress rating from the post-MIST stress rating. To evaluate changes in cortisol concentration throughout the MIST, eight saliva samples were collected with a Salivette (Sarstedt) in the scanner during the interval of scanning. Cortisol concentration was assessed using a human cortisol ELISA Kit (Bio-Swamp). Saliva samples were collected upon participants' arrival (t = −75 min), after 30-min rest (t = −45 min), after entering the scanner (t = −15 min), after 15-min anatomical and resting-state scans (t = 0 min), after each MIST run (3 runs; t = +7/14/21 min), and after leaving the scanner (t = +50 min). Following established procedures, the area under the curve with respect to ground (AUC_g; index of the overall cortisol output) and the area under the curve with respect to increasing (AUC_i; index of the cortisol changes) over the stress exposure [cort4 (t = 0 min) to cort8 (t = +50 min)] was calculated to measure the cortisol response (Pruessner et al., 2003). Both the AUC_g and AUC_i were calculated on the natural log-transformed cortisol concentrations.

2.5 | fMRI data acquisition and preprocessing

See Supporting Information Methods for fMRI data acquisition parameters and preprocessing procedures.

2.6 | Statistical analysis

2.6.1 | Psychological and physiological data

Time (8 timepoints) × *CM (CM, noCM)* × *Diagnosis (HC, MDD)* repeated-measures analysis of covariance (ANCOVA) analyses with age as a covariate was used to assess the main effect of time on cortisol concentration and subjective stress rating separately. In addition, *Diagnosis* × *CM* ANCOVA analyses were conducted to measure the group effects on subjective stress responses (*post-stress minus pre-stress*) and cortisol stress responses (AUC_g, AUC_i).

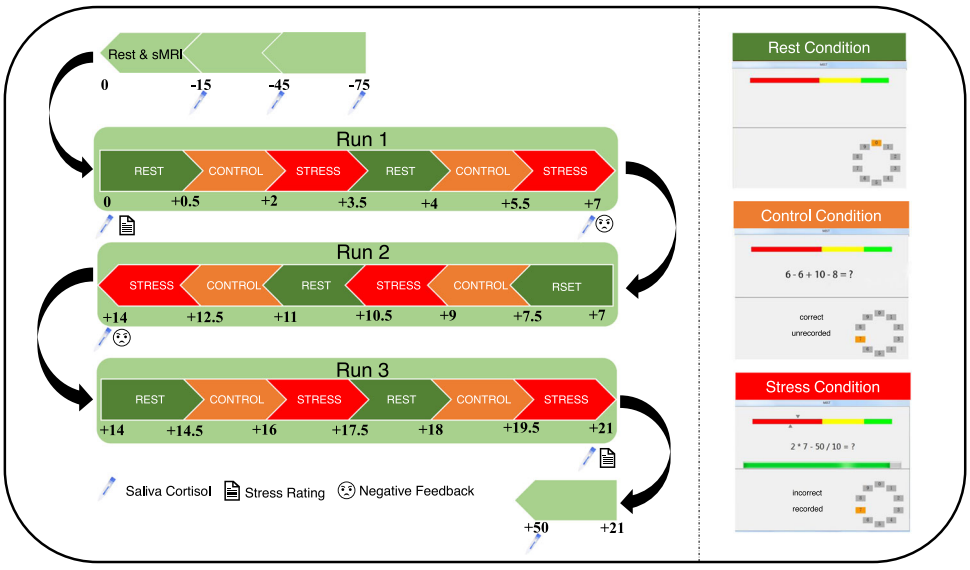

FIGURE 1 Overview of experimental design. The MIST includes 3 runs, and each run lasts 7 min. Eight saliva samples were collected across the MIST and subjective stress levels were collected immediately before and after the MIST. Scripted negative feedback was given after the first and the second MIST runs. MIST, Montreal Imaging Stress Task; sMRI, structural magnetic resonance imaging

2.6.2 | fMRI data

For the first-level analysis, a general linear model including rest, control, and stress conditions was conducted for each participant using Statistical Parametric Mapping (SPM12; The Wellcome Centre for Human Neuroimaging). The first-level individual contrasts (*stress minus control*) were then submitted to group-level analyses. See Figure S1a for the uncorrected whole-brain *t*-map (stress vs. control). For the group-level analyses, a whole-brain *Diagnosis* × *CM* ANCOVA analysis with age as a covariate was conducted to probe possible group effects. All imaging results were corrected using cluster-level family-wise error rate (FWE) correction of $p < .05$ surpassing an initial $p < .001$ voxel threshold.

3 | RESULTS

3.1 | Demographic and clinical characteristics

Clinical and demographic characteristics of four groups are summarized in Table 1. In the current sample, the MDD group was significantly older than the HC group (i.e., across both CM and noCM groups; $F(1, 209) = 26.01$, $p < .001$, $\eta^2 = 0.111$). With regard to years of education, a significant *CM* × *Diagnosis* interaction effect emerged ($F(1, 209) = 25.06$, $p = .008$, $\eta^2 = 0.033$), with both the MDD/CM group ($p_{Bonferroni} = .030$) and the HC/noCM group ($p_{Bonferroni} = .003$) having more years of education than the MDD/noCM group. In addition, there was a significant *CM* × *Diagnosis* interaction on CTQ score ($F(1, 209) = 4.12$, $p = .044$, $\eta^2 = 0.019$), with the MDD/CM group (vs. HC/CM; $p_{Bonferroni} < .001$) and the MDD/noCM group (vs. HC/noCM; $p_{Bonferroni} = .045$) exhibiting higher CTQ scores than their respectively HC group. See Table 1 for other demographic and clinical characteristics across groups.

3.2 | Stress manipulation check

A *Time (8 timepoints)* × *CM (CM, noCM)* × *Diagnosis (HC, MDD)* repeated-measures ANCOVA analysis revealed a significant main effect of *Time* on subjective stress rating ($F(1, 200) = 63.99$, $p < .001$, $\eta^2 = 0.242$) and cortisol concentration ($F(7, 1120) = 8.93$, $p < .001$, $\eta^2 = 0.053$), with increased cortisol concentration (T50 vs. T0, $p_{Bonferroni} < .001$; Figure 2a) and subjective stress level (post-MIST vs. pre-MIST, $p_{Bonferroni} < .001$; Figure 2b) after the onset of the MIST, which indicated that psychosocial stress was successfully induced by the MIST. However, we did not observe significant *Time* × *Diagnosis*, *Time* × *CM*, or *Time* × *Diagnosis* × *CM* interaction effects with regard to both subjective stress ratings and cortisol concentration (*ps* > .05), suggesting the groups had similar affective and cortisol responses.

In addition, we investigated group effects on subjective stress level changes (*post-stress minus pre-stress*) and cortisol stress responses (AUC_g and AUC_i). No significant main effects of *Diagnosis*, *CM*, or interaction effect of *Diagnosis* × *CM* emerged (*ps* > .05; Table S1).

3.3 | Group effects on stress-related neural activation

A whole-brain *CM* × *Diagnosis* ANCOVA with age as a covariate revealed a significant *CM* × *Diagnosis* interaction effect in a cluster in the mPFC ($k = 143$, $x/y/z = -2/54/6$, $F(1, 208) = 21.86$, $p_{FWE} = .010$; Figure 3a; Table 2), which was the only cluster exhibiting an interaction effect surviving multiple comparison correction. The main effects of *Diagnosis* and *CM* did not survive FWE correction ($p_{FWE} > .05$). The results were confirmed when excluding age as a covariate (see Supporting Information Results; Table S2).

Bonferroni-corrected simple effects analyses clarified that the MDD/CM group exhibited less mPFC deactivation in comparison to the HC/CM group ($p_{Bonferroni} = .003$; Figure 3b), whereas the MDD/noCM group exhibited greater mPFC deactivation in comparison to the HC/noCM group ($p_{Bonferroni} = .002$; Figure 3b). Moreover, the MDD/CM group had less mPFC deactivation in comparison to the MDD/noCM group ($p_{Bonferroni} < .001$; Figure 3b); finally, the HC/CM group showed a trend of greater mPFC deactivation relative to HC/noCM group ($p_{Bonferroni} = .066$; Figure 3b). All these results remained significant after excluding two extreme outliers who had values outside the 1st quartile ± 3 × interquartile range of the contrast values of mPFC activation (1, MDD/CM; 1, HC/noCM).

3.4 | Group effects on stress-related mPFC-seed connectivity

A psychophysiological interaction (PPI) analysis was performed using the mPFC cluster as a seed to determine possible CM and MDD associations with stress-modulated functional connectivity. See Supporting Information Methods for the detailed processes of PPI analysis. Figure 4a shows the main effect of stress on mPFC-seed functional connectivity, which highlights a pattern of decreased connectivity with default mode network (DMN) regions and increased connectivity with dorsal prefrontal/parietal regions. A whole-brain *CM* × *Diagnosis* ANCOVA on PPI contrasts revealed a significant main effect of *CM* on connectivity between mPFC and left SFG (*CM* > *noCM*; $k = 139$, $x/y/z = -20/48/42$, $F(1, 208) = 22.89$; $p_{FWE} = .003$; Figure 4b; Table 2) and right posterior cerebellum (*CM* > *noCM*; $k = 155$, $x/y/z = 30/-72/-36$; $F(1, 208) = 24.01$, $p_{FWE} = .001$; Figure 4c; Table 2). No main effects of *Diagnosis* or *CM* × *Diagnosis* interaction effect emerged ($p_{FWE} > .05$). The results were confirmed when not including age as a covariate (see Supporting Information Results; Table S2).

TABLE 1 Demographic and clinical characteristics

Characteristics	HC/ noCM (*N* = 94) Mean (SD)	HC/CM (*N* = 43) Mean (SD)	MDD/ noCM (*N* = 32) Mean (SD)	MDD/CM (*N* = 44) Mean (SD)	*Diagnosis*		*CM*		*Diagnosis × CM*	
					F	*p*	*F*/*t*	*p*	*F*	*p*
Age (years)	21.54 (4.24)	20.93 (4.39)	25.38 (8.30)	25.91 (7.68)	26.01	<.001	0.001	.979	0.41	.521
Education (years)	14.65 (1.58)	14.12 (1.64)	13.48 (2.29)	14.43 (2.29)	2.37	.126	0.57	.451	7.16	.008[a]
HAMD	–	–	22.03 (4.69)	22.82 (4.71)	–	–	−0.72	.474	–	–
BDI-II	4.59 (4.34)	6.72 (5.70)	27.86 (10.23)	30.96 (9.53)	522.95	<.001	6.34	.013	0.22	.640
STAI-S	36.26 (7.44)	41.74 (7.95)	57.53 (11.55)	59.07 (10.08)	217.39	<.001	7.19	.008	2.27	.133
CTQ sum	32.27 (4.00)	44.75 (8.99)	35.21 (5.02)	51.98 (10.70)	23.20	<.001	192.24	<.001	4.12	.044[b]
Sexual abuse	5.15 (0.49)	5.81 (1.47)	5.05 (0.18)	6.20 (1.68)	0.82	.368	33.51	<.001	2.51	.115
Physical abuse	5.23 (0.69)	6.28 (2.26)	5.51 (0.95)	7.95 (4.21)	8.65	.004	27.65	<.001	4.43	.037[c]
Emotional abuse	6.20 (1.48)	8.35 (3.16)	7.06 (2.06)	11.27 (4.57)	20.55	<.001	58.30	<.001	6.16	.014[d]
Physical neglect	6.77 (1.49)	10.71 (2.58)	6.70 (1.51)	10.36 (2.73)	0.46	.501	156.79	<.001	0.21	.649
Emotional neglect	8.91 (2.37)	13.60 (4.29)	10.89 (2.57)	16.18 (4.38)	21.28	<.001	102.10	<.001	0.37	.546

Note: *$p < .05$, **$p < .01$, ***$p < .001$.

Abbreviations: BDI-II, Beck depressive inventory-II; CM, childhood maltreatment; CTQ, childhood trauma questionnaire; HAMD, Hamilton depression rating scale; HC, healthy controls; MDD, major depressive disorder; STAI, state and trait anxiety inventory.

[a]MDD/CM > MDD/noCM*; HC/noCM > MDD/noCM**

[b]MDD/noCM > HC/noCM*; MDD/CM > HC/CM***; HC/CM > HC/noCM***; MDD/CM > MDD/noCM***.

[c]MDD/CM > HC/CM**; HC/CM > HC/noCM*; MDD/CM > MDD/noCM***.

[d]MDD/CM > HC/CM***; HC/CM > HC/noCM***; MDD/CM > HC/CM***.

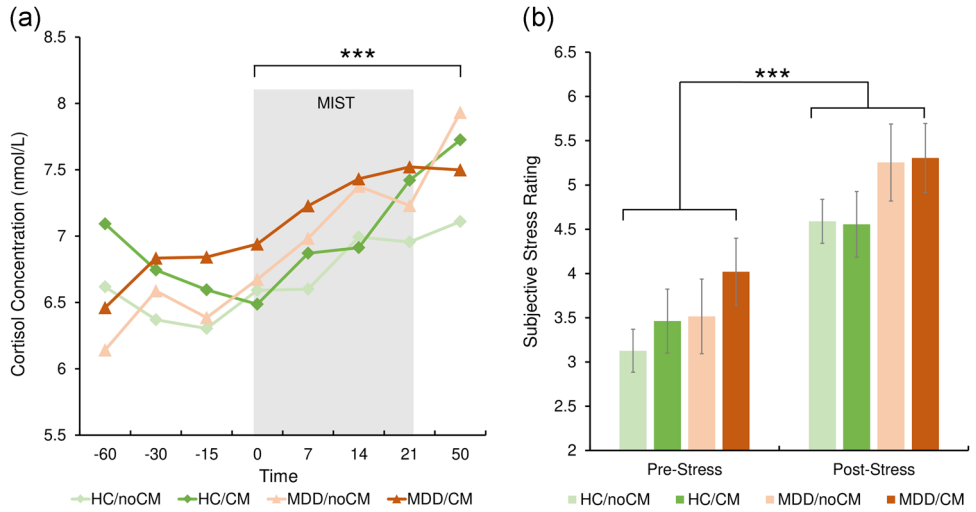

FIGURE 2 Subjective and cortisol stress responses. (a) The significant main effect of *Time* in cortisol concentration over the stress exposure. (b) The significant main effect of *Time* in subjective stress rating over the stress exposure. Estimated-mean is plotted, and the error bar represents a standard error. CM, childhood maltreatment; HC, healthy controls; MDD, major depressive disorder; MIST, Montreal Imaging Stress Task. $^{***}p_{Bonferroni} < .001$

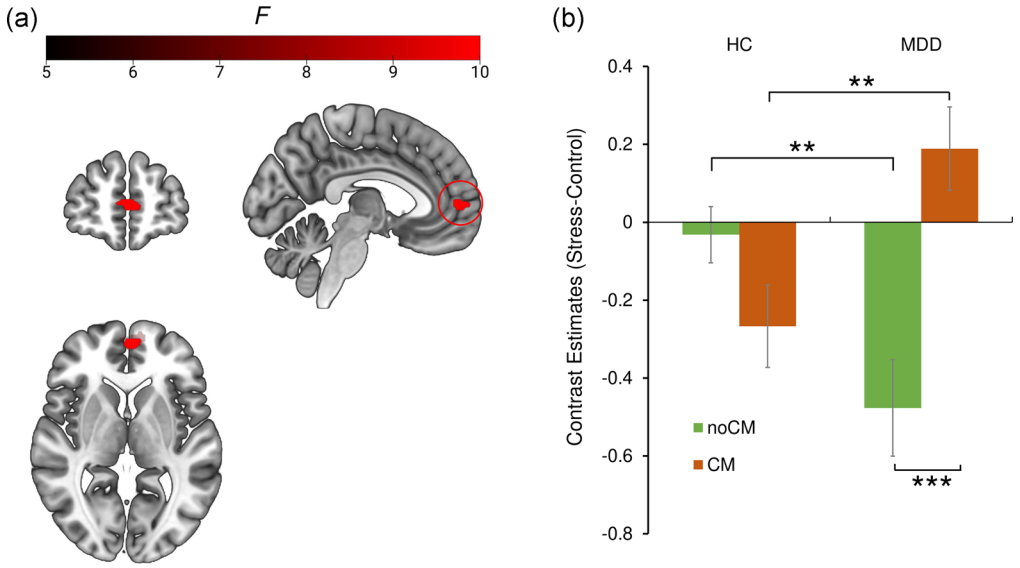

FIGURE 3 Significant *CM* × *Diagnosis* interaction in the medial prefrontal cortex (mPFC). (a) Location of mPFC exhibiting significant *CM* × *Diagnosis* interaction. (b) Bonferroni simple effects analysis of mPFC. Estimated-mean are plotted, and error bar represents SE. CM, childhood maltreatment; HC, healthy controls; MDD, major depressive disorder. $^{**}p_{Bonferroni} < .01$, $^{***}p_{Bonferroni} < .001$

3.5 | Correlation analysis

See Supporting Information Methods and Results (Table S3) for the associations between neural activation/connectivity and cortisol response measures as well as with depressive symptoms.

3.6 | Sensitivity analyses

Sensitivity analyses were conducted to test whether different types of CM (i.e., sexual abuse, physical abuse, emotional abuse, physical neglect, emotional neglect, abuse maltreatment, and neglect maltreatment) differentially affected the main findings (i.e., mPFC deactivation, functional connectivity between mPFC-SFG; functional connectivity between mPFC–cerebellum). Generally, the results of these sensitivity analyses revealed that the MDD/CM group exhibited higher stress-related effects in comparison to MDD/noCM in terms of activation/connectivity regardless of which kind of criteria were used to identify maltreated individuals (Table S4). Finally, we considered the dimension model of adversity proposed by McLaughlin et al. (2019) which proposes that distinct dimensions (threat vs. deprivation)

TABLE 2 Group differences in neural stress responses to acute psychosocial stress

Brain regions	BA	MNI coordinates x	y	z	F	Cluster size	p_{uncorr}	p_{FWE}
Whole-brain activity: CM × Diagnosis interaction								
mPFC	10	−2	54	6	21.86	143	<.001	.010
		−12	60	6	17.23			
mPFC-seed connectivity: Main effect of CM								
Posterior		30	−72	−36	24.01	155	<.001	.001
Cerebellum		34	−68	−42	14.61			
SFG	8, 9	−20	48	42	22.89	139	<.001	.003
		−20	50	34	16.04			
		−26	40	46	15.44			

Abbreviations: BA, Brodmann area; CM, childhood maltreatment; FWE, family-wise error rate correction; MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; SFG, superior frontal gyrus.

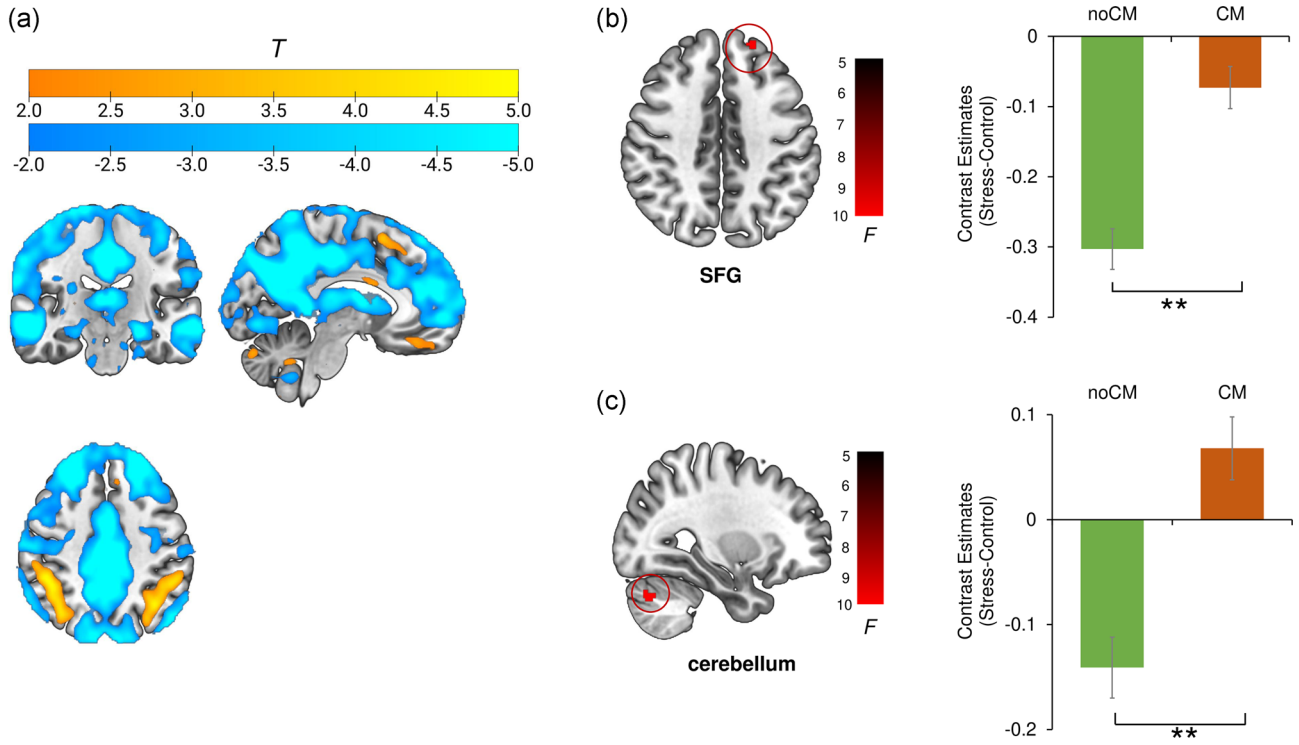

FIGURE 4 mPFC-seed functional connectivity changes to acute psychosocial stress. (a) main effect of stress on mPFC-seed functional connectivity. (b) Main effect of *CM* on mPFC-SFG connectivity (stress-control). (c) main effect of *CM* on mPFC-cerebellum connectivity (stress-control). Estimated-mean are plotted, and error bar represents SE. SFG, superior frontal gyrus; CM, childhood maltreatment. $^{**}p_{FWE} < 0.01$

of adversity may have differential effects on neural development. When applying either abuse (threat) or neglect (deprivation) criteria, our findings of MDD/CM *versus* MDD/noCM remained significant (see composite score section in Table S4). See Supporting Information Methods for details of performing sensitivity analyses.

4 | DISCUSSION

The overarching goal of the current study was to test whether CM and MDD interacted in shaping neural patterns in response to a well-established acute psychosocial stressor. The fMRI findings revealed that the MDD/CM group and MDD/noCM group exhibited

dissociable, stress-related mPFC responses when compared to HCs with a history of CM. Specifically, the MDD/CM group exhibited *reduced* stress-related mPFC deactivation relative to HC/CM group, whereas the MDD/noCM group exhibited *greater* stress-related mPFC deactivation in comparison to the HC/noCM group. In addition, participants reporting CM (irrespective of MDD diagnosis) exhibited greater stress-related mPFC-SFG connectivity and mPFC-cerebellum connectivity relative to participants without past CM. Collectively, these fMRI findings provide novel insights into the potential interaction between CM and MDD psychopathology.

Consistent with our hypothesis, the MDD/CM and MDD/noCM group exhibited distinct neural alterations during psychosocial stress processing in the mPFC. The mPFC is a critical region involved in the pathophysiology of MDD and has been linked to CM (Belleau et al., 2019; Cassiers et al., 2018; Hart & Rubia, 2012). Critically, the mPFC is regarded as an important region of the DMN which is implicated in self-referential processing (Gusnard et al., 2001). Thus, the observed increased deactivation of mPFC in MDD/noCM (vs. HC/noCM) and decreased deactivation in MDD/CM (vs. HC/CM) may implicate reduced engagement of the DMN amongst those with MDD and noCM and greater engagement of the DMN amongst those with MDD and with CM in response to stress. This suggests that both patterns of decreased and increased involvement of the DMN under stress may be maladaptive. The increased mPFC deactivation seen in the MDD/noCM group (vs. HC/noCM) could reveal less neural resources were allocated to the DMN network with the aim to maintain task performance during psychosocial stress processing. The negative correlation between stress-related mPFC deactivation and depressive symptoms observed in MDD/noCM group further suggests that this neural pattern could be maladaptive. For the MDD/CM group, the decreased mPFC deactivation (vs. HC/CM) could reveal increased self-focused thinking under stress. Overall, the current findings suggest that the MDD/CM group may have a unique neurobiological profile during stress compared to the MDD group without a history of CM.

Of note, the mPFC has also been implicated in stress regulation (Herman et al., 2005). In line with this, in the current study, the mPFC was characterized by decreased connectivity with DMN regions and increased connectivity with dorsal prefrontal/parietal regions (stress vs. control; see Figure 3a). As an alternate interpretation, the greater deactivation of mPFC in the MDD/noCM group versus the HC/noCM may implicate stress regulation dysfunction; whereas less mPFC deactivation observed in the MDD/CM group versus the MDD/noCM group could provide evidence supporting the stress acceleration theory. This theory suggests that CM might facilitate the maturation of the stress/threat regulation circuit (i.e., mPFC and amygdala) to adapt to CM (Callaghan & Tottenham, 2016). However, this speculation will need to be tested with a more specific task design probing stress regulation.

In contrast to prior findings (Grimm et al., 2014; Seo et al., 2019; Zhong et al., 2020), we did not observe significant neural alterations in the HC/CM group, although the HC/CM versus HC/noCM comparison yielded a trend toward significantly greater deactivation in mPFC. Our prior study—which included 48 HC/CM (24 male/24 female) and 48 HC/noCM (15 male/33 female) participants also included in the current analyses—found that the HC/CM group exhibited significantly greater activation in the dorsolateral prefrontal cortex, insula, precuneus, and greater deactivation in the ventral mPFC relative to the HC/noCM group (Zhong et al., 2020). Both samples revealed that, relative to the HC/noCM group, the HC/CM group exhibited a tendency of greater deactivation in the mPFC, which highlights an important role of mPFC in terms of the interaction between stress and CM. However, the current study, which focused on female participants only, did not replicate other prior findings even though the sample partly overlapped (33/94 female HC/noCM; 24/43 female HC/CM). Possible explanations for this lack of replication are (1) the fact that the effect of CM on brain function might be sex-specific (Colich et al., 2017; Tiwari & Gonzalez, 2018; White et al., 2020) and (2) the improved fMRI preprocessing method used in the current study. Further investigations are warranted to address this question.

With regard to mPFC-seed connectivity, we found that the noCM group exhibited decreased mPFC-SFG connectivity in the stress versus control comparison, whereas the CM group exhibited relatively stable mPFC-SFG connectivity across both conditions. Although not frequently mentioned, the SFG (Brodmann area 8, 9) is also reported as a part of the DMN (Meindl et al., 2010). Consistent with this literature, this region was deactivated in the stress *versus* rest and control *versus* rest comparison (see Figure S1). Along this line, the relatively stable mPFC-SFG connectivity (stress vs. control) observed in CM individuals may reveal maladaptive self-referential processing during psychosocial stress processing. In addition, the noCM group has decreased mPFC-cerebellum connectivity (stress vs. control), whereas the CM group has stable mPFC-cerebellum connectivity across conditions. The cerebellum activity and cerebellum-related connectivity are not frequently investigated in stress research. However, several studies have reported that acute stress may induce the activation of the cerebellum (Kogler et al., 2017; Seo et al., 2011, 2019). One recent review (Moreno-Rius, 2019) proposed that the traumatic/repeated stress may induce dysfunction of cerebellum-based predictive system, and thus promote overestimation of environment-associated negative outcomes and reduce appropriate actions, which may explain why the CM individuals exhibited altered mPFC-cerebellum coupling when experiencing acute psychosocial stress. However, these connectivity findings are relatively novel in terms of the neural mechanism underlying CM; accordingly, replications are warranted.

Some limitations of the current study should be mentioned. First, menstrual cycle information, which could affect neural stress responses (Goldstein et al., 2010), was not collected. Second, the classification of maltreatment was based on retrospective self-reported measurements, although it has been proposed by others that this limitation is not as severe as we may anticipate (Brewin et al., 1993). Third, various stress components induced by the MIST include uncontrollability and social evaluative threat (Dedovic et al., 2009), which may add the complexity of interpretation. Fourth, the

first-episode, noncomorbid unmedicated female MDD sample is less representative of the community, which may limit the generalization of findings. Fourth, the unmatched age, years of education, and CTQ score across groups is a limitation that should be mentioned. Finally, the onset time of CM was not collected. Because distinct brain regions have different maltreatment-sensitivity periods (Pechtel & Pizzagalli, 2011; Teicher et al., 2016), additional studies are needed to test whether the neural alterations observed in this study are affected by the onset time of CM.

In spite of these limitations, the current study represents the first exploration of the potential interaction between CM and MDD psychopathology in terms of neural stress reactivity and some novel findings emerged. The MDD/CM and MDD/noCM patients exhibited opposite neural stress responses in mPFC in relative to HCs, which provides evidence for distinct neurobiological abnormalities in MDD with versus without CM. In addition, compared to those without CM history, individuals with a history of CM exhibited higher mPFC-SFG and mPFC-cerebellum connectivity independent of MDD diagnosis, revealing potential general neural consequences of CM on the development of stress circuitry in females.

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CONFLICT OF INTERESTS

Over the past 3 years, Dr. Diego A. Pizzagalli has received consulting fees from Albright Stonebridge Group, BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Concert Pharmaceuticals, Engrail Therapeutics, Neuroscience Software, Neurocrine Biosciences, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; one honorarium from Alkermes; honoraria from the Psychonomic Society for editorial work; and research funding from NIMH, Dana Foundation, Brain and Behavior Research Foundation, and Millennium Pharmaceuticals. In addition, he has received stock options from BlackThorn Therapeutics and Compass Pathway. All other authors declare that they have no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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