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Association between childhood maltreatment and emotion dysregulation in patients with major depressive disorder and non-suicidal self-injury

Chenyin Sun, Huifeng Zhang, Rubai Zhou, Baichuan Wu, Yiyun Cai, Lvchun Cui, Min Zhang, Daihui Peng

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CS, HZ and RZ are joint first authors.

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Department of Mood Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Correspondence to
Dr Daihui Peng;
pdhsh@126.com

To the editor:

Non-suicidal self-injury (NSSI) is an array of directly prepense or repetitive self-harm behaviours without suicidal intent. Individuals engage in self-injurious behaviours to reduce negative mental and cognitive states or evoke positive emotions.[1] Emotion regulation (ER), the capability to regulate and control emotional responses, is often compromised in NSSI individuals.[2] Major depressive disorder (MDD) is characterised by severely and persistently depressed mood, so patients with MDD are very likely to use NSSI to alleviate negative feelings. Therefore, the clinical importance of studying ER among patients with MDD and NSSI cannot be overemphasised.

The Ottawa Self-Injury Inventory (OSI) is an overall self-report for evaluating NSSI. It covers a range of NSSI functions, which are internal and external ER, social influence and sensation seeking. Internal ER functions reflect motivations for the regulation of internalising symptom-related sadness, numbness and suicidal ideation, while external ER functions reflect motivations for regulating externalising symptom-related frustration or anger. However, published studies have not linked these NSSI functions to clinical symptoms or explored the underlying mechanisms from a psychological perspective. The amplitude of low-frequency fluctuations (ALFF) is a key metric within resting-state functional magnetic resonance imaging (rs-fMRI) representing regional spontaneous neuronal activity. The prefrontal cortex (PFC) (BA8-BA14, BA24, BA25, BA32, and BA44-BA47 of the Brodmann brain atlas) functions in ER by exerting top-down control over limbic regions, enabling individuals to manage emotional responses through cognitive processes.[3] Abnormal ALFF changes in the PFC of patients with MDD and NSSI have been mentioned.[4] However, the mechanisms underlying PFC functional abnormalities have not been explored from a neurological perspective.

Recent studies have reported that patients with MDD and NSSI had more severe childhood maltreatment experiences.[5] Researchers have also noticed the negative impact of childhood maltreatment on emotional regulation, manifesting as difficulties in coping with negative emotions.[6] Additionally, childhood maltreatment has been found to affect the development and functioning of the PFC.[7] Hence, the emotion dysregulation in patients with MDD and NSSI might be explained by childhood maltreatment.

We hypothesised that patients with MDD and NSSI would have significant associations between emotion dysregulation and childhood maltreatment. If the correlations were present, we would further explore whether ALFF changes mediate the association between childhood maltreatment and ER-related NSSI functions.

A total of 65 subjects with MDD were recruited from the Department of Mood Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine in China from August 2022 to December 2023. The inclusion criteria were: (1) age 18–34 years; (2) Han Chinese; (3) right-handed; and (4) met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for MDD. The exclusion criteria were: (1) a

current episode of a severe physical illness; (2) current or previous DSM-5 diagnoses for schizophrenia or bipolar disorder; (3) current pregnancy or breast-feeding; and (4) current or previous history of substance abuse or mental disorders due to organic diseases; (5) current or previous electroconvulsive therapy or transcranial magnetic stimulation therapy; and (6) contraindications for MRI scans. The patients with MDD were subsequently separated into two groups: 30 with NSSI behaviour (MDD+NSSI) and 35 without NSSI behaviour (MDD-NSSI). The former group must have engaged in NSSI behaviour for more than 5 days over the past year without the intention of suicide, while the latter group must never have had any NSSI behaviour during their lifetime. Additionally, 35 sex-matched and age-matched healthy controls (HCs) were obtained from the community through online recruitment. One patient from the MDD+NSSI group, three patients from the MDD-NSSI group and three subjects from the HC group were excluded because of excessive head movement during MRI scans, yielding a final sample of 29 subjects with MDD+NSSI, 32 subjects with MDD-NSSI and 32 HCs. The study flowchart is illustrated in the online supplemental figure 1.

MDD was diagnosed by two senior psychiatrists utilising the Mini-International Neuropsychiatric Interview (M.I.N.I.). The Hamilton Depression Rating Scale (Cronbach's α=0.880) was used to detect depressive symptoms and the Hamilton Anxiety Rating Scale (Cronbach's α=0.919) was used to identify anxiety symptoms. The M.I.N.I. Suicidality Inventory was used to assess suicidal risk, and the Childhood Trauma Questionnaire (CTQ) (Cronbach's α=0.809) was performed to estimate childhood maltreatment. The OSI (Cronbach's α=0.942) was used for assessing NSSI behaviour in the MDD+NSSI group.

The MRI images were gathered by Siemens 3.0 T MAGNETOM Prisma scanner with a 64-channel head coil. The parameters for the MRI were shown in online supplemental table 1. The rs-fMRI images were preprocessed using the Data Processing and Analysis for Brain Imaging (DPABI_V8.1, https://rfmri.org/DPABI) software packages based on MATLAB2022a. The preprocessing steps involved: (1) transforming image format; (2) eliminating the first 10 time points; (3) slice timing correction; (4) head-motion correction by excluding patients with mean frame-wise displacement (FD) Jenkinson>0.2 mm. This metric quantifies the average movement of the head between consecutive frames during the fMRI scan to evaluate the extent of motion artefacts; (5) spatial normalisation by standardising functional images to the Montreal Neurological Institute (MNI) space using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra and resampling to a resolution of 3×3×3 mm^3; (6) spatial smoothing by a 6 mm full-width at half-maximum Gaussian kernel; (7) linear detrending; and (8) nuisance covariate regression including head motion (Friston 24), white matter, cerebrospinal fluid and mean global signals. The ALFF for each voxel was calculated and then divided by the mean whole-brain ALFF to conclude the normalised mALFF value for statistical analysis. The PFC was considered as the region of interest (ROI) (online supplemental figure 2), which served as a mask for subsequent between-group ALFF comparisons.

Demographic and clinical data were calculated using SPSS V.26.0 with non-parametric tests and χ^2 tests, with Bonferroni correction applied for multiple comparisons. The statistical significance level was affirmed at p<0.05. The rs-fMRI data was processed based on DPABI_V8.1. Analysis of covariance tests was used to evaluate the ALFF within the ROI among groups, with gender, age, education and FD mean Jenkinson as covariates. The outcomes were corrected for multiple comparisons using the least significant difference correction. The results were then corrected for cluster-level analysis using the Gaussian random field (GRF) method, with voxel level p<0.001 and cluster level p<0.05. Corrected brain regions were deemed to be masks for post hoc comparisons between groups, using the same GRF parameters. The ALFF of the significant brain regions was extracted. Spearman correlation was applied to examine the correlation between CTQ scores, OSI scores and ALFF in SPSS V.26.0, with False Discovery Rate (FDR) correction applied for multiple comparisons. The mediation analysis was conducted using the PROCESS V.3.5 macro in SPSS V.26.0 to test whether ALFF could explain the relationship between CTQ scores and OSI scores.

Demographic and clinical information is summarised in the online supplemental tables 2–4 and the online supplemental figure 3. Significant group differences among the three groups were observed in the right orbitofrontal area (OFC) (BA11_R) (F=12.729, p<0.05, GRF corrected) and the left dorsal anterior cingulate cortex (dACC) (BA32_L) (F=15.107, p<0.05, GRF corrected). Post hoc analysis indicated that the MDD+NSSI group had significantly higher ALFF in the bilateral OFCs (BA11_R and BA11_L) (BA11_R: t=4.548, p<0.05, GRF corrected; BA11_L: t=4.525, p<0.05, GRF corrected) than the HC group. The MDD+NSSI group showed significantly higher ALFF in the left dACC (BA32_L) (t=4.821, p<0.05, GRF corrected) than the MDD-NSSI group (online supplemental table 5, figure 1 and online supplemental figure 4). In the MDD+NSSI group, correlation analyses specified that internal ER was significantly positively correlated with total childhood maltreatment score (r=0.504, p=0.024), sexual abuse (r=0.464, p=0.034) and physical neglect (r=0.426, p=0.047). The ALFF in the right OFC was significantly positively correlated with internal (r=0.561, p=0.014) and external (r=0.544, p=0.021) ER. It was also significantly positively correlated with sexual abuse (r=0.623, p=0.002) (table 1 and online supplemental figure 5). No significant mediating effects were discovered between NSSI functions, ALFF and childhood maltreatment in the MDD+NSSI group (all p>0.05).

This exploration aimed to confirm the psychological and neurological mechanisms referring to the correlation of emotional dysregulation with childhood maltreatment

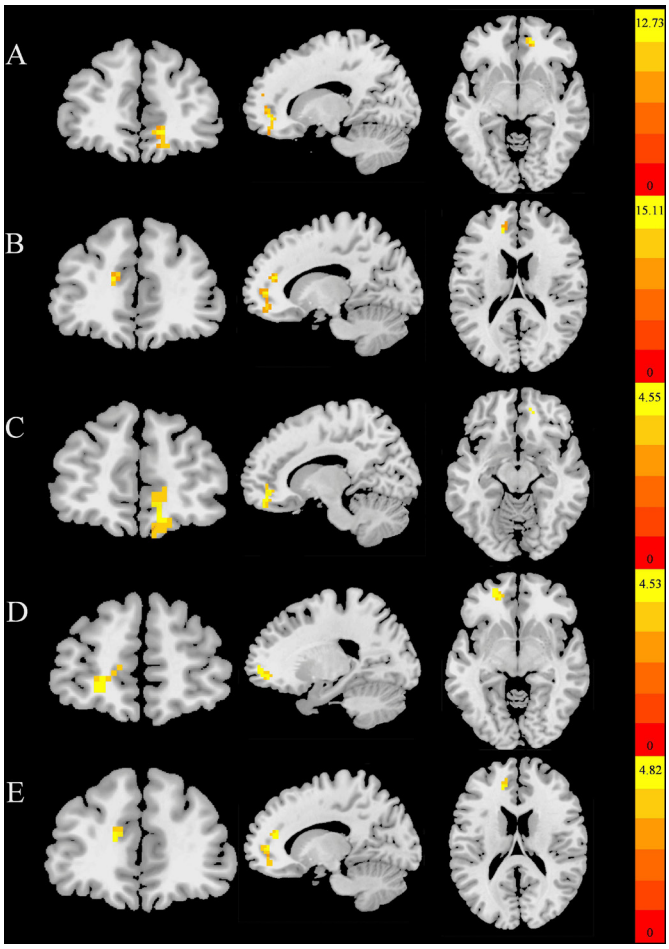

Figure 1 Statistical maps showing brain regions of the prefrontal cortex with significant differences in the amplitude of low-frequency fluctuations among the groups of patients with major depressive disorder and non-suicidal self-injury (MDD+NSSI), those with major depressive disorder without non-suicidal self-injury (MDD-NSSI), and the healthy controls (HC). The first column is the coronal view; the second column is the sagittal view; the third column is the axial view. (A) Right orbitofrontal area (OFC) among the three groups. (B) Left dorsal anterior cingulate cortex (dACC) among the three groups. (C) Right OFC between the MDD+NSSI and the HC groups. (D) Left OFC between the MDD+NSSI and the HC groups. (E) Left dACC between the MDD+NSSI and the MDD-NSSI groups. In (A) and (B), the colour bar represents the F value of ANOVA tests among the three groups. In (C), (D) and (E), the colour bar represents the t-value of the post hoc t-tests between the two groups. Voxel level p<0.001, cluster level p<0.05, GRF corrected. ANOVA, analysis of variance; GRF, Gaussian random field.

in patients with MDD and NSSI. We found a significant between-group difference in the bilateral OFCs and left dACC. In patients with MDD and NSSI, from a psychological perspective, internal ER was significantly correlated with the total score of childhood maltreatment, sexual abuse and physical neglect. From a neurological perspective, the ALFF in the right OFC was significantly correlated with both internal and external ER and sexual abuse. Both psychological and neurological results suggested that emotional dysregulation in patients with MDD and NSSI was linked to childhood maltreatment.

The association between ER-related NSSI functions and childhood maltreatment suggested that individuals with more severe childhood maltreatment experiences were more apt to treat NSSI as a means of coping with inner pain, reflecting significant deficits in ER. Emotion dysregulation has been identified as a mediating junction between childhood maltreatment and NSSI,[8] indicating that from a psychological mechanism perspective, emotional dysregulation in patients with MDD and NSSI was linked to childhood maltreatment. The higher ALFF in the OFC could reflect the brain's compensatory efforts to manage an overactive or dysregulated emotional processing system. Two task-fMRI studies found significantly increased activity in the OFC of patients with NSSI when viewing NSSI-related images.[9 10] Furthermore, the OFC plays a key role in reward processing. A monetary incentive delay task indicated that adolescents with NSSI showed significantly decreased OFC activation under reward anticipation.[11] The OFC activation deficits might lead them to rely on NSSI as an alternative means of ER. Additionally, two studies uncovered that abnormal functions in the OFC were connected with childhood maltreatment. One study indicated a significant positive correlation between childhood maltreatment and increased OFC response to aversive cues,[12] and another study reported significantly lower OFC activation but higher functional connectivity of the amygdala with OFC during cognitive reappraisal in maltreated individuals.[13] Although there is currently no research on the correlation of OFC with childhood maltreatment in patients with NSSI or MDD and NSSI, the existing evidence is consistent with our findings, suggesting that childhood maltreatment may lead to abnormal OFC activity in patients with MDD and NSSI. Since the OFC has crucial functions in emotional regulation, this could contribute to developing NSSI behaviours.

Interestingly, the links between childhood maltreatment and emotional dysregulation observed were predominantly related to sexual abuse. Previous evidence has indicated the link of sexual abuse to NSSI[14] and has verified the correlation of sexual abuse with emotional dysregulation.[15] Other results also demonstrated that emotional dysregulation in patients with MDD and NSSI was related to physical neglect. However, there is a gap in existing research in this area. We speculate that undergoing physical neglect may lead patients to ignore bodily sensations and alleviate the psychological distress caused by negative emotions through NSSI. Further investigation is needed to validate these hypotheses.

This study had several limitations. First, the small sample size limits the statistical efficacy to detect more subtle distinctions between groups. This might also explain one of the reasons why no mediating effect was found in this study. Second, we did not control for medication use among the patients with MDD. Although we made efforts to conduct evaluations and MRI scans as

Table 1 Spearman correlations between emotion regulation-related non-suicidal self-injury functions, the amplitude of low-frequency fluctuations in brain regions of the prefrontal cortex with significant differences among the groups and childhood maltreatment

		NSSI functions		Brain regions		
Variables		**Internal ER**	**External ER**	**R OFC**	**L OFC**	**L dACC**
Childhood maltreatment	r	0.504*	0.318	0.415	0.140	0.081
	p	0.024	0.218	0.076	0.704	0.810
Emotional abuse	r	0.331	0.292	0.138	0.156	0.132
	p	0.118	0.225	0.475	0.704	0.761
Physical abuse	r	0.223	0.081	0.313	0.140	0.128
	p	0.315	0.674	0.136	0.704	0.761
Sexual abuse	r	0.464*	0.426	0.623*	0.412	0.415
	p	0.034	0.095	0.002	0.157	0.151
Emotional neglect	r	0.351	0.159	0.301	0.041	–0.011
	p	0.111	0.460	0.136	0.832	0.955
Physical neglect	r	0.426*	0.252	0.380	–0.090	–0.159
	p	0.047	0.281	0.083	0.772	0.761
R OFC	r	0.561*	0.544*	–	–	–
	p	0.014	0.021	–	–	–
L OFC	r	0.108	0.314	–	–	–
	p	0.649	0.218	–	–	–
L dACC	r	0.046	0.209	–	–	–
	p	0.811	0.356	–	–	–

FDR corrected.
*p<0.05.
dACC, dorsal anterior cingulate cortex; ER, emotion regulation; FDR, False Discovery Rate; L, left; NSSI, non-suicidal self-injury; OFC, orbitofrontal area; R, right.

soon as possible after enrolment, we failed to eliminate the potential impact of medication on brain function. Third, task-fMRI was not applied, so we were unable to observe changes in brain activity during active ER. To address these limitations, future studies should aim to recruit larger sample sizes and unmedicated patients or consider a medication wash-out period before MRI scans when ethically appropriate. Task-fMRI should also be considered to obtain more direct evidence on the neurological mechanisms of ER.

The findings from the present study revealed that patients with MDD and NSSI demonstrated ER-related NSSI functions and abnormal neural activity in the PFC, both of which were associated with childhood maltreatment. It was the first study to obtain the correlation between emotional dysregulation and childhood maltreatment in patients with MDD and NSSI from both psychological and neurological mechanisms. These findings offered a novel perspective on understanding NSSI behaviours in patients with MDD and emphasised the significance of childhood maltreatment in regulating emotions for patients with MDD and NSSI.

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Contributors CS designed the study, collected the data, analysed the data and wrote the original manuscript. HZ and RZ designed the MRI parameters, collected the data, supervised the study and revised the manuscript. BW, YC, LC and MZ enrolled subjects, collected the data and supervised the study. DP designed the study, provided funding and revised the manuscript. DP is the guarantor. All authors contributed to the article and approved the submitted version.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human subjects and was approved by the Medical Ethics Committee of the Shanghai Jiao Tong University School of Medicine Affiliated Shanghai Mental Health Center (2022-49R). Participants gave informed consent to participate in the study before taking part.

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ORCID iDs
Chenyin Sun http://orcid.org/0009-0005-3789-9763
Baichuan Wu http://orcid.org/0000-0002-0569-5951
Daihui Peng http://orcid.org/0000-0003-4338-967X

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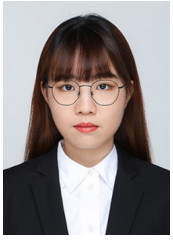

Chenyin Sun obtained a bachelor's degree in Clinical Medicine from Shanghai Jiao Tong University School of Medicine in 2022. She has been pursuing her master's degree in Psychiatry and Mental Health at Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine since 2022. She has participated in several clinical cohorts of depression as a research assistant during her studies. Her main research interests include neuroimaging and EEG studies in major depressive disorder patients with nonsuicidal self-injury.