

# An Effect of Chronic Negative Stress on Hippocampal Structures and Functional Connectivity in Patients with Depressive Disorder

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**Purpose:** Depressive disorder is a mental health disorder with complicated etiopathogenesis. Environmental stress and neurodevelopment combined with other factors contribute to the occurrence of depression. Especially for the depressive disorder with chronic negative stress, it has characteristics of recurrence and poor curative effect because of unclear mechanism. Here, we investigated the hippocampal structures and functional connectivity (FC) according to resting-state functional magnetic resonance imaging in patients with depression who underwent chronic negative stress.

**Patients and Methods:** A total of 65 patients with depression (34 underwent chronic negative stress and 31 non-underwent chronic negative stress) and 30 healthy controls who did not undergo chronic negative stress were included in the study. The volumes of hippocampal subfields, seed-based FCs between hippocampus and the whole brain voxels, and ROI-wise-based FC between hippocampal subfields were compared among the three groups.

**Results:** In the patients with depression who underwent chronic negative stress, the volumes of right\_GC-ML-DG-head, right\_CA4-head and right\_CA3-head increased, FCs between Temporal\_Mid\_R, Precuneus\_R, Frontal\_Sup\_R, Temporal\_Sup\_R, Angular\_L, Frontal\_Inf\_Tri\_R, Supp\_Motor\_Area\_R, Precentral\_L and hippocampus increased, and FCs between parasubiculum and CA3, and presubiculum and CA1 decreased. When compared to the patients who did not undergo chronic negative stress, the patients who underwent chronic negative stress had larger volumes of right\_GC-ML-DG-head and right\_CA3-head, higher FCs between Frontal\_Sup\_R, Frontal\_Inf\_Tri\_R and hippocampus, and lower FCs between presubiculum and CA1.

**Conclusion:** The depression underwent chronic negative stress may experience disrupted hippocampal structures and functional connectivity. It may be one of potential depressive disorder subtypes.

**Keywords:** depressive disorder, chronic stress, hippocampus, functional connectivity

## Introduction

Major depressive disorder (MDD) is a common psychiatric disorder with persistent depressed mood, anhedonia, or hopelessness. MDD is often associated with impaired social function and even leads to suicide in severe cases.<sup>1</sup> Depression is the main cause of mental health related disease burden and disability internationally. In 2019, MDD affected 280 million people globally.<sup>2</sup>

The antidepressant medication treatment is the main therapy for treating depression, but the remission rate is barely satisfactory, especially when the patients are only treated with drugs. Only 1/3 of patients respond to the antidepressant medication, and often suffer from side effects, such as nausea, vomiting, sleep interruption, sedation, sexual dysfunction and weight gain induced by drugs. In addition, nearly 15–30% of patients may develop into treatment-resistant depression.<sup>3–5</sup>

The risk factors, including genetic, immune, and environmental factors, for the onset of depressive disorder are comprehensive, and life events have been found to be important causes for depression.<sup>6</sup> Studies showed that prolonged exposure to stress increased vulnerability to depression and other mood disorders, and led to memory disorder, cognitive disorder and even changes of the brain structure.<sup>7</sup> Life events affect the onset and symptoms of depressive disorder, and also prognosis and recurrence.<sup>8</sup> The positive correlation was found between negative life events and severity of depression.<sup>9</sup> A study examined five stress exposures on depression in 878 Afro-Caribbean women and found chronic stress was associated with increased risk for both recent (past week) and more distal (past-year and lifetime) major depressive episodes.<sup>10</sup> In a 10-year cohort study, negative life events was one of the predictors for vulnerable and chronic high-risk groups with depressive and posttraumatic stress disorder symptoms, which were more likely to experience poor quality of life in adulthood.<sup>11</sup> The research on first-episode MDD showed cumulative effects of adverse childhood experiences and negative life events were associated with suicidal behaviors, cognitive impairment and phenome features.<sup>12</sup> So the chronic negative stress may have strong effects on the clinical features of major depressive disorder. The MDD with chronic negative stress may be worth researching and using rather than the binary diagnosis of MDD based on the DSM-5 or ICD. However, objective evidence are still lacking to prove the differences between MDD with and without chronic negative stress.

Hippocampus may participate in cognitive and emotional regulation, and the current view is that the dorsal hippocampus is implicated in memory as well as cognition, and ventral hippocampus mediates the mood.<sup>13</sup> In addition, recent studies focused more on the changes of hippocampal subfields. A study extracted 12 hippocampal subfield volumes per hemisphere in 4174 participants, and showed larger right hippocampal fissure was associated with depressive symptoms, and larger bilateral hippocampal fissure, larger right molecular layer and smaller right cornu ammonis (CA)3 were associated with chronic depressive symptoms.<sup>14</sup> Except for hippocampal and the subfields volumes, recent studies also investigated the hippocampal functional abnormalities in MDD. According to seed-based analysis, weaker connectivity of the right hippocampal subregion to the temporal cortex (extending to the insula) and basal ganglia, enhanced connectivity of the right subiculum to the bilateral lingual gyrus were exhibited, and FC between the right CA1 and right fusiform, between the right hippocampal amygdala transition area and the bilateral basal ganglia, were negatively related with depression severity;<sup>15</sup> decreased FC between right hippocampus and bilateral medial superior frontal gyrus in MDD group.<sup>16</sup> According to ROI-wise-based analysis, the hippocampus-right angular gyrus FC had the highest predictive strength for the clinical remission induced by Ketamine in major depression.<sup>17</sup> The brain image evidence supported hippocampal structural and functional connectivity participated in the depressive disorder.

Adult hippocampal neurogenesis in human brain was demonstrated, and the environmental components, such as stress and life events, have significant impacts on adult hippocampal neurogenesis.<sup>18</sup> That becomes the research focus in the depression underwent stress, and also provided the new strategy for exploring the pathogenesis.<sup>19–21</sup> Chronic unpredictable restraint stress over 4 weeks for rat decreased total hippocampal volume, reflecting loss of volume in dorsal and ventral hippocampus,<sup>22</sup> reduced the length and volume of myelinated fibers in CA1 region and DG, and the rats showed depressive-like behaviors.<sup>23</sup> Volumetric analysis of the brain that underwent neonatal maternal separation in adult mice revealed that the left hippocampus was smaller, and the neuronal integrity of right hippocampus reduced.<sup>24</sup> In the chronic restraint stress-induced depression model, the volume of the hippocampal hilus decreased significantly.<sup>25</sup> In major depressive disorder patients, the whole brain analysis identified reduced hippocampal gray matter volume was a common feature of major depressive disorder patients, and the left hippocampal gray matter volume was also associated with stressful life events.<sup>26,27</sup> Another study investigated the differences of hippocampal subfield volumes using 7-Tesla MRI, and analyzed the association between life-stressor and hippocampal subfield volumes, found right-hemisphere CA2/3 subfield volume reduced in MDD patients, and left CA1, left CA4/DG, right subiculum total, left hippocampus total, and right hippocampus total were negatively associated with life-stressor checklist scores.<sup>28</sup>

In summary, the evidence above suggests hypotheses that depressive disorder underwent chronic negative stress, especially the life stress, may be one potential subtype of MDD, and hippocampus may participate in the the pathogenic process of depression in those who underwent chronic stress. However, there is little research evidence now to support this hypotheses in these patients, and the role of hippocampus is worth further discussion. In this study, patients with depression who underwent chronic stress were included, the features of structural, seed-based and ROI-wise-based functional connectivity of hippocampus and subfields were analyzed and screened.

## Materials and Methods

### Participants

#### Patients

Sixty-five first-onset patients with major depressive disorder were recruited from Hebei Provincial Mental Health Center of China during January, 2021 and October, 2022. The age of patients ranged from 18 to 45. The patients were right-handed and diagnosed using Diagnostic and Statistical Manual of Mental Disorders 5th edition by psychiatrists and met the criteria for major depressive disorder. The clinical symptoms were assessed using 17-item Hamilton Depression Rating Scale (HAMD-17), and the total score was  $\geq 17$ . All the patients never had manic or manic symptoms episode history. The patients were never treated with antidepressant therapy, hormones, antibiotics, or other drugs that affect the secretion and metabolism of immune and neurotransmitters before included in the study. All participants submitted written informed consent before conducting the study. Patients with other psychiatric disorders, serious neurological or medical disorders, receiving MECT or rTMS treatment, and MRI scan contraindication were excluded.

#### Health Controls

Thirty health controls were right handed and recruited from the community. The age, gender and education level were matched with patients. All the controls were screened to ensure the lifetime absence of psychiatric illness. The scores of HAMD-17 for controls were  $< 7$ . All of them submitted written informed consent. The controls with positive family history were excluded, and other exclusion criteria were the same with patients.

### Chronic Negative Stress Evaluation

We evaluated the chronic negative stress with Life Events Scale (LES).<sup>29</sup> It is a self reporting scale, with good reliability and validity, widely used in China. The LES measures the numbers and sensory stress of stressful life events the subjects have been exposed to. There are 48 items in the scale, including 3 dimensions. The subjects need to recall the life events occurred within at least one year, evaluate the nature (positive or negative) of the events, as well as the impact extent and duration on mental state. The impact extent is divided into 5 levels which ranges from 0 to 4 points. The duration ranges from 1 to 4 (1=within 3 months, 2= within 6 months, 3= within one year, 4=more than one year). The greater mental stress is indicated by higher scores of LES. Based on previous research, the negative life events have greater impact on physical and mental health, and the effects of the positive life events needs to be studied. The evidence also supported chronic stress may increase the risk of depression.<sup>30–33</sup>

Taking into account the feature of LES and the study evidence, the study focused on the effects of chronic negative life events. To assess the presence of chronic negative life stress, it should meet the standards as following: the participants reported more than one negative life stress, impact extent reached moderate and above (score $\geq 2$ ),<sup>33</sup> and the duration lasted more than 1 year (score=4).<sup>34</sup> The participants who could not meet the standards above simultaneously were regarded as not having undergone chronic negative life stress.

### fMRI Data Acquisition and Processing

fMRI data were collected by a 3.0T GE Signa scanner. The imaging sessions included structural T1 and a resting condition FC.

The structural T1 images were acquired with the following parameters: repetition time (TR)=6.7ms, echo time (TE)=2.7ms, flip angle(FA)=15°, field of view (FOV)=256mm×256mm, matrix=256×256, slice thickness=1mm, slices=200. The structural T1 images were conducted with FreeSurfer 7.3.2. FS 6.0 version, which was employed to perform the hippocampal subfields.<sup>35</sup> The volumes of the subfields, including parasubiculum, presubiculum, subiculum, cornu ammonis (CA1, CA3 and CA4), GC-ML-DG, molecular layer, HATA, fimbria, hippocampal fissure, hippocampal tail and whole hippocampus, were returned.

The resting-state functional images were acquired using the following parameters: TR=2000ms, TE=30ms, FA=90°, FOV=220mm×220mm, matrix=64×64, slice thickness=3mm, slices=35. The functional images data was conducted using the SPM12 software. The first five volumes were discarded. Scans with head motion of more than 3mm in the x, y, or z direction or 3° of any angular motion were excluded. The remaining images were normalized to a standard Montreal Neurological Institute (MNI) template, resampled into 3mm×3mm×3mm voxel size,

smoothed with 6mm×6mm×6mm full-width-at-half-maximum Gaussian kernel. Multiple regression models were employed to remove the effects of confounding factors, including white matter signals, cerebrospinal fluid signals, and 24 motion parameters. Finally, the images were temporally band-pass filtered at the range of 0.01Hz-0.08Hz.

## Functional Connectivity (FC) Analysis

For seed-based FC analysis, the bilateral hippocampus regions defined from Anatomical Automatic Labeling (AAL) atlas were selected as seeds. The correlation analysis was conducted between the seed regions and the whole brain voxels, and then the resulting  $r$  values were converted according to Fisher's  $r$ -to- $z$  transformation. For ROI-wise-based FC analysis, the average time series across all voxels of each hippocampal subregion was computed as a reference time course separately for each subject, and then the correlation coefficients were converted according to Fisher's  $r$ -to- $z$  transformation.

## Statistical Analysis

SPSS 22.0 software was used to analyze the demographic and clinical variable. The fMRI data were analyzed mainly on the Matlab and GraphPad Prism platform. ANCOVA was performed to access differences in volumes for hippocampal subfields among the patients with depression who underwent chronic stress, the patients with depression who did not undergo chronic stress and health controls while adjusting for the effects of age, gender and educational level. The findings were considered significant at  $P < 0.05$ , and then the significant results were analyzed with Fisher's LSD. Age, gender and education were modeled as covariates of no interests, and ANOVA was employed to compare the differences of seed-based FC among 3 groups, significant clusters were identified by using a Gaussian random field cluster level threshold of  $P < 0.05$  which corresponded to a voxel  $P < 0.001$  at corrected level with FWE, and the significant results were corrected using Bonferroni's multiple comparisons test. The values of ROI-wise-based FC were also compared among groups by ANOVA and results were considered significant at corrected  $P < 0.05$  (using Bonferroni's multiple comparisons test).

## Results

### Demographic and Clinical Characteristics

34 patients with depression who underwent chronic negative stress, 31 patients with depression who did not undergo chronic negative stress and 30 health controls were included in the study.

The age range for the subjects was 18–45. There were no significant differences in regard to age ( $F=0.06$ ,  $P=0.94$ ), gender ( $\chi^2=0.66$ ,  $P=0.72$ ), educational level ( $\chi^2=8.03$ ,  $P=0.09$ ), occupational status ( $\chi^2=4.33$ ,  $P=0.12$ ), marital status ( $\chi^2=2.79$ ,  $P=0.59$ ), residence ( $\chi^2=2.50$ ,  $P=0.29$ ), smoking history ( $\chi^2=0.35$ ,  $P=0.84$ ), and alcohol use ( $\chi^2=0.78$ ,  $P=0.68$ ) among the participants. The parenting-pattern ( $\chi^2=22.17$ ,  $P=0.001$ ) were significantly different among the 3 groups. Amid the depressive patients, coddling parenting, authoritative parenting and neglecting parenting patterns were more common than controls. The demographic data were presented in [Table 1](#).

All the patients had no somatic diseases nor positive family history of mental illness. The results for comparing the clinical features showed longer course ( $Z=-2.58$ ,  $P=0.01$ ), higher LES scores ( $t=2.48$ ,  $P=0.02$ ) in the patients with depression who underwent chronic negative stress. There was no significant difference in HAMD-17 scores ( $t=0.74$ ,  $P=0.46$ ), suicide behavior ( $\chi^2=1.88$ ,  $P=0.17$ ) or psychotic symptoms ( $\chi^2=1.15$ ,  $P=0.28$ ) between the two groups. The clinical data were showed in [Table 2](#).

### Hippocampal Subfields Analysis

Due to poor quality image, 1 participant was excluded in patients with depression who did not undergo chronic negative stress group. Thus, 94 subjects were included for hippocampal subfields analysis.

The volumes of right\_GC-ML-DG-head ( $F=3.27$ ,  $P=0.04$ ), right\_CA4-head ( $F=3.17$ ,  $P=0.047$ ) and right\_CA3-head ( $F=4.16$ ,  $P=0.02$ ) showed significant differences among the 3 groups ([Table 3](#)). According to Fisher's LSD analysis, the results supported that the volume of right\_GC-ML-DG-head increased in the patients with depression who underwent chronic negative stress compared with the patients who did not undergo chronic negative stress ( $P=0.03$ ) and controls ( $P=0.03$ ); the volume of right\_CA4-head are higher in the patients with depression who underwent chronic negative stress than controls ( $P=0.02$ ); and the

**Table 1** Comparison of Demographic Data Among the Patients with Depression Who Underwent Chronic Negative Stress, the Patients with Depression Who Did Not Undergo Chronic Negative Stress and Health Controls

Variables	Underwent chronic negative stress (n=34)	Non-underwent chronic negative stress (n=31)	Control (n=30)	$F/\chi^2$	P
<b>Age (<math>\bar{x} \pm s</math>)</b>	28.38±7.71	28.68±8.88	29.13±8.84	0.06	0.94
<b>Gender (n(%))</b>				0.66	0.72
Male	7 (20.6)	9 (29.0)	8 (26.7)		
Female	27 (79.4)	22 (71.0)	22 (73.3)		
<b>Education (n(%))</b>				8.03	0.09
Middle school and below	5 (14.7)	7 (22.6)	4 (13.3)		
Senior middle school	5 (14.7)	9 (29.0)	2 (6.7)		
University and above	24 (70.6)	15 (48.4)	24 (80.0)		
<b>Occupation (n(%))</b>				4.33	0.12
Unemployed	24 (70.6)	14 (45.2)	17 (56.7)		
Employed	10 (29.4)	17 (54.8)	13 (43.3)		
<b>Marital status (n(%))</b>				2.79	0.59
Unmarried	18 (52.9)	14 (45.2)	18 (60.0)		
Married	14 (41.2)	15 (48.4)	12 (40.0)		
Divorced	2 (5.9)	2 (6.5)	0		
<b>Residence (n(%))</b>				2.50	0.29
Town	16 (47.1)	17 (54.8)	20 (66.7)		
Rural area	18 (52.9)	14 (45.2)	10 (33.3)		
<b>Smoking (n(%))</b>				0.35	0.84
Yes	4 (11.8)	4 (12.9)	5 (16.7)		
No	30 (88.2)	27 (87.1)	25 (83.3)		
<b>Alcohol use (n(%))</b>				0.78	0.68
Yes	15 (44.1)	12 (38.7)			
No	19 (55.9)	19 (61.3)			
<b>Parenting-pattern (n(%))</b>				22.17	0.001
Coddling pattern	3 (8.8)	7 (22.6)	0 (0.0)		
Authoritative pattern	11 (32.4)	8 (25.8)	4 (13.3)		
Neglecting pattern	10 (29.4)	5 (16.1)	3 (10.0)		
Democratic pattern	10 (29.4)	11 (35.5)	23 (76.7)		

**Table 2** Comparison of Clinical Data Between the Patients with Depression Who Underwent Chronic Stress and the Patients with Depression Who Did Not Undergo Chronic Stress

Variables	Underwent chronic negative stress (n=34)	Non-underwent chronic negative stress (n=31)	$Z/t/\chi^2$	P
<b>Course (M(P25, P72))</b>	3(1.58,4.00)	1(0.58,2.66)	-2.58	0.01
<b>HAMD-17 scores (<math>\bar{x} \pm s</math>)</b>	24.82±4.94	23.84±5.77	0.74	0.46
<b>LES scores (<math>\bar{x} \pm s</math>)</b>	44.82±6.54	22.84±5.92	2.48	0.02
<b>Suicide behavior (n(%))</b>				
Yes	6 (17.6)	2 (6.5)	1.88	0.17
No	28 (82.3)	29 (93.5)		
<b>Psychotic symptoms (n(%))</b>				
Yes	5 (14.7)	2 (6.5)	1.15	0.28
No	29 (85.3)	29 (93.5)		

(Continued)

**Table 2** (Continued).

Variables	Underwent chronic negative stress (n=34)	Non-underwent chronic negative stress (n=31)	Z/t/ $\chi^2$	P
<b>Family history (n%)</b>				
Yes	0 (0)	(0)	–	–
No	34 (100)	31 (100)		
<b>Somatic illness (n%)</b>				
Yes	0 (0)	0 (0)	–	–
No	34 (100)	31 (100)		

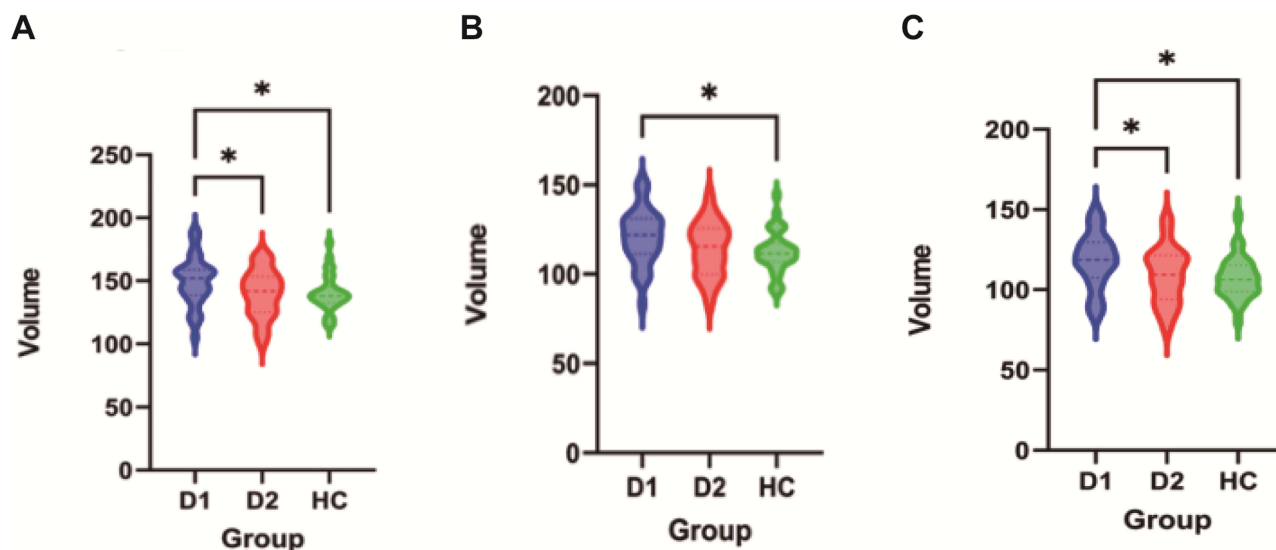
**Table 3** Comparison of Hippocampal Subfields Volumes Among the Patients with Depression Who Underwent Chronic Negative Stress, the Patients with Depression Who Did Not Undergo Chronic Negative Stress and Health Controls

ROI ( $\bar{x} \pm s$ )	Underwent chronic negative stress (n=34)	Non-underwent chronic negative stress (n=30)	Control (n=30)	F	P
right_GC-ML-DG-head	149.90±19.18	140.27±18.65	140.14±14.60	3.27	0.04
right_CA4-head	120.96±15.46	114.15±14.97	112.57±12.00	3.17	0.047
right_CA3-head	118.09±16.96	108.90±17.41	107.62±13.09	4.16	0.02

right\_CA3-head increased in the patients with depression who underwent chronic negative stress compared with the patients who did not undergo chronic negative stress ( $P=0.02$ ) and controls ( $P=0.01$ ) (Figure 1A–C).

## Functional Connectivity Results

ANOVA results of seed-based FC analysis revealed the significant differences for FCs between Temporal\_Mid\_R, Precuneus\_R, Frontal\_Sup\_R, Temporal\_Sup\_R, Angular\_L, Frontal\_Inf\_Tri\_R, Supp\_Motor\_Area\_R, Precentral\_L



**Figure 1** Comparison of hippocampal subfields volumes among the 3 groups. (A) The difference of volumes for right\_GC-ML-DG-head; (B) The difference of volumes for right\_CA4-head; (C) The difference of volumes for right\_CA3-head. D1: Patients with depression who underwent chronic negative stress, D2: Patients with depression did not undergo chronic negative stress, HC: Health controls. \* $P<0.05$ .

**Table 4** The Differences of Seed-Based FCs Between Hippocampus and Whole Brain Among the Patients with Depression Who Underwent Chronic Negative Stress, the Patients with Depression Did Not Undergo Chronic Negative Stress and Health Controls

Brain Regions	MNI			Cluster Size (mm <sup>3</sup> )	T Value
	X	Y	Z		
Temporal_Mid_R	51	3	-24	224	14.07
Precuneus_R	9	-63	24	598	16.75
Frontal_Sup_R	21	57	12	71	15.95
Temporal_Sup_R	57	-45	15	64	11.64
Angular_L	-54	-54	24	91	10.44
Frontal_Inf_Tri_R	51	21	27	175	14.16
Supp_Motor_Area_R	12	24	51	160	15.98
Precentral_L	-36	9	45	104	13.59

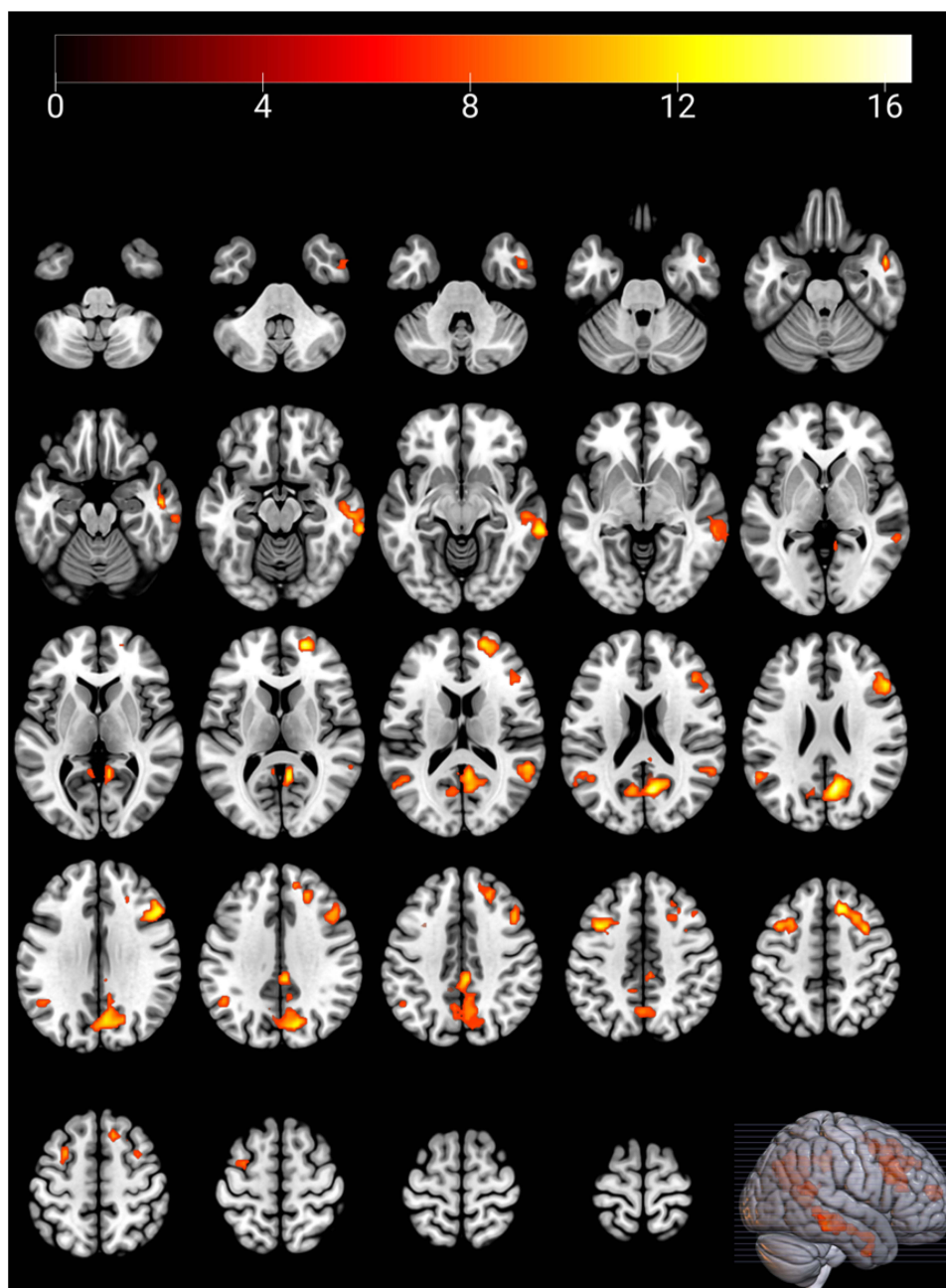
and bilateral hippocampus. There were no regions with decreased FC (Table 4, Figure 2). Bonferroni's multiple comparisons test showed increased FC between Frontal\_Sup\_R and hippocampus ( $P < 0.001$ ), as well as increased FC between Frontal\_Inf\_Tri\_R and hippocampus ( $P = 0.013$ ) in the patients with depression who underwent chronic negative stress compared to patients with depression who did not undergo chronic negative stress (Figure 3A–H).

The ROI-wise FC analysis showed significant differences for FCs from parasubiculum to CA3 ( $F = 3.58$ ,  $P = 0.03$ ), as well as presubiculum to CA1 ( $F = 5.74$ ,  $P = 0.005$ ) among the 3 groups (Figure 4). After Bonferroni's multiple comparisons test, the parasubiculum showed decreased FC with CA3 ( $P = 0.03$ ) in the patients with depression who underwent chronic negative stress compared to controls, and presubiculum showed lower FC with CA1 ( $P = 0.003$ ) in the patients with depression who underwent chronic negative stress than the patients with depression who did not undergo chronic negative stress (Figure 5A and B).

## Discussion

This study investigated the changes of hippocampal structure and functional connectivity in the patients with depression who underwent chronic negative stress. Compared with the depressive patients who did not undergo chronic negative stress and controls, the volumes of right\_GC-ML-DG-head, right\_CA4-head and the right\_CA3-head increased in the patients with depression who underwent chronic negative stress, FCs between Frontal\_Sup\_R, Frontal\_Inf\_Tri\_R and bilateral hippocampus increased, and FCs between parasubiculum and CA3, and presubiculum and CA1 decreased in the patients with depression who underwent chronic stress. The study results presents the characteristic changes of hippocampus exist in depressive disorder with chronic negative stress, which may be the potential subtype of MDD.

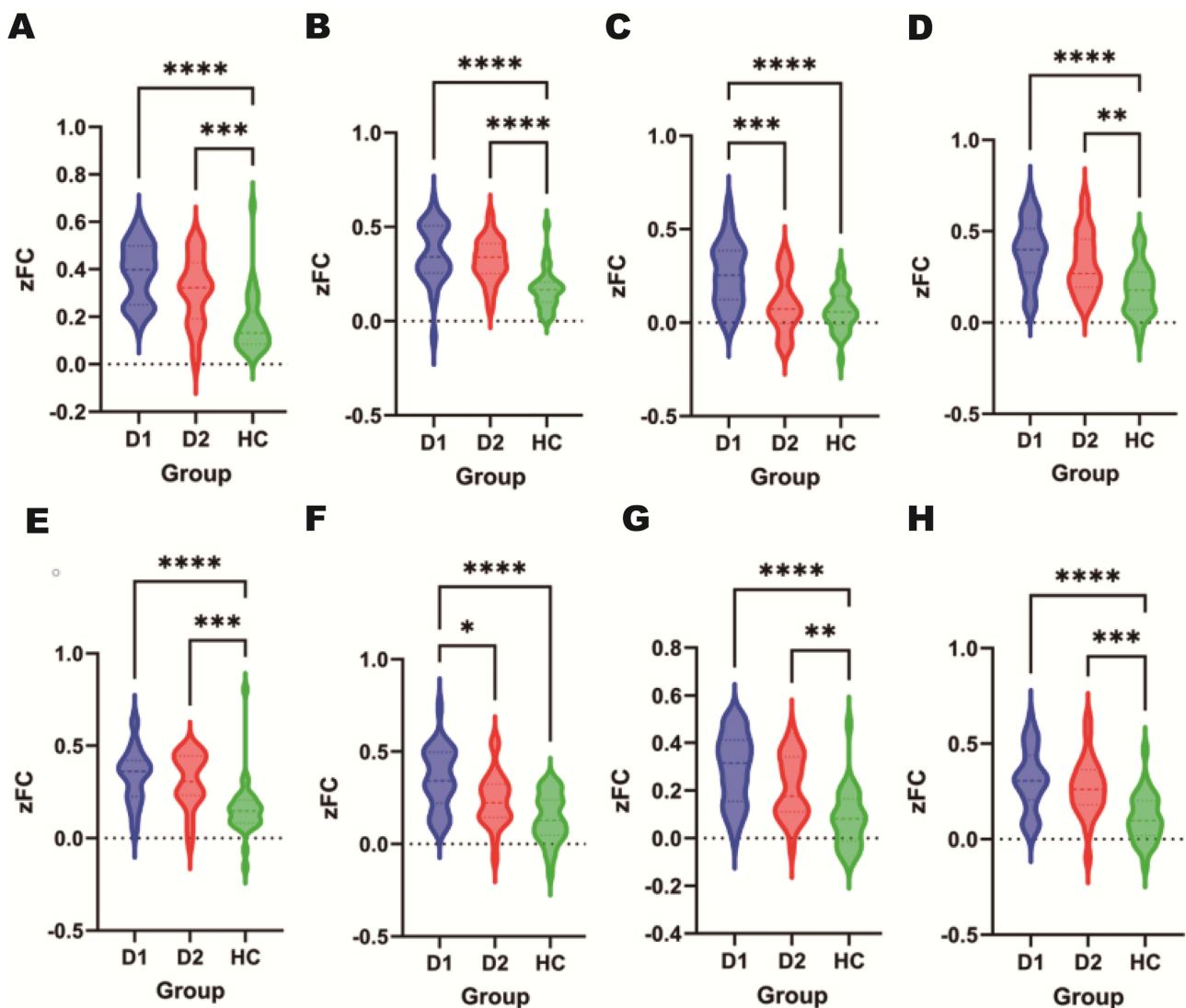
Considering the demographic and clinical characteristics of the depressive disorders, we analyzed the features in the depressive patients who underwent chronic negative stress. Our findings suggested that the parenting-pattern may be related to the onset of depression. Coddling parenting, authoritative parenting and neglecting parenting were more common in the depressive patients, and democratic pattern was more common in health controls. Previous studies also supported our findings, showing that stressful life events and maladaptive parenting patterns were correlated with depression.<sup>36,37</sup> But we failed to find the differences for the parenting-pattern between the patients who underwent chronic negative stress and those who did not. There were also a lack of positive evidence in the two groups. The scores of LES are higher in patients with depression who underwent chronic negative stress, indicating that these patients experienced more mental pressure. The study also showed longer illness course in depression with chronic negative stress. Sanwald S et al provided evidence that life stress was negatively associated with the age of depression onset, and positively associated with primary emotions,<sup>38</sup> which also partly supported the results of the study. A previous study of Goldstein BL et al predicted higher depression symptoms in patients with higher levels of stressful life events,<sup>39</sup> but our study did not find significant differences in scores of HAMD-17 between patients who underwent chronic negative stress



**Figure 2** Significantly different brain regions of seed-based functional connectivity between hippocampus and whole brain among the three groups. zFCs increased between hippocampus and the brain regions marked with color, and there were no regions with reduced FC. After FWE correction, the voxel  $P < 0.001$  and cluster  $P < 0.05$ .

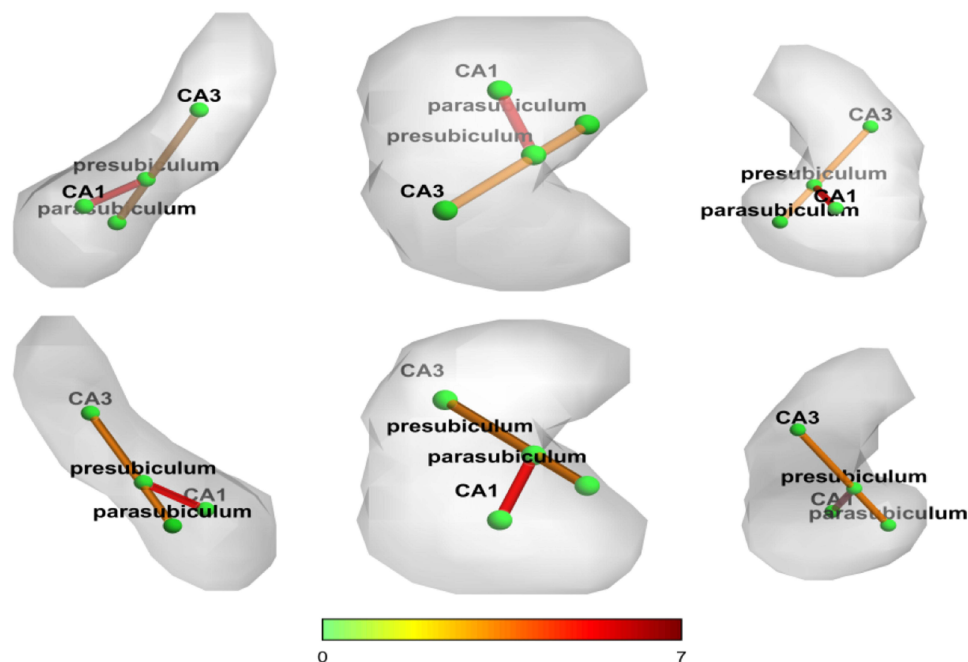
and those who did not. Because of the smaller sample size, we were not able to classify the severity levels in patients according to the scores of HAMD-17 and clarify the relationship between chronic negative stress and depressive symptoms. The review reported that exposure to traumatic events might develop post traumatic neuropsychiatric sequelae, such as posttraumatic stress, major depression, and increased suicidal risk.<sup>40</sup> However, this research could not find significant differences of suicide behavior between depressive patients who underwent chronic negative stress and those who did not. The relationship among chronic negative stress, depression and suicide may be complex, and the factors including stress types, depressive symptoms and severity may affect the final outcomes, therefore, all the variables need to be discussed in future studies.



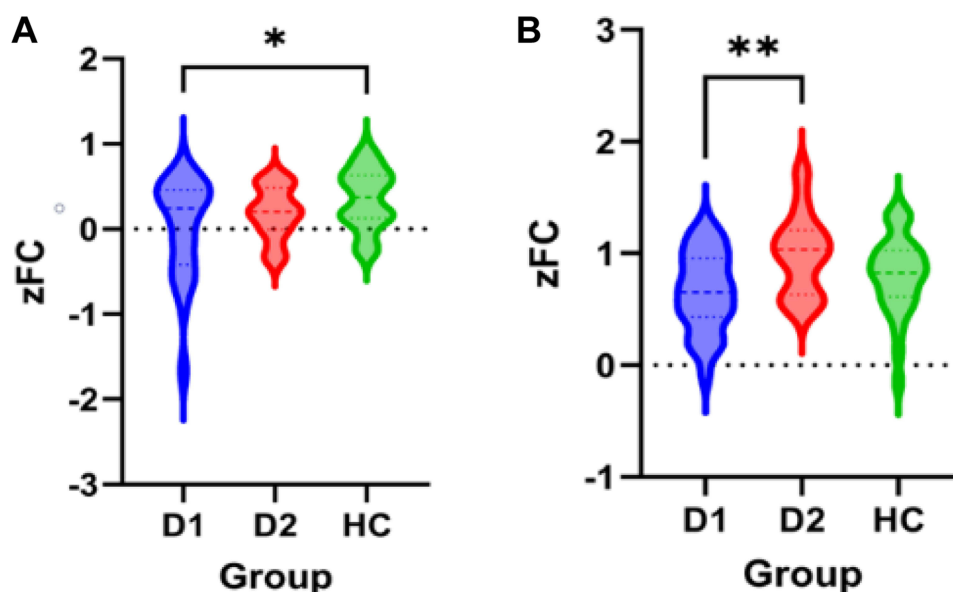


**Figure 3** Significantly different brain regions of seed-based functional connectivity between hippocampus and whole brain among the 3 groups. (A) The difference of zFC between Temporal\_Mid\_R and bilateral hippocampus; (B) The difference of zFC between Precuneus\_R and bilateral hippocampus; (C) The difference of zFC between Frontal\_Sup\_R and bilateral hippocampus; (D) The difference of zFC between Temporal\_Sup\_R and bilateral hippocampus; (E) The difference of zFC between Angular\_L and bilateral hippocampus; (F) The difference of zFC between Frontal\_Inf\_Tri\_R and bilateral hippocampus; (G) The difference of zFC between Supp\_Motor\_Area\_R and bilateral hippocampus; (H) The difference of zFC between Precentral\_L and bilateral hippocampus. D1: Patients with depression who underwent chronic negative stress, D2: Patients with depression did not undergo chronic negative stress, HC: Health controls. \*:  $P < 0.05$ , \*\*:  $P < 0.01$ , \*\*\*:  $P < 0.001$ , \*\*\*\*:  $P < 0.0001$ .

Hippocampus as a core region was studied in depressive disorder. An article in 2020 targeted on hippocampal volume changes reviewed 39 studies, 11 of which investigated hippocampal substructures. The results showed the left and right hippocampi were, respectively, 92% and 91.3% of the volume found in controls.<sup>41</sup> But these results did not show in other studies, neither did they find the hippocampal volume changes in depressive patients compared to controls.<sup>42,43</sup> It prompted that inconsistent conclusions might be related to the characteristics of subjects, such as depressive subtypes, exposing stress, therapy, severity level and so on. On the other hand, the volume changes may happen more in hippocampal subfields than in the whole hippocampus. In this study, the confounding factors were controlled as much as possible and focused more on the volume changes of hippocampal subfields. The volumes of right\_GC-ML-DG-head, right\_CA4-head and right\_CA3-head increased in patients with depression who underwent chronic negative stress compared to the controls. The volumes of right\_GC-ML-DG-head and right\_CA3-head in the patients with depression who underwent chronic negative stress increased compared to those who did not. Above results suggest that whether one undergoes chronic negative stress or not may potentially be depressive disorder subtypes. A study in 2019 also found that early stress exposure increased the volumes of



**Figure 4** Significantly different functional connectivity analysis of hippocampal subfields among the 3 groups. Statistically significant zFCs between hippocampal subregions marked with color.



**Figure 5** Significantly different functional connectivity among hippocampal subfields among the 3 groups. **(A)** The difference of zFC between parasubiculum and CA3; **(B)** The difference of zFC between presubiculum and CA1. D1: Patients with depression who underwent chronic negative stress, D2: Patients with depression did not undergo chronic negative stress, HC: Health controls. \*:  $P < 0.05$ , \*\*:  $P < 0.01$ .

hippocampus, in particular within the CA and DG,<sup>44</sup> and another study showed a trend for higher total hippocampal volume in subjects who experienced stressful life events, yet a trend for lower total hippocampal volume in those who reported childhood maltreatment.<sup>45</sup> These reports exposed the effects of stress on hippocampal volume which also was expounded in our study, but effects may differ according to varied stress types. The chronic negative stress was focused in our study, and may have the trend for a higher hippocampal subfields volumes rather than the total hippocampus. But it is necessary to clarify that increased hippocampal subfields volume does not mean the enhanced hippocampal function. Instead, it may cause functional problems,

such as displayed inflammatory cell infiltration, swelling, vacuolar degeneration and necrosis and shrinkage of the neurons in hippocampus.<sup>46,47</sup>

Stress may affect brain functional connectivity.<sup>48</sup> In healthy people, the left hippocampal connectivity with inferior parietal lobe was significantly correlated with chronic stress.<sup>49</sup> Chronic restraint stress (CRS) depression model in rats showed hyperconnectivity in right retrosplenial cortex, visual cortex, and inferior colliculus and in bilateral thalamus, superior colliculus, dentate gyrus, and CA3.<sup>50</sup> These revealed that chronic stress may have effects on functional connectivity in hippocampus and other brain regions. Recent studies also focused on the relationship between stress and hippocampal functional connectivity in depressive patients. One study assessed 34 first-episode, drug-naïve MDD patients with childhood trauma questionnaires and calculated the functional connectivity for ten hippocampal subregions, and found that functional connectivity alterations of CA1 were related to childhood trauma among the 34 patients.<sup>51</sup> Another study investigated the mediating role of hippocampal connectivity in early-life socioeconomic deprivation and symptoms of depression and anxiety in the participants aged 23–24. It reported negative relationship between early-life socioeconomic deprivation and depressive symptoms, and global connectivity of the right hippocampus.<sup>52</sup> In adolescents with MDD, connectivity between left hippocampus and bilateral orbital frontal cortex and right inferior temporal gyrus decreased, connectivity between left hippocampus and bilateral orbital frontal cortex was negatively correlated with the conflict scores of the Family Environment Scale, and it demonstrated that family environment contributed to MDD through hippocampal connectivity.<sup>53</sup> Hendrix CL et al exposed the relationship between stress and hippocampus prior to birth, completing a fetal resting-state functional MRI scan during second or third trimester of pregnancy for the pregnant mothers, and reported that self-reported distress of the pregnant mother positively correlated with the higher function between the hippocampus and right posterior parietal association cortex.<sup>54</sup> These prove that stress events in various stages of development of human, s and the hippocampal functional changes may contribute to the occurrence of depressive disorder. Because few evidences stated the relationship between chronic negative stress and hippocampal function in patients with depression, this study focused on exploring the correlation of chronic negative life events with hippocampal functional connectivity in first-episode depressive patients. Consensus view is that functional connectivity changes between the hippocampus and other brain regions. But the significant features may be different in depressive patients who underwent chronic negative stress. Compared to healthy control, FCs between hippocampus and Temporal\_Mid\_R, Precuneus\_R, Frontal\_Sup\_R, Temporal\_Sup\_R, Angular\_L, Frontal\_Inf\_Tri\_R, Supp\_Motor\_Area\_R and Precentral\_L increased in the depressive patients who underwent chronic negative stress, but increased FCs only occurred between hippocampus and Frontal\_Sup\_R and Frontal\_Inf\_Tri\_R compared to depressive patients who did not undergo chronic negative stress. These results also support our theory mentioned – whether one undergoes chronic negative stress or not may potentially be different depressive disorder subtypes. Current research also rarely investigates functional connectivity of hippocampal subfields in patients with depression who underwent chronic negative stress. A study showed FC of cornu ammonis 2, 3 and the dentate gyrus with bilateral caudate nucleus and precuneus was increased in chronic stress,<sup>55</sup> however there were only college students with moderate stress indicated by Student-Life Stress Inventory, and depressive subjects were not included. For trauma-exposed adults, the FCs between left hippocampal CA1, left DG, and the posterior cingulate cortex presented weaker positive.<sup>56</sup> Although there were no consistent results in current studies, it also supported that stress may affect the FC of hippocampal subfields. In our study, we focused more on the impact of chronic negative stress and found that FCs between parasubiculum and CA3, and presubiculum and CA1 decreased in depressive patients who underwent chronic negative stress. Maybe non-homogeneous research subjects, different types of stress, and so on contribute to the inconsistent results, and also may have brought different effects for the hippocampal functional connectivity.

In our study, it found the hippocampal structural and functional differences in depressive patients. Researchers promote both structural and functional change in regional and network plasticity of hippocampus potentially related to depressive disorder and antidepressant response.<sup>57</sup> New articles also discussed the relationship between structural and functional connectivity in MDD, and found lower coupling strength between structural and functional connectivity existed in adolescent MDD group,<sup>58</sup> and reduced decoupling of rostral anterior cingulate cortex with hippocampus and other extended task-specific regions during task performance in MDD participants.<sup>59</sup> So it clarified that both hippocampal structure and functional connectivity, even the coupling relationship between them contributed to the depressive pathogenesis. Meanwhile, the chronic negative stress may participate in the mechanism of the present results. There was a study that found three weeks of chronic restraint stress induced the changes in the density of dendritic spine shape subtypes in both CA1 and CA3 apical dendrites, suggesting a prolonged stressful challenge affected intrahippocampal connectivity.<sup>60</sup> Another study in chick's hippocampal complex indicated the different stressful

conditions may have different effects on hippocampus: the neurons undergo structural modifications when the stress achieved to a certain level; and repeated exposure to chronic stress lead to the neuronal structural disruption by retraction in the dendritic and axonal length, and decreasing in dendritic spines induced less synaptic connections.<sup>61</sup> So based on this evidence, we could speculate the chronic negative stress may also cause the disruption of microstructure of hippocampus and the subregions which may be the underlying mechanisms for differences of hippocampal volumes and functional connectivity in depressive patients. Certainly, there may be more complex pathologic processes for the depressive patients who underwent chronic negative stress. The research also supported atrophy of neurons and degradation of signal integrity in cortical and hippocampal regions implicated in depression induced by chronic stress related to elevated adrenal glucocorticoids and inflammatory cytokines as well as other factors.<sup>62</sup> We only illustrated the depressive disorder underwent chronic negative stress presented the differences in hippocampal volumes and functional connectivity, and prompted it may be the potential subtype in depressive disorder. However, the underlying mechanism needs further exploring from both microscopic and molecular perspectives.

Our study had several limitations. First, it was a cross-sectional study that only presented the relationship among chronic negative stress, hippocampus and depressive disorder, but could not ascertain the causality. Second, because of the difficulty of enrolling subjects, we failed to include the healthy controls who underwent chronic negative stress, and the number of subjects with suicide behaviour, psychotic symptoms, or positive family history was too small, we could not discuss the impact level of chronic negative stress on depression and its clinical features. Third, for the stress types, we focused on the chronic negative stress rather than early life stress, maybe we could explore the characteristic or additive effects of different types of stress next. Fourth, we analyzed the FCs with hippocampus as the seed, maybe we could investigate the FCs changes with other brain regions as seed in larger scale. In addition, a study presented the relationship among depression, lifestyle factors and the brain structures of depressive patients did not change after following up with 9 years,<sup>63</sup> which supported the course of the depressive disorder may have no impact on the brain structures to some extent. But it still cannot explain the course or other clinical features have no effects on hippocampal structures and functional connectivity, which remains to be considered in future study.

## Conclusion

Our findings offer preliminary evidence for impact of chronic negative stress on the hippocampal structures and functional connectivity in adults with depressive disorder diagnosis.

## Ethics Statement

This study had been approved by the Clinical Research Ethics Committee of Hebei Provincial Mental Health Center, China (NO.202213). Informed written consent was obtained from all the participants after detailed understanding of the research. It was compliant with the guidelines outlined in the Declaration of Helsinki.

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## Disclosure

The authors report no conflicts of interest in this work.

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