



A shared effect of paroxetine treatment on gray matter volume in depressive patients with and without childhood maltreatment: A voxel-based morphometry study

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Summary

Aims: This study assessed whether antidepressant drug treatment has a common effect on gray matter (GM) volume in MDD patients with and without childhood maltreatment (CM).

Methods: T1-weighted structural magnetic resonance imaging data were collected from 168 participants, including 51 MDD patients with CM, 31 MDD patients without CM, 48 normal controls with CM, and 38 normal controls without CM. MDD patients received 6 months of treatment with paroxetine, and 24 patients with CM, and 16 patients without CM received a second MRI scan. A whole-brain voxel-based morphometry approach was used to estimate GM volume in each participant at two time points. Two-way analysis of variance (ANOVA) was used to determine the effects of MDD and CM on GM volume at baseline. Repeated measures two-way ANOVA was used to determine the treatment-by-CM interactive effect and main effect of treatment during paroxetine treatment. We further investigated the relationship between GM volume and clinical variables.

Results: At baseline, significant MDD-by-CM interactive effects on GM volume were mainly observed in the left parahippocampal gyrus, left entorhinal cortex, and left cuneus. GM volume was significantly lower mainly in the right middle temporal gyrus in patients with MDD than in normal controls. We did not find any significant treatment-by-CM interactive effects. However, a treatment-related increase in GM was found in the right middle temporal gyrus in both MDD groups.

Conclusions: These results suggest that paroxetine treatment operates via a shared neurobiological mechanism in MDD patients with and without CM.

KEYWORDS

antidepressant drug, childhood stress, depression, follow-up, MRI

1 | INTRODUCTION

Major depressive disorder (MDD) is one of the most prevalent mental disorders in the world, with a lifetime prevalence of approximately 20%.¹ Environmental stress, especially childhood maltreatment (CM), is one of the highest risk factors for the onset of MDD.² Here, CM includes physical, emotional, and sexual abuse as well as physical and emotional neglect that occurs before an individual is 16 years old.³ Compared to MDD patients without a history of CM, MDD patients with a history of CM exhibit more severe depressive symptoms.⁴ Notably, reports of treatment outcomes in patients with depression who experienced CM are inconsistent, with some studies showing that depressive patients with CM compared with those without CM often exhibit poor treatment outcomes, such as a reduced response to antidepressant drugs or residual subthreshold symptoms.^{4–6} However, other studies have suggested that MDD patients with and without CM experience the same treatment effects when using antidepressant drug therapy.^{7,8}

Recently, the rapid development of magnetic resonance imaging (MRI) has provided an unprecedented opportunity for noninvasive investigations of abnormal brain structures in patients with MDD. Depressive disorder is associated with changes in gray matter (GM) volume in many brain regions, including frontal-limbic system regions and the caudate, temporal lobe, and cerebellum.^{9,10} Moreover, neuroimaging studies focused on CM have revealed CM-related changes in GM volume in the hippocampus, medial prefrontal cortex and orbitofrontal cortex in both healthy subjects and current MDD patients.^{11–16} A significant MDD-by-CM interactive effect was found in the prefrontal cortex in a study that recruited relatively large numbers of MDD patients and controls.¹⁷ Together, these findings demonstrate that CM and MDD exert interactive effects on GM volume. Furthermore, the results of structural neuroimaging studies of MDD treatment often suggest that GM volumes are altered after treatment in certain regions^{18–21} including the temporal lobe.²¹ However, no study has explored the effect of CM on GM volume in MDD patients during antidepressant treatment. This question has important significance to our understanding of the pathophysiology underlying the changes that occur in MDD patients with and without CM during treatment.

Here, we collected T1-weighted structural MRI data from 168 participants, including 51 MDD patients with CM, 31 MDD patients without CM, 48 normal controls (NCs) with CM and 38 NCs without CM. After 6 months of treatment with paroxetine, 24 patients with CM and 16 patients without CM received a second MRI scan.

We used a whole-brain voxel-based morphometry (VBM) approach to estimate GM volume in each participant at each time point. We further studied MDD-by-CM interactive effects and treatment-by-CM interactive effects on GM volume at baseline and follow-up time points, respectively. Finally, the correlations between abnormalities in GM volume and the symptoms of MDD patients were also explored at baseline and follow-up.

2 | METHODS

2.1 | Participants

A total of 168 participants were enrolled in this study, including 82 MDD patients and 86 NCs. MDD patients were recruited from the inpatient or outpatient departments of the Zhumadian Psychiatry Hospital, Henan province, China. The diagnosis of MDD was confirmed by two well-trained psychiatrists using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV (SCID). NCs from the local area were recruited by flyers placed in the community. The inclusion criteria for patients with MDD were as follows: 18–55 years, acutely depressed and medication-free for not less than 2 weeks, and the severity of depression assessed by the 24-item Hamilton Rating Scale for Depression (HAM-D) with a score of at least 20.²² The following exclusion criteria for patients were applied: comorbid Axis I or Axis II disorder or a personal history of bipolar disorder. NCs were required to be between 18 and 55 years of age, have a HAM-D score <7 and no current or history of psychiatric disorders. For both groups, additional exclusion criteria included substance abuse or dependence, neurological or internal illness, or any contraindication for MRI scans.

For each participant, the history of CM occurring before the participant reached 16 years old was evaluated with the Childhood Trauma Questionnaire (CTQ).^{23–25} The credibility and efficiency of this scale have been previously demonstrated.^{23–25} Twenty-five items were included in the questionnaire and classified into five subscales. Participants were identified as positive for CM (ie, moderate to severe CM) if their scores exceeded any one subscale cutoff (ie, emotional abuse more than 12, physical abuse more than 9, sexual abuse more than 7, emotional neglect more than 14, or physical neglect more than 9).²⁵ According to these criteria, we further divided all subjects into the following four groups: 51 MDD patients with a history of CM (MDD-CM), 31 MDD patients without a history of CM (MDD-nCM), 48 NCs with a history of CM (NC-CM), and 38 NCs without a history of CM (NC-nCM).

All participants gave both written and verbal informed consent. This study was approved by the Human Investigation Committees of the Zhumadian Psychiatry Hospital and the Second Xiangya Hospital, Central South University of China.

2.2 | Paroxetine administration

All subjects were scanned at baseline, and patients received a 6-month course of paroxetine treatment based on the judgment of the physician and the patient's consent. In the first week, patients received 10 mg paroxetine, which was the minimum dosing level for this study. In the second week, patients received 20 mg paroxetine or higher dose levels depending on illness symptoms, clinical antidepressant effects, and side effects. The maximum dose was 60 mg of paroxetine. Symptoms of depression were assessed using the HAMD every month for the following 6 months. In the sixth month, the patients received a second MRI scan. Of the initial 82 patients, one had excessive head motion, and five experienced manic onset during the 6-month study period. Therefore, data from 48 MDD-CM and 28 MDD-nCM participants were used for baseline analysis. During treatment, seven patients received electroconvulsive therapy or other antidepressant drugs depending on their depressive symptoms, and 29 patients did not continue participation. In all, 40 patients, including 24 MDD-CM and 16 MDD-nCM patients who received paroxetine treatment, finished 6 months of treatment and received a second MRI scan. A total of 18 NC-CM and 10 NC-nCM subjects returned for the second MRI. Of note, two patients received additional irregular transcranial magnetic stimulation therapy; one patient received this treatment once, and the other received it three times. Therefore, we also performed post hoc paired sample *t* tests in regions with significant treatment effects to assess whether the treatment effect remained significant after excluding these two individuals (see results in Appendix S1).

2.3 | MRI data acquisition

Participants in this study were scanned on a 3T GE scanner (Signa HDxT 3.0T). During the scan, foam padding and earbuds were used to limit head motion and attenuate scanner noise. Participants were required to keep still with their eyes closed. High-resolution structural images were collected using the following 3D magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted sequence: repetition time = 6.8 milliseconds, echo time = 2.5 milliseconds, flip angle = 7°, field of view = 256 × 256 mm², matrix = 256 × 256, thickness = 1 mm, voxel size = 1 × 1 × 1 mm³, slice = 256, and scan time = 6 minutes.

2.4 | Voxel-based morphometry analysis

Image preprocessing and GM volume calculations were performed using the VBM8 (<https://dbm.neuro.uni-jena.de/vbm/>) toolbox based on statistical parametric mapping software (SPM8, University College of London, London, UK. <https://www.fil.ion.ac.uk/spm>). Briefly, the

T1-weighted image of each participant at each time point was first corrected for image-intensity nonuniformity. The corrected images were then segmented into GM, white matter, and cerebrospinal fluid. Using the Diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL)²⁶ algorithm, these segmented tissue images were then spatially normalized to the customized template in the standardized anatomic space. DARTEL-based deformations were iteratively applied to the segmented tissue images to obtain a good alignment of GM morphology across the subjects. Subsequently, GM tissue images were normalized to the Montreal Neurological Institute space using DARTEL transformations, and the GM volume scale was acquired by Jacobian determinants. Finally, the normalized GM volume images were smoothed with a Gaussian filter of 8 mm full width at half maximum (FWHM).

2.5 | Statistical analysis

For the demographic and clinical data, two-way analysis of variance (ANOVA) was used to identify significant interactive or group effects (factor 1: MDD, factor 2: CM) for age, education, and CTQ scores among the four groups. Differences in gender were assessed using Pearson's chi-squared test. Moreover, differences in clinical information between the two patient groups were identified by two-sample *t* test.

To assess the differences in GM volume among the four groups at baseline, we performed two-way analysis of covariance (ANCOVA) (factor 1: MDD, factor 2: CM) and post hoc analyses with gender, age, and education as covariates in a voxelwise fashion. The MDD-by-CM interactive effect, main effect of MDD, and main effect of CM were estimated for each voxel. The significance level was set as the cluster-forming threshold of $P < 0.01$ with a Gaussian random field (GRF)-corrected $P < 0.05$ at the cluster level (To further strictly control for the risk of false positives and enhance spatial specificity, we applied two additional cluster-forming thresholds of $P < 0.001$ and $P < 0.005$. Moreover, given that there were no significant differences in demographic variables among the four groups, we reanalyzed data without adding covariates in the statistical model. Please see the relevant results in the Appendix S1). For each region with significant interactive or main effects, the mean GM volume was extracted, and partial correlations were used to investigate its relationship with clinical variables across all patients. Notably, partial correlations between the mean GM volume and CTQ were carried out in all individuals after controlling for gender, age, and education.

To investigate whether treatment had different effects on the two MDD groups, we performed the following statistical analyses, which were restricted to regions showing significant interactive or group effects at baseline. First, paired *t* tests were performed between the two time points in the NC group to exclude any regions with significant normal time-related changes. Then, repeated measurement ANCOVA and post hoc analyses were performed on longitudinal changes in GM volume in the two patient groups to determine the group by treatment interaction effect and the main effects of treatment (within-subject factor, after 6 months and at

TABLE 1 Sample characteristics

Baseline	MDD-CM (n = 48)	MDD-nCM (n = 28)	NC-CM (n = 48)	NC-nCM (n = 38)	Statistics
Age (y)	33.2 ± 8.7	36.1 ± 7.8	33.0 ± 7.8	33.8 ± 7.4	$F_{\text{inter}(1, 159)} = 0.630; P = 0.429^a$ $F_{\text{MDD}(1, 159)} = 0.882; P = 0.349^a$ $F_{\text{CM}(1, 159)} = 2.096; P = 0.155^a$
Gender (M/F)	20/28	12/16	24/24	19/19	$\chi^2_{(3)} = 1.021; P = 0.796^b$
Education (y)	10.7 ± 3.8	10.8 ± 4.2	11.0 ± 3.2	12.8 ± 3.7	$F_{\text{inter}(1, 159)} = 2.041; P = 0.142^a$ $F_{\text{MDD}(1, 159)} = 3.553; P = 0.061^a$ $F_{\text{CM}(1, 159)} = 2.854; P = 0.093^a$
CTQ	45.5 ± 10.3	31.9 ± 5.5	44.7 ± 9.0	30.2 ± 4.3	$F_{\text{inter}(1, 159)} = 0.008; P = 0.929^a$ $F_{\text{MDD}(1, 159)} = 0.377; P = 0.540^a$ $F_{\text{CM}(1, 159)} = 104.419; P < 0.001^{a*}$
Emotional abuse	1.8 ± 0.4	1.1 ± 0.3	1.8 ± 0.4	1.0 ± 0.0	$F_{\text{inter}(1, 159)} = 0.069; P = 0.793$ $F_{\text{MDD}(1, 159)} = 0.016; P = 0.900$ $F_{\text{CM}(1, 159)} = 151.433; P < 0.001^*$
Physical abuse	6.4 ± 2.2	5.4 ± 0.9	6.1 ± 1.8	5.5 ± 0.9	$F_{\text{inter}(1, 159)} = 0.271; P = 0.604$ $F_{\text{MDD}(1, 159)} = 0.338; P = 0.562$ $F_{\text{CM}(1, 159)} = 10.654; P = 0.001^*$
Sexual abuse	5.5 ± 1.3	5.1 ± 0.4	5.5 ± 1.5	5.2 ± 0.6	$F_{\text{inter}(1, 159)} = 0.005; P = 0.945$ $F_{\text{MDD}(1, 159)} = 0.119; P = 0.731$ $F_{\text{CM}(1, 159)} = 2.941; P = 0.088$
Emotional neglect	14.5 ± 5.6	7.8 ± 3.1	14.2 ± 4.3	7.3 ± 2.2	$F_{\text{inter}(1, 159)} = 0.023; P = 0.880$ $F_{\text{MDD}(1, 159)} = 0.027; P = 0.871$ $F_{\text{CM}(1, 159)} = 89.575; P < 0.001^*$
Physical neglect	11.0 ± 3.0	6.3 ± 1.5	11.1 ± 3.2	6.5 ± 1.6	$F_{\text{inter}(1, 159)} = 0.021; P = 0.885$ $F_{\text{MDD}(1, 159)} = 0.035; P = 0.853$ $F_{\text{CM}(1, 159)} = 109.106; P < 0.001^*$
Onset age (y)	30.1 ± 8.5	31.8 ± 7.5	NA	NA	$T_{(75)} = -0.855; P = 0.395^c$
Episodes (number)	2.0 ± 1.4	2.2 ± 1.4	NA	NA	$T_{(75)} = -0.523; P = 0.603^c$
Current illness duration (mo)	3.7 ± 3.5	3.3 ± 4.4	NA	NA	$T_{(75)} = 0.530; P = 0.598^c$
Total illness duration (mo)	39.6 ± 52.7	53.9 ± 55.8	NA	NA	$T_{(75)} = -1.114; P = 0.269^c$
HAMD	35.4 ± 7.2	31.2 ± 5.7	NA	NA	$T_{(75)} = 6.140; P = 0.015^{c*}$
Follow-up	MDD-CM (n = 24)	MDD-nCM (n = 16)	NC-CM (n = 18)	NC-nCM (n = 10)	
HAMD	5.13 ± 8.2	1.25 ± 2.2	NA	NA	$T_{(39)} = 1.849; P = 0.072$

Data are presented as the mean ± standard deviation (SD).

* $P < 0.05$.

^a P value obtained by two-way analysis of variance.

^b P value obtained by two-tailed Pearson's chi-square test.

^c P value obtained by independent-sample t test.

baseline) and CM (between-subject factor, with and without CM) using gender, age, and education as covariates. The significance level was set as the cluster-forming threshold of $P < 0.01$ with a GRF-corrected $P < 0.05$ at the cluster level. Moreover, for regions with significant interactive or main treatment effects, correlation analyses were performed to assess the relationships between changes in GM volume and changes in clinical variables during the 6-month treatment period in patients.

3 | RESULTS

3.1 | Demographic and clinical characteristics

The demographic and clinical characteristics of the study population are provided in Table 1. No significant differences were observed in gender, age, and education among the four groups (ie, MDD-CM, MDD-nCM, NC-CM, and NC-nCM) (all P -values > 0.61).

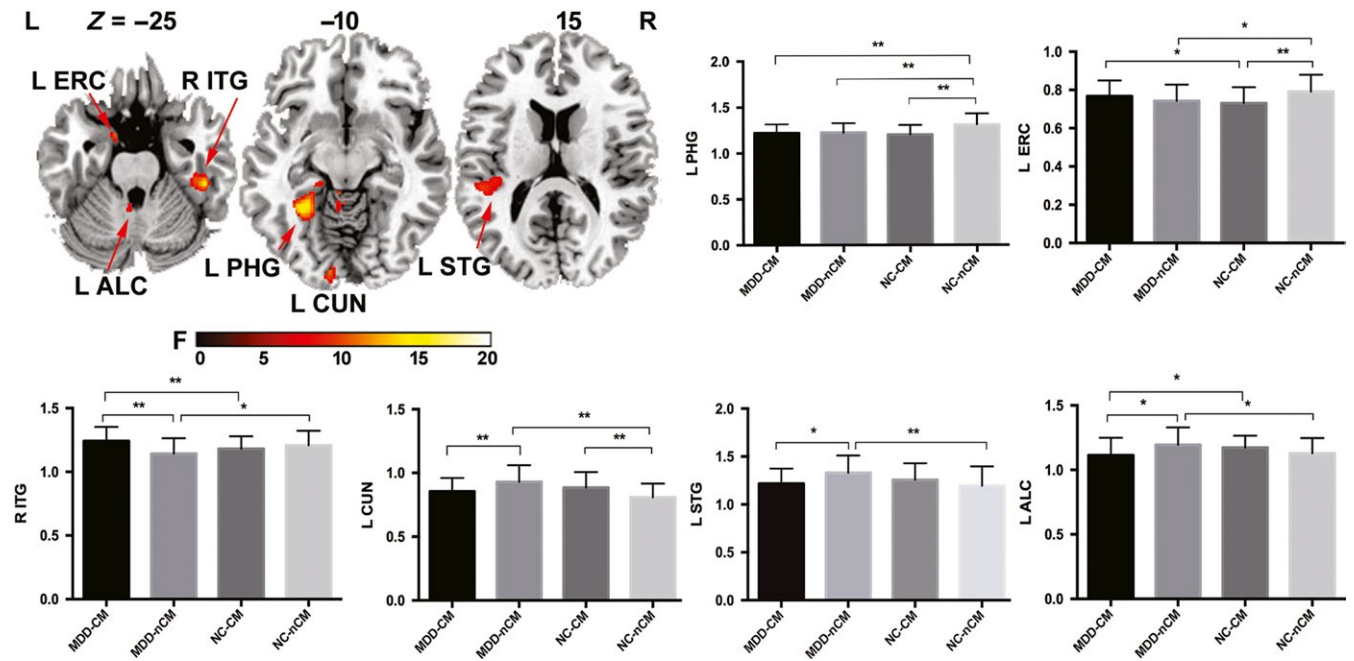


FIGURE 1 MDD-by-CM interactive effect on gray matter volume at baseline. Axial sections showing the regions with significant MDD-by-CM interactive effects on gray matter volume (corrected $P < 0.05$). L, left; R, right; PHG, parahippocampal gyrus; ERC, entorhinal cortex; ITG, inferior temporal gyrus; CUN, cuneus; STG, superior temporal gyrus; ALC, anterior lobe of the cerebellum

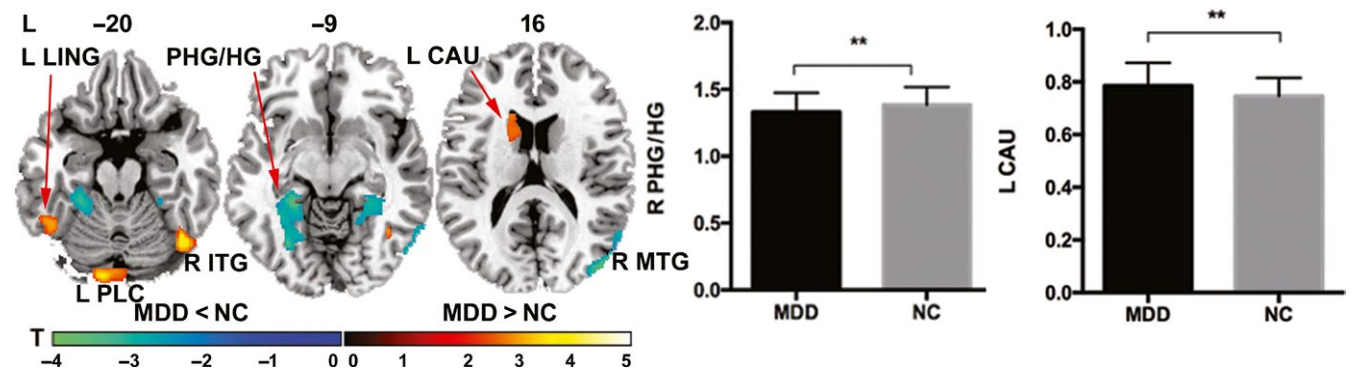


FIGURE 2 Main effect of MDD on gray matter volume at baseline. Axial sections showing the regions with a significant main effect of MDD on gray matter volume (corrected $P < 0.05$). The color map indicates the t values of post hoc analyses, with a warm color indicating a larger gray matter volume and a cold color indicating a smaller gray matter volume in MDD. L, left; R, right; PHG/HG, parahippocampal gyrus/hippocampus; MTG, middle temporal gyrus; CAU, caudate; PLC, posterior lobe of the cerebellum; ITG, inferior temporal gyrus; LING, lingual gyrus

Individuals with CM had significantly higher CTQ scores than did nCM individuals ($P < 0.001$). Moreover, HAMD scores were significantly higher in MDD-CM patients than in MDD-nCM patients at baseline ($P = 0.015$). No significant differences were found in the age of onset, number of episodes, current illness duration, or total illness duration between the two patient groups (all P -values > 0.269).

Both MDD groups had significantly lower HAMD scores (both P -values < 0.001) after the 6-month treatment period than at baseline. However, no significant group-by-time interaction effect or main effect of CM was found in HAMD scores between the two MDD groups (Table 1).

3.2 | Gray matter volume differences at baseline

At baseline, VBM analysis revealed a significant MDD-by-CM interactive effect on GM volumes in the left parahippocampal gyrus, left entorhinal cortex, right inferior temporal gyrus, left cuneus, left superior temporal gyrus, and left anterior lobe of the cerebellum. Post hoc analysis revealed differences in the patterns of alterations in GM volumes among the four groups. For instance, the GM volume of the left parahippocampus was not significantly different between the two MDD groups but was significantly smaller in the NC-CM group than in the NC-nCM group. The volume of the left cuneus was significantly smaller in the MDD-CM group than in the MDD-nCM

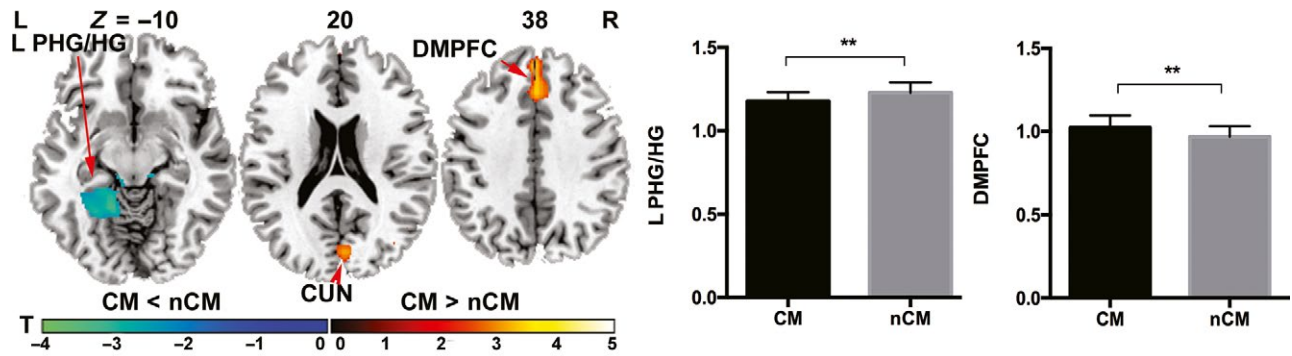


FIGURE 3 Main effect of CM on gray matter volume at baseline. Axial sections showing the regions with significant main effects of CM on gray matter volume (corrected $P < 0.05$). The color map indicates the t values of post hoc analyses, with a warm color indicating a larger gray matter volume and a cold color indicating a smaller gray matter volume in participants with CM than in participants without CM. L, left; R, right; PHG/HG, parahippocampal gyrus/hippocampus; DMPFC, dorsal medial prefrontal cortex; CUN, cuneus

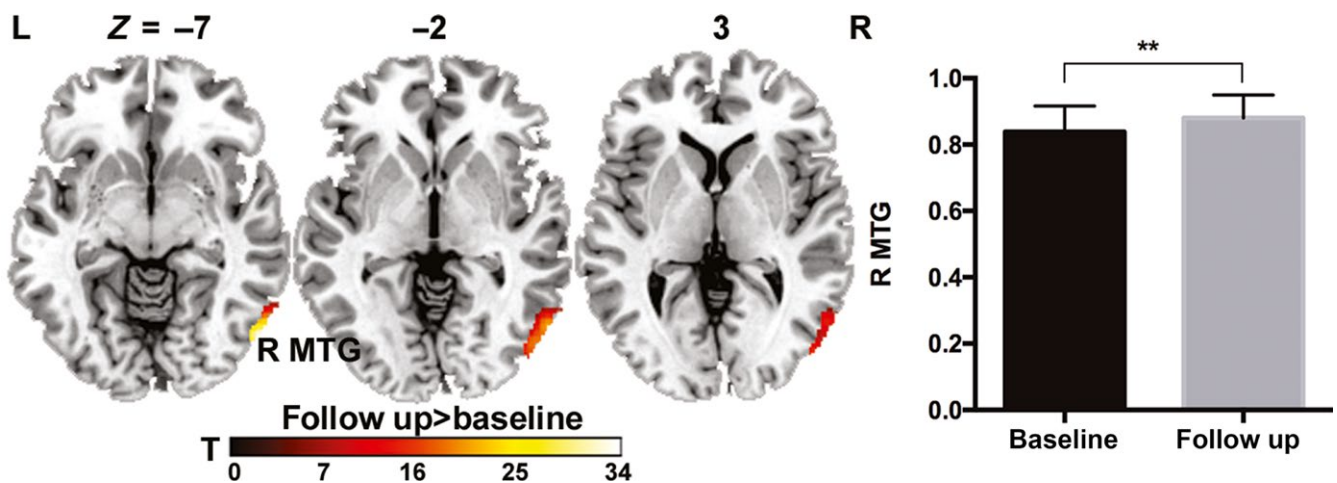


FIGURE 4 Treatment effect on gray matter volume in MDD patients. Axial sections showing the regions with significant treatment effects on gray matter volume in patients with MDD (corrected $P < 0.05$). The color map indicates the t values of post hoc analyses, with a warm color indicating higher gray matter volume after 6 mo of paroxetine treatment. L, left; R, right; MTG, middle temporal gyrus

group but significantly larger in the NC-CM group than in the NC-nCM group (Figure 1). Significant MDD-related effects were found in the bilateral parahippocampal gyrus/hippocampus and the right middle temporal gyrus (MDD<NC), left caudate, left posterior lobe of the cerebellum, right inferior temporal gyrus, and left lingual gyrus (MDD>NC; Figure 2). Significant CM effects were observed in the left parahippocampal gyrus/hippocampus (CM<nCM), dorsal medial prefrontal cortex (DMPFC) extending to the supplementary motor area (SMA) and cuneus (CM>nCM; Figure 3).

3.3 | Treatment effects on gray matter volume

We did not observe any significant treatment-by-CM interactive effects on GM volume. However, we found a significant treatment-related main effect in the right middle temporal gyrus in which GM volume was significantly higher in both MDD groups after 6 months of treatment with paroxetine. This result indicated that the effects of antidepressant

treatment on GM volume did not discriminate between MDD patients with and without CM (Figure 4). The cluster sizes, corrected P -values and other details of above reported clusters were showed in Table 2.

3.4 | Correlation between gray matter volume and clinical variables

At baseline, the GM volume of the right middle temporal gyrus was significantly and negatively correlated with HAMD scores ($R = -0.241$, $P = 0.040$) in all MDD patients when gender, age, and education were used as covariates. The GM volume of the left parahippocampal gyrus/hippocampus was significantly and negatively correlated with CTQ scores across all individuals ($R = -0.221$, $P = 0.005$) when gender, age, and education were used as covariates. Moreover, we found a significantly negative correlation between changes in GM volume in the right middle temporal gyrus and changes in HAMD scores in MDD patients ($R = -0.315$, $P = 0.048$; Figure 5). Additionally, we found a tendency

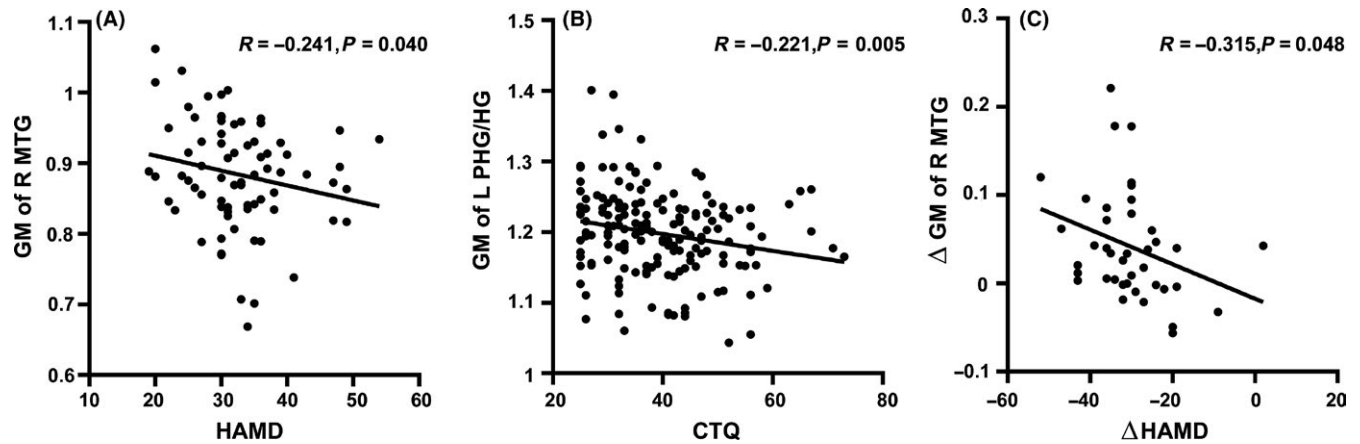


FIGURE 5 Correlations between gray matter volume and clinical variables. (A) Correlation between the adjusted gray matter volume of the right middle temporal gyrus and adjusted HAMD scores across all MDD patients at baseline when gender, age, and education were used as covariates. (B) Correlation between the adjusted gray matter volume of the left parahippocampal gyrus/hippocampus and adjusted CTQ across all participants at baseline when gender, age, and education were used as covariates. (C) Correlation between changes in the gray matter volume of the right middle temporal gyrus and changes in HAMD scores across all MDD patients

toward a positive correlation between the average daily dose of paroxetine and volume changes in the right middle temporal gyrus in MDD patients ($R = 0.326, P = 0.052$).

4 | DISCUSSION

In the current study, we found significant MDD-by-CM interactive effects on GM volume mainly in the left parahippocampal gyrus, entorhinal cortex, and right inferior temporal gyrus. The GM volumes of the right middle temporal gyrus and parahippocampal gyrus/hippocampus were significantly smaller in patients with MDD than in healthy controls at baseline. More importantly, a treatment-related increase in GM volume occurred in the right middle temporal gyrus in both MDD groups. Moreover, changes in GM volume of the region were correlated with changes in HAMD scores.

Our results demonstrate that the GM volume of the right middle temporal gyrus is smaller in MDD patients than in healthy controls at baseline. The middle temporal gyrus is suggested to participate in visual and auditory functions, which are crucial to the emotional processing of facial moods and working memory.²⁷ Dysfunctions in emotional regulation and cognitive function are widely reported in the pathophysiology of depression.²⁸ Moreover, the GM volume of this region increased after 6 months of paroxetine treatment, which is in agreement with previous studies focusing on antidepressant pharmacotherapy effects on GM volume in depressive patients.¹⁸ A possible reason that antidepressant drugs can reverse GM volume changes in depressive patients might be due to their capacity to alter synaptic plasticity and the expression of neurotrophic factors.²⁹ Selective serotonin reuptake inhibitors (SSRIs) exert effects on brain structures, including the temporal lobe, through the serotonergic system in MDD patients.³⁰ Moreover, the change in GM volume was significantly associated with the reversal of depressive symptoms.

In our results, MDD patients demonstrated increased GM volume of the middle temporal gyrus regardless of CM, indicating that the two groups of patients shared targets in GM volume during SSRI treatment. Hence, our study provides neurobiological evidence underlying the clinical observation that MDD patients with or without CM have the same outcomes when using antidepressant drugs.

Our results demonstrate that parahippocampal gyrus/hippocampus volume is smaller in MDD patients with CM, MDD patients without CM and healthy controls with CM than in controls without CM. The hippocampus is involved in regulating emotion that appears to be critical to the biological basis of MDD and has sensitivity to stress that occurs in childhood. The hippocampus is vulnerable to the neurotoxic effects of excessive glucocorticoid levels, which often indicate high levels underlying chronic stress³¹ and might explain the hippocampal atrophy often observed in individuals with CM.^{11,32} However, GM volume reduction in the hippocampus is frequently reported in patients with MDD.^{33–35} Recent studies have suggested that hippocampal volume reductions may result from CM but not MDD because a significant correlation between hippocampal volume and depression is lost when CM is considered as a covariant.^{13,16,35} Here, our results indicate that hippocampal atrophy is not largely due to CM in depression. Moreover, findings regarding whether an antidepressant drug can reverse hippocampal atrophy remain inconsistent. For instance, Vermetten et al showed that reduced hippocampal volume was reversed after 9–12 months of paroxetine treatment in 20 patients with posttraumatic stress disorder.³⁶ Some longitudinal studies suggest that hippocampal volume does not change after SSRI treatment in depression.^{37,38} We did not find during-treatment effects in the hippocampus in MDD patients with or without CM, providing experimental evidence that the volume of hippocampus has not reverse after SSRI treatment in depression. These varying results may be largely due to different treatment periods and patient heterogeneity. Long-term

TABLE 2 Brain regions showing significant effects

Brain Region	BA	Direction	x	y	z	F-value	Corrected P-value	Cluster size (mm ³)
Baseline MDD-by-CM interactive effect								
Left parahippocampal gyrus	NA	MDD-CM<NC-nCM MDD-nCM<NC-nCM NC-CM<NC-nCM	-28.5	-46.5	-12	15.67	7.7 × 10 ⁻⁵	2389.5
Left entorhinal cortex	34	MDD-CM>NC-CM MDD-nCM<NC-nCM NC-CM<NC-nCM	-15	-12	-33	13.61	9.9 × 10 ⁻⁵	2332.13
Right inferior temporal gyrus	20	MDD-CM>MDD-nCM MDD-CM>NC-CM MDD-nCM<NC-CM	46.5	-31.5	-21	15.90	0.007	1400.63
Left cuneus	17	MDD-CM<MDD-nCM MDD-nCM>NC-nCM NC-CM<NC-nCM	-7.5	-72	6	13.91	2.4 × 10 ⁻⁶	3263.63
Left superior temporal gyrus	22	MDD-CM<MDD-nCM MDD-nCM>NC-nCM	-51	-33	13.5	9.85	0.019	1204.88
Left anterior lobe of the cerebellum	NA	MDD-CM<MDD-nCM MDD-CM<NC-CM MDD-nCM>NC-nCM	-6	-49.5	-19.5	11.10	0.011	1316.25
Baseline MDD main effect								
Left parahippocampal gyrus/hippocampus	NA	MDD<NC	-24	-37.5	-10.5	14.22	1.1 × 10 ⁻⁷	4215.38
Right parahippocampal gyrus/hippocampus	NA	MDD<NC	31.5	-43.5	-13.5	9.92	0.026	1167.75
Right middle temporal gyrus	21	MDD<NC	60	-63	1.5	13.98	1.8 × 10 ⁻⁷	4083.75
Left caudate	NA	MDD>NC	-15	27	10.5	11.63	0.001	1852.88
Right inferior temporal gyrus	20	MDD>NC	43.5	-66	-19.5	16.35	0.016	1269.00
Left posterior lobe of the cerebellum	NA	MDD>NC	-52.5	-51	-25.5	12.37	0.004	1552.50
Left lingual gyrus	18	MDD>NC	-10.5	-88.5	-19.5	13.71	0.034	1117.13
Baseline CM main effect								
Left parahippocampal gyrus/hippocampus	NA	CM<nCM	-3	-45	6	15.73	6.9 × 10 ⁻⁸	4961.25
Dorsal medial prefrontal cortex	9/6	CM>nCM	-6	-3	61.5	20.39	2.8 × 10 ⁻¹⁰	6962.63
Right cuneus	17	CM>nCM	1.5	-78	9	10.08	0.032	1265.63
Treatment effect								
Right middle temporal gyrus	21	Follow-up>Baseline	54	-72	-9	34.62	0.002	3354.75

BA, Brodmann Area; MDD, major depressive disorder; CM, childhood maltreatment; NA, not available; NC, normal control.

antidepressant treatment more likely led to hippocampal volume changes than did short-term treatment.³⁹ MDD-by-CM interactive effects were also observed in the entorhinal cortex, inferior temporal gyrus, cuneus, superior temporal gyrus and so on. The entorhinal cortex and cuneus are involved in episodic memory,^{40,41}

and the inferior temporal gyrus is involved in semantic memory.⁴² Prior studies suggested that both MDD patients with and without CM demonstrated abnormalities in memory retrieval,⁴³ and our results might indicate a possible neurobiological mechanism for this functional reduction. MDD patients with CM showed a significantly

larger volume of the superior temporal gyrus than did MDD patients without CM. The superior temporal gyrus is involved in emotional processing, which is strongly associated with depression.⁴⁴ Similar to our results, Rottstädt et al revealed a larger GM volume of the superior temporal gyrus in MDD patients than in healthy controls.⁴⁵ Another study also found superior temporal gyrus volume abnormalities in MDD patients.⁴⁴ In addition, the posterior superior temporal gyrus is in the primary auditory cortex, which often shows impairment in individuals with CM, particularly those with parental verbal abuse.^{46,47}

Compared with participants without CM, participants with CM had larger GM volumes in the DMPFC and SMA. The DMPFC and SMA are involved in cognitive control, especially error monitoring.⁴⁸ Error detection might be a crucial capacity for maltreated individuals because mistakes can result in harsh punishment in an adverse environment.^{49–51} Thus, maltreated children often have a highly active error-monitoring system.⁴⁸ Similar to our study, another study found that the GM volumes of the DMPFC in maltreated participants were larger than those in nonmaltreated participants.¹⁶ The GM volumes of the caudate, posterior lobe of the cerebellum and left lingual gyrus in MDD patients were larger than those in healthy controls. The caudate, especially the ventral caudate, is involved in reward-related and emotion processing.⁵² The posterior lobe of the cerebellum and left lingual gyrus are also involved in cognitive and affective processes.⁹ Abnormal GM volumes of these brain regions have been previously reported in MDD patients.^{53,54} These results collectively suggest that abnormalities in brain circuits related to reward and emotion regulation underlie the clinical symptoms observed in patients with MDD.

4.1 | Limitations and further considerations

There are several issues that warrant further consideration. First, during the follow-up stage, we collected data from only part of the MDD patients at baseline, largely because of a large migration of workers in the countryside. However, there was no significant difference in the baseline HAMD scores ($P = 0.127$) between MDD patients with and without follow-up scans, indicating unbiased sampling in the follow-up data. Second, we found shared structural brain alterations during treatment in MDD patients with and without CM. A substantial amount of evidence has revealed significant changes in brain functional neuroimaging in patients with MDD after treatment compared to that at baseline. MDD patients with and without CM have shared or different treatment effects on functional brain characteristics that must be further studied. Finally, psychological therapy might be more effective than drug therapy in MDD patients with a history of CM.^{7,8} However, whether there are differences in neuroimaging-detectable changes between maltreated MDD patients treated with psychological therapy and those treated with antidepressant drug therapy remains to be explored.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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