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Smaller hippocampal tail volume is associated with plasma CCL11 levels in patients with major depressive disorder

Longhai Wu[1], Yilin Liu[1], Lingtao Kong[2], Xintong Yan[1], Yihui Lu[1], Xiaowei Jiang[3], Yifang Zhou[2], Qikun Sun[4] and Feng Wu[1]

[1]Department of Psychiatry, The First Hospital of China Medical University, Shenyang, China; [2]Department of Psychiatry, Shengjing Hospital of China Medical University, Shenyang, China; [3]Brain Function Research Section, Department of Radiology, The First Hospital of China Medical University, Shenyang, China and [4]Department of Radiation Oncology, The First Hospital of China Medical University, Shenyang, China

Original Article

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Corresponding Author:
Feng Wu;
Email: wufeng@cmu.edu.cn

Longhai Wu and Yilin Liu contributed equally to this work and share first authorship.

Abstract

Background. This study investigates structural abnormalities in hippocampal subfield volumes and shapes, and their association with plasma CC chemokines in individuals with major depressive disorder (MDD).

Methods. A total of 61 patients with MDD and 65 healthy controls (HC) were recruited. All participants underwent high-resolution T1-weighted imaging and provided blood samples for the detection of CC chemokines (CCL2, CCL7, and CCL11). Comparisons of hippocampal subregion volumes, surface shapes, and plasma CC chemokine concentrations were conducted between the MDD and HC groups. Furthermore, partial correlation analysis was performed to assess the relationship between structural abnormalities (hippocampal subfield volume and shape) and plasma CC chemokine levels.

Results. The MDD group exhibited a significant reduction in the volume of the left hippocampal tail compared to the HC group ($F = 9.750$, Bonferroni-corrected $p = 0.026$). No significant outward or inward deformation of the hippocampus was detected in MDD patients relative to the HC group (all FWE-corrected $p > 0.05$). Additionally, plasma CCL11 levels were elevated in the MDD group compared to the HC group ($F = 9.982$, $p = 0.002$), with these levels showing a positive correlation with the duration of the illness ($r = 0.279$, $p = 0.029$). Partial correlation analysis further revealed a negative correlation between the smaller left hippocampal tail volume and plasma CCL11 levels in MDD patients ($r = -0.416$, $p = 0.001$).

Conclusion. Abnormally elevated plasma CCL11 in MDD patients may mediate damage to specific hippocampal substructures.

Introduction

The hippocampus is an essential node in the prefrontal–hippocampal–amygdalar emotional processing circuit (Han et al., 2023; Yang & Wang, 2017). It is primarily involved in generating and regulating emotions and emotional memory (Lemke et al., 2022; Qasim, Mohan, Stein, & Jacobs, 2023; Rubin-Falcone et al., 2020). Some studies utilizing magnetic resonance imaging (MRI) have found that hippocampal structural abnormalities in patients with major depressive disorder (MDD) often occur in functionally specialized local structures rather than throughout the entire hippocampus (Roddy et al., 2019). For instance, compared to healthy controls (HC), patients with MDD exhibit significant volume reductions in the hippocampal Cornu Ammonis 1 (CA1) and subiculum subregions, which are significantly negatively correlated with life stressors (Alper et al., 2023). Notably, volume reductions in the hippocampal granule cell and molecular layer of the dentate gyrus (GC-ML-DG), as well as in the molecular layer, are associated with anhedonia (Wu et al., 2023). Longitudinal studies have shown that the reduced volumes of the hippocampus–amygdala transition area (HATA), CA4, and GC-ML-DG in MDD patients significantly increase following antidepressant or electroconvulsive therapy. Moreover, these subregions may serve as biomarkers for predicting the remission of depressive symptoms in response to treatment (Xu et al., 2023; Zhou et al., 2020). It has also been reported that a history of childhood maltreatment may be an important factor contributing to volume alterations in hippocampal substructures such as the anterior hippocampus and CA in MDD patients (Aghamohammadi-Sereshki et al., 2021). In addition, patients with MDD classically demonstrate shape changes in areas such as the CA and subiculum (Ho et al., 2022; Watanabe et al., 2017). The etiology of MDD-associated hippocampal structural irregularities is currently unknown, but it may be related to neuroinflammation arising from immune system dysfunction (Wu & Zhang, 2023).

Recently, multiple human trials have observed abnormally elevated levels of various CC chemokines (or β-chemokines) in the peripheral circulation of MDD patients (Gao et al., 2022;

Klaus et al., 2021). CC chemokines are small peptides belonging to one of the four major chemokine subfamilies (CXC, CC, CX3C, and XC), which can initiate the recruitment of immune cells to inflammatory areas (Lei et al., 2023; Miller & Mayo, 2017). According to studies on animal models, CC chemokines significantly influence the neuron–microglia crosstalk by activating C-C motif chemokine receptors (CCRs) on hippocampal neurons and microglia (Käufer et al., 2018; van der Meer, Ulrich, Gonźalez-Scarano, & Lavi, 2000; Zhang et al., 2016). For example, C-C motif chemokine ligand 2 (CCL2) has been demonstrated to activate the CCR2 on mouse hippocampal neurons and suppress neurogenesis in that region (Chen et al., 2023). Furthermore, increased concentrations of C-C motif chemokine ligand 7 (CCL7) in the hippocampal region of mice have been shown to cause deficits in spatial cognition (Tanabe et al., 2025). One study found that C-C motif chemokine ligand 11 (CCL11) acts on the CCR3 of hippocampal neurons, inducing dendritic spine loss in mouse hippocampal cultures (Zhu, Xu, Sun, Zhu, & Sui, 2017). Parajuli et al. confirmed that CCL11 activates CCR3 on microglia, promoting their migration and the production of reactive oxygen species, which leads to neuronal death (Parajuli, Horiuchi, Mizuno, Takeuchi, & Suzumura, 2015).

These studies suggest that CC chemokines may mediate inflammatory damage to hippocampal neurons in MDD, but there is no supporting evidence from human studies. Investigating the relationship between hippocampal structural alterations and CC chemokine levels in MDD patients can further elucidate the underlying neuroinflammatory mechanisms of hippocampal damage. The hippocampus is a heterogeneous structure comprising multiple structural and functional units, with each subfield characterized by distinct cellular components, tissue types, and neurophysiological properties (Ayhan et al., 2021; Cembrowski & Spruston, 2019). Consequently, the various subregions may exhibit differential sensitivities to inflammatory factors. It is more meaningful to explore the relationship between anomalies in specific hippocampal regions and CC chemokine levels.

In this study, we examined abnormalities in the subfield volume and surface morphology of hippocampus in patients with MDD to identify early and localized hippocampal structural variations. We also measured the plasma concentrations of three CC chemokines with a high affinity for CCRs on hippocampal neurons, namely CCL2, CCL7, and CCL11 (Shao et al., 2022; Tateyama et al., 2022; Zhu, Xu, Yuan, Ma, & Gao, 2023). Additionally, a partial correlation analysis was performed to assess the potential relationship between structural anomalies (including subfield volume and shape) and plasma CC chemokine levels in MDD. We hypothesize that MDD patients have regionally specific alterations in the hippocampus that are associated with the levels of CC chemokines in the plasma.

Methods

Participants

A group of 61 individuals with MDD was recruited from the First Hospital of China Medical University from 2019 to 2022. To match the MDD group, we enrolled 65 HC from the community, ensuring comparability in age and gender. All subjects were native Chinese speakers, right-handed, and their ages ranged from 18 to 45 years. In accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, trained evaluators conducted the Structured Clinical Interview for DSM-5 Disorders, Research Version (SCID-5-RV) with all participants to diagnose or exclude both current and historical psychiatric disorders. The 17-item Hamilton Depression Rating Scale (HAMD-17) was employed to measure the severity of depression. The cognitive function of all participants was assessed using the Chinese version of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB). The exclusion criteria encompassed the following: (a) current or past diagnoses of other DSM-5 disorders, including bipolar disorder, schizophrenia, personality disorders, or intellectual disabilities; (b) substance use disorders; (c) a history of neurological diseases; (d) a history of severe physical illnesses, such as hypertension, diabetes, or autoimmune diseases; and (e) a family history of mental illness in first-degree relatives of the HC subjects.

All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by the Medical Research Ethics Committee of the First Hospital of China Medical University (ethical approval numbers: [2012] 25–1). Written informed consent was obtained from all participants.

MRI scan

T1-weighted images for all participants were obtained using a three-dimensional Fast Spoiled Gradient Echo (3D-FSPGR) sequence on a Signa HDx 3.0 Tesla superconducting MRI scanner. The imaging parameters were configured as follows: a repetition time (TR) of 7.1 ms, an echo time (TE) of 3.2 ms, a flip angle of 13°, a field of view (FOV) measuring 240 mm × 240 mm, 176 slices with a thickness of 1 mm, voxel dimensions of 1.0 × 1.0 × 1.0 mm^3, a matrix size of 240 × 240, and a total scan duration of 8 minutes and 22 seconds.

Image preprocessing

The preprocessing of hippocampal subfield volumes was conducted utilizing the FreeSurfer software package, version 7.4.1 (http://surfer.nmr.mgh.harvard.edu/). The hippocampus was automatically segmented using the *recon-all* pipeline and the *segment amygdalo-hippocampal* command. This method utilized a statistical atlas constructed from two manually delineated datasets of hippocampal subfields and adjacent structures (ultra-high-resolution ex vivo MRI and T1-weighted in vivo images) to segment the hippocampus into 12 subregions within a Bayesian framework (Iglesias et al., 2015). These subregions were as follows: parasubiculum, presubiculum, subiculum, CA1, CA3, CA4, GC-ML-DG, HATA, fimbria, molecular layer, fissure, and hippocampal tail (Figure 1). Total volumes of the left and right hippocampus, volumes of each subregion, and estimated total intracranial volume (eTIV) were then extracted.

The preprocessing of hippocampal shape was performed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL), version 6.0.7 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). The FMRIB's Integrated Registration and Segmentation Tool (FIRST) performed automated segmentation of subcortical structures using deformable shape models. These models were derived from training data comprising 336 manually labeled T1-weighted MRI of subcortical structures, capturing the variability in shape and appearance of specific brain structures (Patenaude, Smith, Kennedy, & Jenkinson, 2011). During the segmentation process, the shape model was adapted to individual T1-weighted images through a Bayesian statistical approach, enabling the identification and quantification of subcortical structures. Ultimately, this process generated vertex meshes of the hippocampus in both hemispheres.

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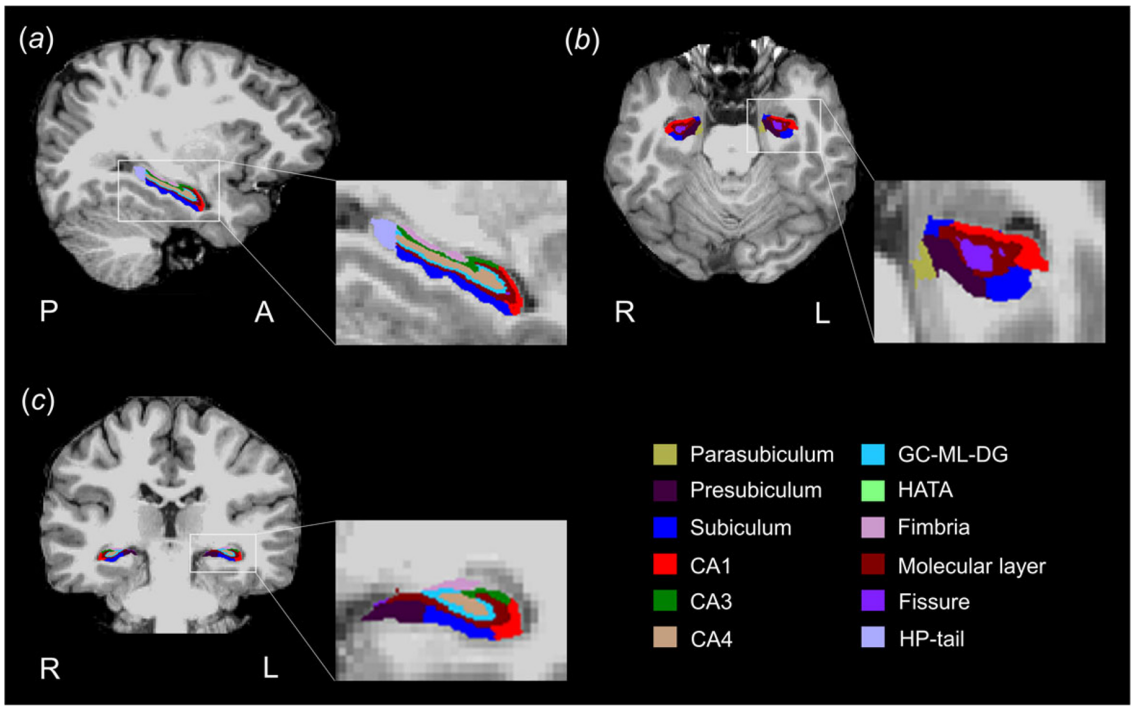

Figure 1. Subregions of hippocampus in one of the subjects. Twelve subfields were identified in the hippocampus. Panels (a), (b), and (c) correspond to the sagittal, axial, and coronal views, respectively. Note: CA, 'cornu ammonis'; GC-ML-DG, 'granule cell and molecular layer of the dentate gyrus'; HATA, 'hippocampal–amygdaloid transition area'; HP-tail, 'hippocampal tail'; A, 'anterior'; P, 'posterior'; L, 'left'; R, 'right'.

Two researchers independently assessed the quality of all images produced by FreeSurfer and FSL. Outliers were identified when the volume of subregions deviated by more than ±5 standard deviations from the mean. Additionally, the quality control process for hippocampal morphological analysis followed the FSL FIRST guidelines (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST/UserGuide/). Notably, no subjects were excluded from the analysis.

Measurements of CC chemokines

Peripheral blood samples (approximately 10 ml) were collected from all participants in the morning session. The samples were centrifuged at 2000 rpm for 10 minutes at −4 °C to isolate plasma, which was then stored at −80 °C until measurement. Plasma concentrations of CCL2, CCL7, and CCL11 were measured in duplicate with Luminex technology. Luminex technology is based on fluorescently coded microspheres, enabling the simultaneous detection and quantification of multiple cytokines. Cytokine detection for all subjects was conducted by two technicians in accordance with the manufacturer's instructions. Information regarding the subjects' groupings was kept confidential from the operators.

Statistical analysis

Data on demographics, clinical scales, CC chemokines, and hippocampal volumes were analyzed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). We used the Shapiro–Wilk test to check whether the data were normally distributed. Box plots were generated to identify outliers. Statistical differences in demographic and clinical characteristics between the two groups were assessed using the chi-square (χ^2) test, the independent samples *t*-test, or the Mann–Whitney *U* test. Differences among groups in hippocampal subfield volumes, plasma CC chemokine concentrations, and cognitive function scores were examined utilizing a multivariate general linear model (GLM). The Bonferroni correction method was applied for multiple comparisons in the analysis of hippocampal subfield volumes and cognitive function.

The morphological deviations of each subject's hippocampal surface were quantified using the *first_utils* vertex-wise analysis script. This approach calculates the perpendicular distance of each surface mesh vertex from the group average shape in Montreal Neurological Institute (MNI) space, representing local shape expansion or contraction. Group differences in hippocampal shape were assessed using a vertex-wise GLM. A directional (one-tailed) nonparametric permutation test, employing 10,000 permutations with demeaning, was conducted using FSL's *randomise* tool to assess statistical significance. To enhance sensitivity to spatially continuous effects while avoiding arbitrary threshold selection, the statistical significance of vertex-wise differences was evaluated using the threshold-free cluster enhancement (TFCE) method (Smith & Nichols, 2009). Family-wise error (FWE) correction was employed to control for multiple comparisons across the hippocampal surface (Winkler, Ridgway, Webster, Smith, & Nichols, 2014).

We also performed a partial correlation analysis to evaluate the relationship between alterations in structures (subfield volume and shape) and plasma CC chemokine levels. All statistical tests were two-tailed, except for the permutation test used in hippocampal shape analysis. All significance thresholds were set at $p < 0.05$.

Results

Demographic and clinical data of participants

The demographic and clinical data of participants in the MDD and HC groups are outlined in Table 1. The MDD group consisted of 61 participants, while the HC group included 65 individuals. There

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Table 1. Demographic, clinical characteristics, and plasma CC chemokine levels of the participants

Variables	MDD (n = 61) mean (SD)/n (%)	HC (n = 65) mean (SD)	$t/\chi^2/F$	p
Age (years)	25.69 (6.14)	24.38 (4.61)	−1.342	0.182
Gender (female/male)	40/21	43/22	0.050	0.945
BMI (kg/m^2)	22.19 (4.07)	21.97 (3.91)	−0.310	0.757
Education level (years)	15.38 (2.38)	16.17 (1.85)	2.100	**0.038**
Duration of illness (months)	17.68 (21.12)	NA		
HAMD–17 scores	20.70 (7.74)	1.32 (0.75)	−20.153	**<0.001**
eTIV (mm^3)	1419465.92 (205608.87)	1485061.58 (206489.57)	1.786	0.077
First-episode patients	42 (68.85%)	NA		
Medication cases	41 (67.21%)	NA		
Antidepressant cases	36 (59.02%)	NA		
Sedative-hypnotic cases	20 (32.79%)	NA		
CHM-treated cases	17 (27.87%)	NA		
CC chemokines (pg/ml)				
CCL2	108.89 (32.65)	111.78 (29.02)	0.409	0.523
CCL7	452.14 (156.62)	421.57 (133.27)	2.074	0.152
CCL11	126.92 (73.83)	88.35 (54.16)	9.982	**0.002**

Note: BMI, body mass index; CCL11, C-C motif chemokine ligand 11; CCL2, C-C motif chemokine ligand 2; CCL7, C-C motif chemokine ligand 7; CHM, Chinese herbal medicine; eTIV, estimated total intracranial volume; HAMD-17, 17-item Hamilton Rating Scale for Depression; HC, healthy controls; MDD, major depressive disorder; Medication cases, the number of patients receiving antidepressant treatment at the time of the MRI scan; n, number of subjects; SD, standard deviation; Values are expressed as mean (SD) or n (%).

were no significant differences in age ($t = -1.342$, $p = 0.182$), gender ($\chi^2 = 0.050$, $p = 0.945$), body mass index (BMI) ($t = -0.310$, $p = 0.757$), or eTIV ($t = 1.786$, $p = 0.077$) distribution between the MDD and HC groups. Significant differences were observed between participants with MDD and HC in terms of educational level ($t = 2.100$, $p = 0.038$) and HAMD-17 scores ($t = -20.153$, $p < 0.001$).

Among the 61 MDD patients, 42 individuals (68.85%) were experiencing their first depressive episode. Furthermore, at the time of the MRI scan, 41 patients (67.21%) were receiving pharmacological treatment. Specifically, 36 patients (59.02%) were administered antidepressant medications, 20 patients (32.79%) were prescribed sedative-hypnotic medications, and 17 patients (27.87%) were using traditional Chinese herbal therapies.

Hippocampal subregion volume analysis

The volumes of the entire hippocampus and its subregions are presented in Table 2. After adjusting for covariates including age, gender, education level, and eTIV, the MDD group demonstrated a significant reduction in the volume of the left hippocampal tail compared to the HC group ($F = 9.750$, Bonferroni-corrected $p = 0.026$). Additionally, there was an observed trend toward a reduced volume in the right hippocampus ($F = 4.383$, uncorrected $p = 0.038$) and the right fimbria ($F = 4.126$, uncorrected $p = 0.044$).

Hippocampal shape analysis

Shape analysis indicated no significant outward ($T = 1.982$, FWE-corrected $p = 0.562$) or inward ($T = 2.251$, FWE-corrected $p = 0.414$) deformation in the left hippocampus of patients with MDD compared to HC, after controlling for age, gender, and education level. Similarly, no significant outward ($T = 3.044$, FWE-corrected $p = 0.058$) or inward ($T = 2.014$, FWE-corrected $p = 0.560$) deformation was observed in the right hippocampus of MDD patients relative to HC.

Plasma CC chemokines analysis

After adjusting for covariates such as age, gender, and BMI, plasma CCL11 levels in the MDD group were higher than those in the HC group ($F = 9.982$, $p = 0.002$; Figure 2c). There was no significant difference in the plasma concentration of CCL2 ($F = 0.409$, $p = 0.523$; Figure 2a) or CCL7 ($F = 2.074$, $p = 0.152$; Figure 2b) between the MDD and HC groups (Table 1).

Correlation analysis

Pearson correlation analysis indicated that the volume of the left hippocampal tail in patients with MDD did not exhibit a significant correlation with either the duration of illness ($r = -0.068$, $p = 0.607$) or the HAMD-17 scores ($r = -0.006$, $p = 0.965$). Moreover, plasma CCL11 levels in the patient group correlated with the course of the disease ($r = 0.279$, $p = 0.029$; Figure 2d). However, there was no correlation between CCL11 concentration and HAMD-17 scores ($r = 0.083$, $p = 0.523$) in the MDD group.

A partial correlation analysis, adjusted for age, gender, BMI, education level, and eTIV, identified a significant negative correlation between the smaller left hippocampal tail volume and plasma CCL11 levels in MDD group ($r = -0.416$, $p = 0.001$; Figure 2e).

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Table 2. Comparison of hippocampal subregion volumes between patients with MDD and HC

Regions	MDD (n = 61) mean (SD)	HC (n = 65) mean (SD)	*F*	*p*	adjusted-*p*
Left hippocampus	3522.72 (273.39)	3656.55 (299.04)	3.679	0.057	0.741
Parasubiculum	65.48 (12.96)	67.87 (12.16)	0.169	0.681	1.000
Presubiculum	324.60 (37.35)	334.93 (36.80)	0.636	0.427	1.000
Subiculum	462.21 (41.91)	472.43 (44.11)	0.301	0.584	1.000
CA1	644.15 (74.78)	664.29 (41.91)	0.810	0.370	1.000
CA3	192.36 (24.65)	200.20 (25.85)	1.505	0.222	1.000
CA4	242.90 (20.65)	250.13 (25.18)	1.151	0.285	1.000
GC-ML-DG	287.15 (25.30)	295.23 (28.45)	0.862	0.355	1.000
HATA	54.16 (7.42)	57.23 (7.69)	2.751	0.100	1.000
Fimbria	95.38 (16.98)	99.17 (18.67)	0.247	0.620	1.000
Molecular layer	565.58 (49.50)	583.22 (49.12)	1.411	0.237	1.000
Fissure	136.47 (25.08)	142.26 (21.35)	1.596	0.209	1.000
HP-tail	588.74 (61.87)	631.82 (73.09)	9.750	**0.002**	**0.026**
Right hippocampus	3590.70 (230.99)	3727.70 (298.08)	4.383	**0.038**	0.494
Parasubiculum	60.61 (9.85)	64.36 (14.08)	0.784	0.378	1.000
Presubiculum	299.74 (31.20)	314.27 (41.44)	1.802	0.182	1.000
Subiculum	449.54 (44.24)	467.92 (45.06)	3.015	0.085	1.000
CA1	692.81 (58.13)	715.94 (68.82)	1.779	0.185	1.000
CA3	211.50 (22.29)	214.98 (27.79)	0.032	0.858	1.000
CA4	250.13 (19.15)	257.60 (24.31)	1.050	0.308	1.000
GC-ML-DG	294.15 (21.86)	304.20 (27.68)	1.850	0.176	1.000
HATA	57.07 (7.02)	58.38 (8.34)	0.365	0.547	1.000
Fimbria	91.39 (14.50)	99.12 (17.13)	4.126	**0.044**	0.572
Molecular layer	586.69 (39.64)	605.42 (49.00)	2.396	0.124	1.000
Fissure	146.31 (26.76)	146.96 (26.07)	0.007	0.935	1.000
HP-tail	597.08 (64.99)	625.50 (71.64)	3.822	0.053	0.689

Note: MDD, major depressive disorder; HC, healthy controls; n, number of subjects; SD, standard deviation; The volumes of the hippocampus and its subfields are presented as mean (SD) and measured in cubic millimeters (mm^3). CA, Cornu Ammonis; GC-ML-DG, granule cell and molecular layer of the dentate gyrus; HATA, hippocampal–amygdaloid transition area; HP-tail, hippocampal tail. Adjusted-*p* indicates the *p* value after Bonferroni correction.

By contrast, there was no correlation between the volume of the left hippocampal tail and CCL11 levels in the HC group ($r = 0.060$, $p = 0.650$).

Exploratory analysis

To further investigate the relationship between cognitive function levels and hippocampal structural abnormalities in patients with MDD, we evaluated cognitive function in both MDD patients and HC participants using the MCCB. A total of 55 MDD patients and 61 HC completed the cognitive assessments. Consequently, exploratory analyses were performed based on these data (Supplementary material, Part One). Initially, we performed a comparative analysis to examine the differences in the MCCB composite score and seven cognitive domains, which include nine subtests, between the two participant groups, as detailed in Supplementary Table S2. After controlling for age, gender, and education level as covariates, our findings indicated that individuals with MDD demonstrated significantly lower scores compared to the HC group. This was evident in the composite score ($F = 44.946$, Bonferroni-corrected $p < 0.010$), the Symbol Coding subtest within the speed of processing domain ($F = 15.566$, Bonferroni-corrected $p < 0.010$), reasoning and problem-solving ($F = 9.362$, Bonferroni-corrected $p = 0.030$), attention and vigilance ($F = 27.039$, Bonferroni-corrected $p < 0.010$), and social cognition ($F = 9.736$, Bonferroni-corrected $p = 0.020$). Subsequently, partial correlation analysis did not demonstrate a significant relationship between the left hippocampal tail volume and the four cognitive domains previously identified as significantly impaired in the MDD group (all $p > 0.05$).

Furthermore, to examine the impact of medication on hippocampal subfield volumes, shape, and plasma CCL11 levels in MDD patients, we conducted a comparative analysis between medicated and unmedicated subgroups (Supplementary material, Part Two). The analysis revealed no significant differences in hippocampal subfield volumes, shape, or plasma CCL11 levels between these two groups (all $p > 0.05$).

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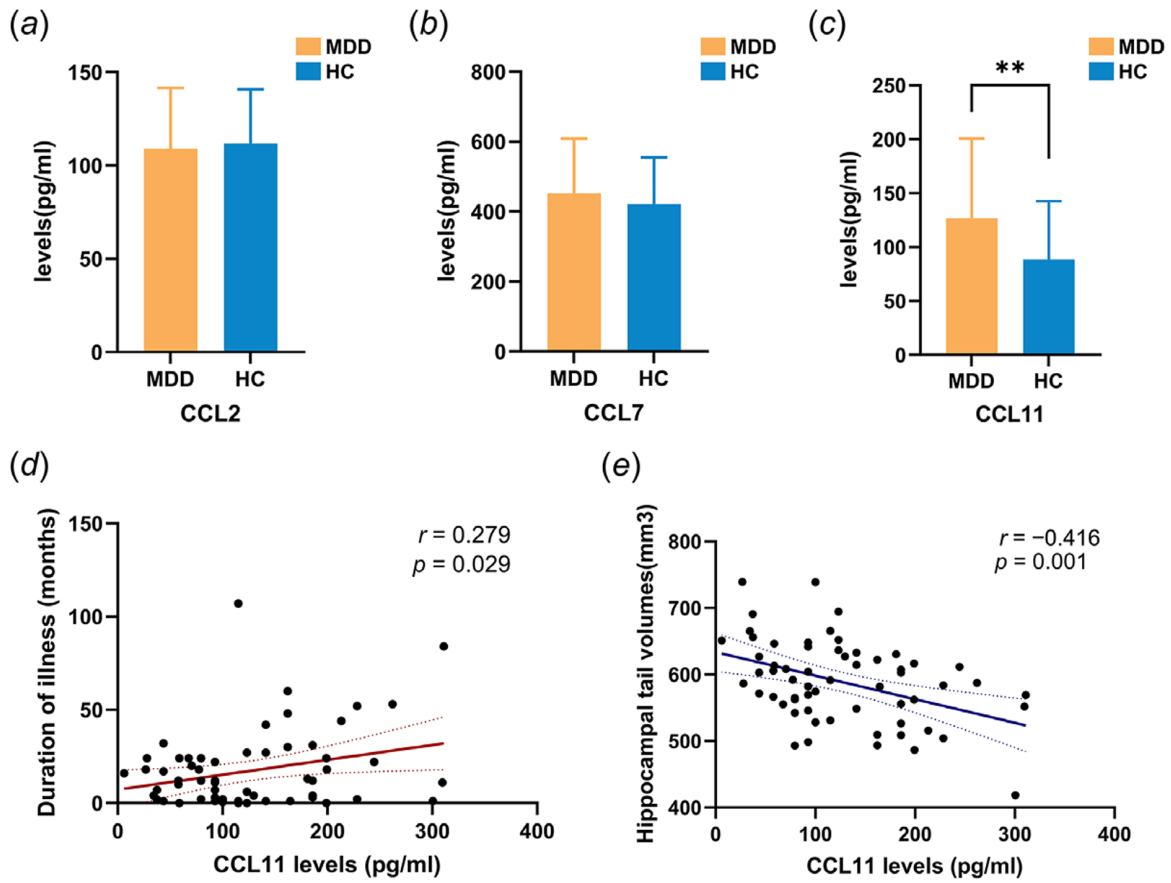

Figure 2. Plasma levels of different CC chemokines in participants and correlation analyses. (a) Comparison of CCL2. (b) Comparison of CCL7. (c) Comparison of CCL11. (d) Correlation between the durations of illness and plasma CCL11 levels. (e) The MDD group showed a significant negative correlation between plasma CCL11 levels and the left hippocampal tail volume. Note: CCL2, 'C-C motif chemokine ligand 2'; CCL7, 'C-C motif chemokine ligand 7'; CCL11, 'C-C motif chemokine ligand 11'.

Discussion

In this study, we found that patients with MDD exhibited a substantial reduction in the volume of the left hippocampal tail. Plasma CCL11 levels were higher in MDD patients compared with the HC group, and these elevated levels showed a positive correlation with the course of the disease. Most importantly, a negative correlation was found between the smaller volume of the left hippocampal tail and plasma CCL11 levels in MDD patients. To the best of our knowledge, this study is the first to identify a potential association between hippocampal tail volume and plasma CCL11 levels in patients with MDD.

Our initial findings suggest that the left hippocampal tail volume in MDD patients is decreased in comparison to HC. A prior study reported a similar decline in hippocampal tail volume among patients with MDD (Maller, Daskalakis, & Fitzgerald, 2007), noting that this change could be reversed by antidepressant treatment (Maller et al., 2018). Indeed, hippocampal tail volume has been considered a biomarker for predicting the response to antidepressant therapy (Nogovitsyn et al., 2020). This reduction may arise from dendritic retraction, diminished neurogenesis in the dentate gyrus, and glial cell loss (Chen et al., 2020; Wu & Zhang, 2023). We did not find significant differences in hippocampal surface shape between MDD patients and HC. Previous studies have reported morphological alterations in subcortical nuclei, including the hippocampus, in patients with MDD (Ho et al., 2022; Yao et al., 2020). Some evidence suggests that such morphological changes in the hippocampus may precede volumetric alterations, potentially serving as a more sensitive indicator of structural abnormalities (Bussy et al., 2021; Yao et al., 2020). The absence of significant findings may be attributable to sample heterogeneity.

Similarly, our results support the evidence that structural alterations in the hippocampus of patients with MDD often occur in specific subregions (Roddy et al., 2019). The hippocampus is a heterogeneous complex structure composed of multiple units (Cembrowski & Spruston, 2019); its functions can be mapped to anatomically and histologically defined substructures (Cembrowski et al., 2018). The hippocampus has extensive neural connections with regions such as the frontal lobe, amygdala, pallidum, and thalamus (Dillingham, Milczarek, Perry, & Vann, 2021; Kamali et al., 2023; Shikano, Ikegaya, & Sasaki, 2021), which form neural circuits including the prefrontal–hippocampal loop (Han et al., 2023), the hippocampal–amygdala loop (Terranova et al., 2022), and reward circuits (Miendlarzewska, Bavelier, & Schwartz, 2016). Reduction of hippocampal tail volume may disrupt the integrity of neural circuits involved in emotion regulation, leading to the pathological progression of depression. Research indicates that γ-aminobutyric acid levels are reduced in the prefrontal cortex of individuals with depression who also exhibit significantly reduced hippocampal volumes (Abdallah et al., 2015). This observation suggests that disruptions in the emotional regulation circuitry may influence the release of terminal neurotransmitters.

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Plasma concentrations of CCL2, CCL7, and CCL11 were compared between patients with MDD and HC. Of the three chemokines, only CCL11 showed a significant elevation in the MDD group, and its levels were positively correlated with illness duration. CCL11 is a multifunctional CC chemokine secreted by peripheral tissues and immune cells that has strong chemotactic activity for eosinophils (Suzuki et al., 2021). Prior studies similarly found substantially higher salivary concentrations of CCL11 in MDD patients compared with HC (Yui, Sasayama, Yamaguchi, & Washizuka, 2022); female MDD patients experiencing suicidal ideation demonstrated even higher levels of CCL11 (Grassi-Oliveira et al., 2012). We speculate that the disproportionate elevation of peripheral CCL11 in MDD patients may be a result of excessive activation of the immune system. The high levels of glucocorticoids (GCs) released during chronic stress can activate glucocorticoid receptors on immune cells to induce cell proliferation and chemokine release (Frank, Thompson, Watkins, & Maier, 2012; Shimba & Ikuta, 2020). While low to moderate concentrations of GCs suppress immune inflammation, prolonged exposure to high levels of GCs has been shown to enhance the production of multiple pro-inflammatory factors in hippocampal cultures (MacPherson, Dinkel, & Sapolsky, 2005).

Most importantly, a negative correlation was found between a smaller volume of the left hippocampal tail and elevated CCL11 in MDD patients. Prior reports have shown that CCL11 interacts with CCR3 on hippocampal neurons, resulting in the loss of dendritic spines (Zhu et al., 2017). CCR3 has been recognized as an important receptor for hippocampal neuronal damage (Duan et al., 2006; Zhu et al., 2017); and its activation can directly impair hippocampal function, decrease neurogenesis, and hasten hippocampal cell apoptosis. Likewise, Parajuli et al. confirmed that CCL11 can also activate CCR3 on microglia, thereby promoting their migration and reactive oxygen species production and ultimately resulting in neuronal death (Parajuli et al., 2015). Moreover, microglia activated via CCR3 have been shown to inhibit hippocampal neurogenesis by decreasing the proliferation of hippocampal neural stem cells, promoting apoptosis of neuronal progenitor cells, and reducing the survival rate of newly formed neurons (Innes, Pariante, & Borsini, 2019). Microglia, which play a pivotal role in inflammatory processes in the central nervous system, are widely distributed throughout hippocampal subregions (Jinno, Fleischer, Eckel, Schmidt, & Kosaka, 2007). Overactivation of hippocampal microglia can increase neuronal apoptosis and inhibit hippocampal neurogenesis (Fang et al., 2023; Moonen et al., 2023). The interactions between microglia and hippocampal neurons represent a potential pathway linking peripheral cytokine toxicity to central neuroinflammation (Guedes, Ferreira, Costa, Cardoso, & Peça, 2022). These findings suggest that CCR3-mediated hippocampal neurotoxicity may occur when high plasma CCL11 levels are present in MDD.

In vitro models have demonstrated that circulating CCL11 is capable of fully traversing the blood–brain barrier (BBB) (Erickson, Morofuji, Owen, & Banks, 2014). Furthermore, CCL11 has been shown to significantly downregulate the transcription and expression of tight junction proteins in endothelial cells (Jamaluddin et al., 2009). These studies provide biological evidence that peripheral circulating CCL11 is capable of entering brain parenchymal regions, such as the hippocampus, likely through its effects on the integrity of the BBB. In various human central nervous system pathophysiological processes, especially hippocampal damage caused by systemic immune-inflammatory diseases such as Alzheimer's disease (Yang et al., 2021), COVID-19 (Díez-Cirarda et al., 2023), and postoperative stress (Lin, Wang, Wang, Chen, & Gao, 2022), elevated peripheral CCL11 may serve as a critical intermediary. Given the current findings, we propose a preliminary hypothesis that elevated peripheral CCL11 might exert selective effects on the hippocampal tail region in MDD, possibly due to regional vascular differences or differential expression of CCR3 (Tatu & Vuillier, 2014). This remains to be tested in future multimodal and longitudinal studies.

Our exploratory analysis revealed cognitive impairments in four domains of the MCCB among patients with MDD, specifically in the areas of speed of processing, visual learning, reasoning and problem-solving, and attention and vigilance. These findings are consistent with those reported in numerous prior studies (Jin et al., 2020; Wang et al., 2024). Nevertheless, no correlations were identified between emotional symptoms or cognitive dysfunction and alterations in the volume of the hippocampal tail in MDD patient group. This suggests that emotional and cognitive impairments may be more dependent on abnormal functional coordination across multiple brain regions rather than localized structural changes within a single hippocampal subregion. For example, aberrant dynamic functional connectivity between the left rostral hippocampus and the cerebellum in MDD patients has been linked to working memory deficits (Shunkai et al., 2023). Therefore, future research should focus on examining the structure–function coupling between the hippocampus and other brain regions, such as the amygdala and prefrontal cortex, through the use of multimodal neuroimaging techniques.

Some studies have found volumetric or shape abnormalities in the CA, molecular layer, subiculum, and dentate gyrus regions of the hippocampus in patients with MDD (Ho et al., 2022; Watanabe et al., 2017). Additionally, increased plasma levels of CCL2 in these patients have been linked to heightened inflammatory responses (Köhler et al., 2018). These differences may arise from sample heterogeneity, including variations in illness severity, disease duration, medication histories, and etiological factors.

Limitations

Our study has several limitations. First, the study involved a relatively small number of participants, and the recruited patients were from a single institution. Second, as a cross-sectional study, we cannot establish a causal relationship between hippocampal structural changes and peripheral CC chemokines. Additionally, not all patients included in the study were first-episode, medication-naïve MDD patients, and the use of antidepressants further increased the heterogeneity within the group. While the subgroup analysis did not demonstrate significant differences in hippocampal subregion volume, shape, or plasma CCL11 levels between medicated and unmedicated MDD groups, the potential impact of medication on hippocampal structure and chemokine levels cannot be definitively excluded. Lastly, some studies suggest that CCL11 is age-dependent, with levels increasing with age (Ivanovska et al., 2020). Although we included age as an important confounding factor in our analysis, the participants were young individuals aged 18–45 years, and the relationship between peripheral CCL11 levels and hippocampal structures in elderly depressed patients requires further research.

Conclusions

We found that the smaller left hippocampal tail volume in the MDD group was negatively correlated with elevated plasma CCL11. Our study indicates that abnormally elevated plasma CCL11 in MDD

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patients may mediate damage to specific hippocampal substructures. The findings provide in vivo evidence supporting the identification of neuroinflammatory mechanisms underlying hippocampal damage in MDD patients.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291725101402.

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Author contribution. Feng Wu and Lingtao Kong designed the study, recruited the patients, confirmed the diagnosis, and acquired funding. Longhai Wu, Yilin Liu, Xintong Yan, Yihui Lu, Xiaowei Jiang, Qikun Sun, Lingtao Kong, and Yifang Zhou collected data. Longhai Wu and Yilin Liu designed the study, analyzed data, and wrote the manuscript. Xiaowei Jiang, Lingtao Kong, Yifang Zhou, and Feng Wu obtained funding and supervised the study. All authors contributed to manuscript revision, read, and approved the submitted version.

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