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Comparison of the chronic unpredictable mild stress and the maternal separation in mice postpartum depression modeling

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ABSTRACT

Postpartum depression (PPD) is a serious mental health concern of new mothers worldwide. In view of the particularity of puerpera, the research on pathogenesis and drug development of PPD are highly dependent on animal models. Although both maternal separation (MS) and chronic unpredictable mild stress (CUMS) modeling approaches have been used in PPD studies, the characteristics of the two rodent models have not been compared to explain which is more advantageous in PPD research. In this study, we applied 21-day MS and CUMS paradigms to induce mouse model of PPD and compared their differences in behavior, physiology and gut microbiota. As a result, the two models exhibited significant increases of immobility time in forced swim test (FST) and tail suspension test (TST), whereas sucrose preference index and pup weight were significantly decreased. Both displayed depression-like behaviors, and CUMS was more obvious, which demonstrated by the lower levels of 5-hydroxytryptamine (5-HT) and higher hypothalamic-pituitary-adrenal (HPA) axis related mRNA expression (corticotropin releasing hormone, corticotropin releasing hormone receptor 1) in CMUS group than that in MS group. The gut microbiota in MS and CUMS groups were significantly different in terms of the relative abundances of *Bacteroidetes, Firmicutes, Proteobacteria*. In conclusion, MS model and CUMS model have different performance in behavior and physiology. The CUMS model showed more obvious parameter changes, which may be more suitable for PPD induced by various social environmental factors.

1. Introduction

Postpartum depression (PPD) refers to the occurrence of depressive symptoms or depressing-like episodes in women during the puerperium, accompanied clinical features include low mood, depression, lack of confidence in life, and increased negative emotions [1]. As a common complication of childbearing, the incidence of PPD is approximate 13–19% of all mothers and reach the highest between weeks and one year after delivery [2,3]. Compared with other physiological stages, the hormone, neurotransmitter and metabolic levels in parturient are obviously different, which makes the etiology of PPD complicated and obviously different from pure depression [1]. Therefore, revealing the etiology and pathogenesis of PPD has become an urgent scientific issue for parturient and infant. At present, due to the speciality of parturient physical and mental state and the puerpera as a breastfeeding task, PPD studies was largely relied on the establishment of animal models, such as chronic unpredictable mild stress (CUMS), maternal separation (MS), postpartum continuous high levels of cortisol model, *etc* [4].

The etiology of PPD includes biological factors and psychosocial factors, among which psychosocial factors are the main aspects. Considering the etiology of clinical PPD, CUMS model [5–7] and MS model [8] are more appropriate to the occurrence of human PPD. Their stress influencing factors can simulate some causes and symptoms of depression patients more accurately. For PPD induced by a single social factor, MS model is developed to mimic the disruption or change in social relation-

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ships that often accompanies PPD in humans. For PPD induced by a variety of social environmental factors, CUMS model simulates the various pressures that postpartum mothers suffer from. The two models simulate different clinical causes, and the symptoms will be different. However, it is unclear which of the two models is more consistent with the clinical features. Therefore, a comprehensive evaluation of the behavioral and physiological indicators of the two models, so as to select the appropriate model, is worthy of further study.

In this study, long-term MS and CUMS were constructed and compared, so as to provide a basic data for model selection of PPD disease research.

2. Materials and methods

2.1. Animals

Newly delivered female BALB/C mice (30–38g) and their littermates were provided by Experimental Animal Center of Southern Medical University, Guangzhou, China (SCXK-Yue2016-0041). The mice were individually housed at room temperature (23 ± 2 °C) with 40 ± 5% humidity and a 12 h light/dark cycle (lights on: 6:00–18:00). All animals were provided free access to food and water. All experiments were performed according to the Regulations on the Administration of Experimental Animals of Southern Medical University, Laboratory Animal Guideline for Ethical Review of Animal Welfare (GB/T 35892-2018) and Laboratory Animal Requirements of Environment and Housing Facilities (GB 14925-2010) and were approved by the Animal Ethics Committee of School of Southern Medical University on October 22, 2021.

2.2. MS and CUMS modeling

Dams were randomly assigned to a MS model (n = 8), a CUMS model (n = 8) and a control group (n = 8). The day of delivery was appointed as postpartum day 0. After this, dams were left undisturbed in the colony room till postpartum day 2.

The operation of MS model was to separate the dams from their pups for 6 h daily (08:30 to 11:30 and 14:30 to 17:30) from postpartum day 2–21 [9–11]. Each dam was moved separately to a cage with the same living conditions.

The operation of CUMS model was to randomly give one of the following stress between 8:00 and 12:00 in the morning from postpartum day 2–21: (1) Swimming with ice water (4 °C) for 5 min; (2) Fasting for 24 h; (3) prohibit water for 24 h; (4) Restriction stress for 2 h; (5) High platform stress for 30 min; (6) Tail clamping stress for 5 min; (7) Tail suspension stress for 5 min [12,13].

2.3. wt of dams and pups

The dams and their pups were weighed on postpartum day 1, 7, 14, 21 and 25 after delivery, respectively. The weight of dams in each group and the total weight of pups were recorded, and the weight trend chart was drawn.

2.4. Behavioral tests

Behavioral tests including maternal behavior, elevated-plus maze test (EPMT), tail suspension test (TST), sucrose preference test (SPT) and forced swimming test (FST), were performed in accordance with procedures described previously [4,7,14–16] with minor modifications. Analyses were performed in a manner with blinded treatment assignments in all behavioral experiments.

2.5. Quantitative RT-PCR

Total RNA was extracted from tissues homogenized in Trizol (Foregene, Chengdu, China). Purified RNA was used for RT-PCR to generate cDNA with a cDNA Reverse Transcription Kit (AG, Hunan, China), and the resulting cDNA was used for quantitative PCR. Quantitative real-time PCR (qPCR) was performed using a Roche LightCycler480IIreal-time PCR. The relative mRNA expression level was determined with the $2^{-\Delta\Delta Ct}$ method with *Gapdh* as the internal reference control. All premiers used in RT-qPCR were presented in Supplementary Table 1.

2.6. Immunohistochemistry

Brain tissue was cut in half in sagittal form and postfixed with 4% paraformaldehyde. Immunostaining was performed on 4-μm-thick sagittal brain sections obtained with a pathology slicer (Shanghai Leica Instrument Co., Ltd). The sections were incubated with brain-derived neurotrophic factor (BDNF) primary antibody (Affinity Biosciences, DF6387) at 1:100 and second antibody using a broad-spectrum SP immunohistochemical kit (Bioss, Beijing, China, SP-0022). Images were acquired using Olympus positive position microscope.

2.7. Enzyme-linked immunosorbent assay (ELISA)

The interleukin (IL)-6 level of the cortical tissue homogenate was tested with ELISA kit (purchased from 4A Biotech Co., Ltd). The estradiol (E2), progesterone (P), prolactin (PRL) levels of the plasma and the 5-hydroxytryptamine (5-HT), dopamine (DA) levels of the cortical tissue homogenate were tested with ELISA kits (Quanzhou Ruixin Biological Technology Co., LTD Quanzhou, China).

2.8. 16S rDNA sequencing

PCR amplification targeted the V3–V4 [17] region of the 16s rDNA. The 5′ ends of the primers were tagged with specific barcods per sample and sequencing universal primers. The PCR products were purified by AMPure XT beads (Beckman Coulter Genomics, Danvers, MA, USA) and quantified by Qubit (Invitrogen, USA). The amplicon pools were prepared for sequencing and the size and quantity of the amplicon library were assessed on Agilent 2100 Bioanalyzer (Agilent, USA) and with the Library Quantification Kit for Illumina (Kapa Biosciences, Woburn, MA, USA), respectively. The libraries were sequenced on NovaSeq PE250 platform.

2.9. Statistical analysis

All data except 16S rDNA sequencing, presented as mean SEM, were calculated and demonstrated using the statistical software GraphPad-Prism8.3.0 (San Diego, USA). Images were quantified using the Image Pro Plus software. One-way or two-way analysis of variance (ANOVA) and Dunnett's post hoc test for multiple comparisons was applied to compare the behavioral test results, and to establish statistically significant differences.

3. Results

3.1. Comparisons of behaviors between MS model and CUMS model

First, we investigated the weight changes of pups and dams. On the postpartum 25, the pups average weight of stress model showed significantly reduced and CUMS model reduced more obviously (Fig. 1B). The ratio analysis of the weight of dams on day 25 and day 1 showed that there was no significant difference in the weight ratio of dams in each group, and the ratio was less than 1 (Fig. 1C).

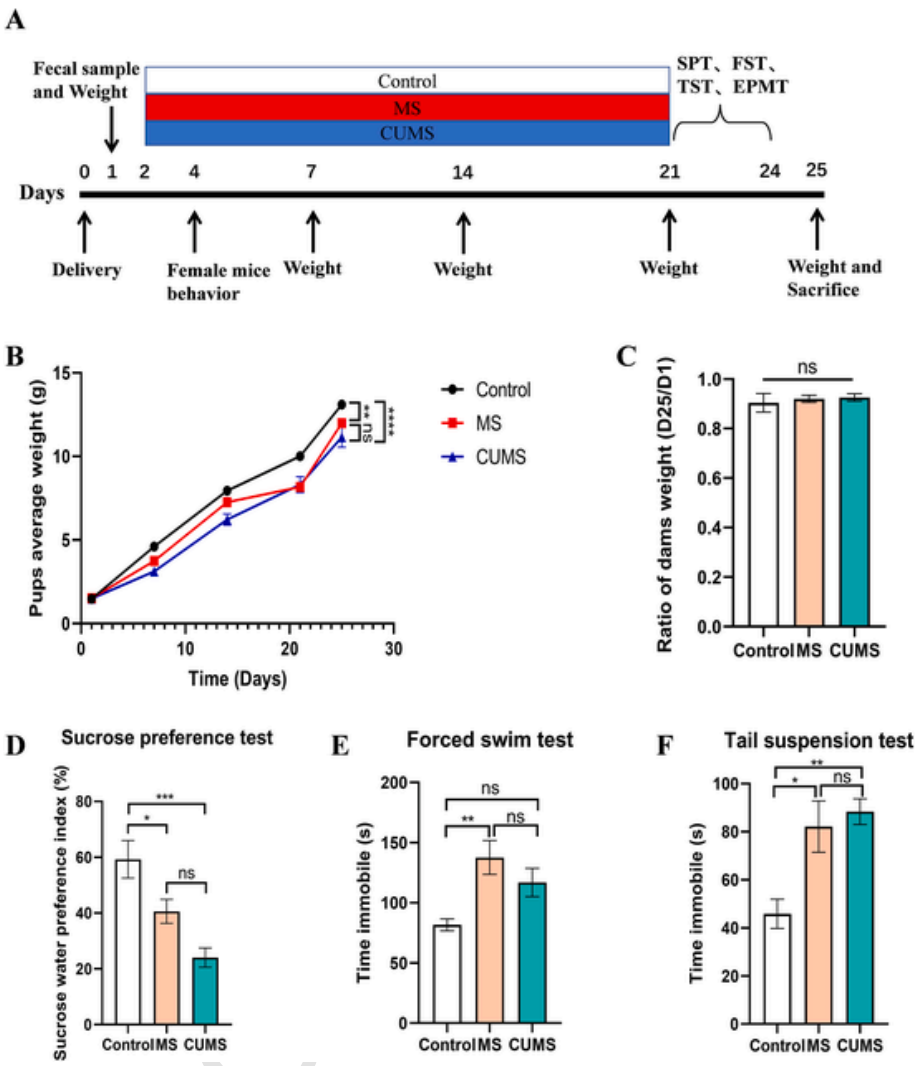

Fig. 1. MS and CUMS induced depression-like behaviors in mice. (A) Time schedule of the whole experimental design. (B) Changes in average body weight of pups of each group ($n = 6$). (C) Changes in dams weight of each group ($n = 6$). (D) SPT: Sucrose water preference index ($n = 6$). (E) FST: time of immobility ($n = 6$). (F) TST: time of immobility ($n = 6$). Data is expressed as the mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$, ns means non-significant.

We then compared the behavioral phenotypes of the two models. MS model showed significantly decreased sucrose water preference index from control group ($P < 0.05$, Fig. 1D) in SPT and significantly increased immobile durations from control group in FST ($P < 0.01$, Fig. 1E) and TST ($P < 0.05$, Fig. 1F). CUMS model exhibited significantly decreased sucrose water preference index from control group ($P < 0.001$, Fig. 1D) in SPT and significantly increased immobile durations from control group in TST ($P < 0.01$, Fig. 1F). MS model showed more depression-like behaviors in FST. CUMS model showed more depression-like behaviors in SPT and TST.

There was no significant difference in the time spent in the closed arm area and the incubation period of holding pups in the mouth in each group (Figs. S1A and B).

3.2. The expression of PPD related genes in brain were detected by RT-qPCR

To further investigate differences between MS and CUMS model, RT-qPCR was conducted to amplify related genes in the neuroinflammation signaling pathway and Hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis plays a major regulatory role in the postpartum period. In Fig. 2A, corticotropin releasing hormone (*Crh*) and corticotropin releasing hormone receptor 1 (*Crhr1*) showed a significant increase in CUMS model when compared to MS model and control group. Neuroinflammation and BDNF are indicators of PPD. The relative mRNA expressions of *Il1b*, *Caspase1*, *Nlrp3*, *Il6*, *Tnfa* and *Bdnf* in the hippocampus showed no significant difference (Fig. 2B). In the cortex, the relative mRNA expressions of *Il1b*, *Caspase1* and *Nlrp3* decreased in MS model but no significant differences. The relative mRNA expression of *Il6* significantly decreased in both MS and CUMS models compared with control group ($P < 0.05$). The relative mRNA expression of *Tnfa* in MS model and CUMS model was decreased, and showed significant difference in MS model compared with control group ($P < 0.01$, Fig. 2C).

3.3. The contents of related substances in plasma and cortex were detected by ELISA

The study found that estrogen changes significantly in PPD, so plasma levels of E2, P and PRL were determined by ELISA. The results showed that there were no significant differences in E2, P and PRL among all groups. E2 had a downward trend in MS model and CUMS model (Fig. 3A), while PRL had a downward trend in CUMS model (Fig. 3C). These results suggest that plasma E2 and PRL levels in CUMS model were lower than those in MS model. We also measured the levels of monoamine neurotransmitters and IL-6 in the cortex. IL-6 content in cerebral cortex decreased in the stress model, and showed significant

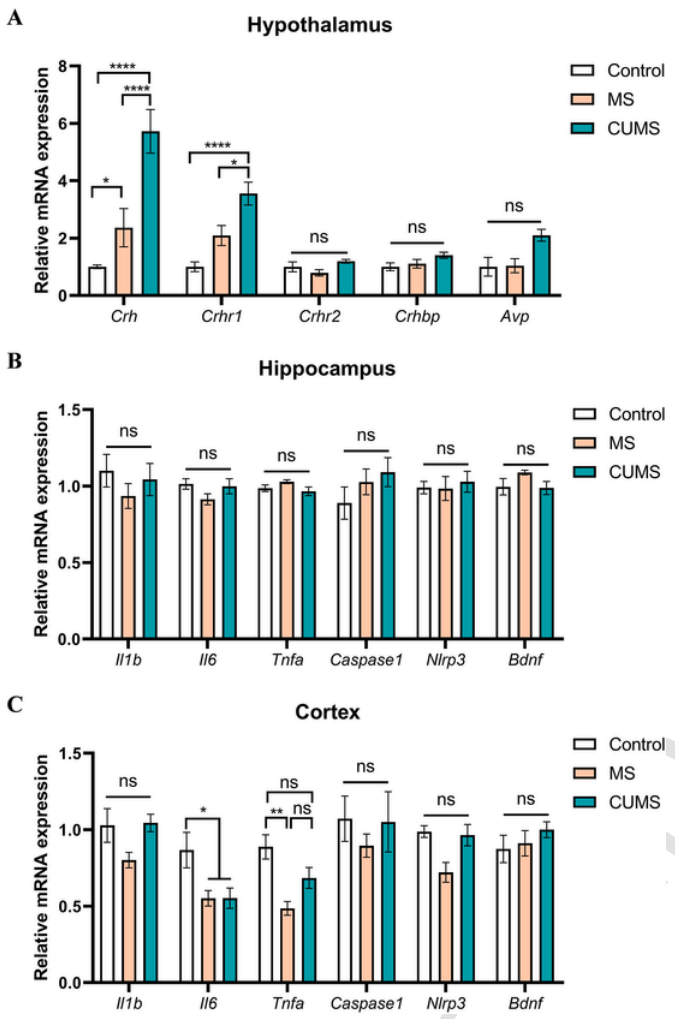

Fig. 2. MS and CUMS induced gene expression changes determined by RT-qPCR. (A) Relative mRNA expression of HPA axis related genes in hypothalamus tissue (n = 4–8). (B) Relative mRNA expression of cytokines in hippocampus tissue (n = 6). (C) Relative mRNA expression of cytokines in cortex tissue (n = 6). Data is expressed as the mean ± SEM. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, ns means non-significant.

difference in MS model compared with control group (P < 0.01, Fig. 3D). The level of 5-HT in the cortex of CUMS model decreased more obviously than the MS model (P < 0.01, Fig. 3E). There was no significant difference in cortical DA levels among all groups (Fig. 3F).

3.4. CUMS model and MS model showed different changes in BDNF

To investigate the changes of BDNF in the brain, the protein expression of BDNF in CA1, CA3 and DG regions was detected by immunohistochemistry. The dark brown area indicated positive BDNF protein, the higher the positive, the higher the expression of BDNF protein. The BDNF positive expression of hippocampal CA3 region in the control group was significantly higher than that in the MS model (P < 0.05), and slightly higher than that in the CUMS model (Fig. 4).

3.5. 16s rDNA sequencing

3.5.1. Alpha diversity

The observed species and shannon index in CUMS model were significantly lower than that in control group (P < 0.05, Fig. 5A and B). In conclusion, species richness, evenness, and α diversity was the lowest in CUMS model.

3.5.2. Beta diversity

The samples of each group were close to each other, and the microbial composition and structure of the samples were similar (Fig. 5C). The results showed no significant difference in β diversity among groups.

3.5.3. Composition of bacterial community structure

As showed in Fig. 5D and E, the bray-Curtis distance clustering tree structure is on the left. On the right is the relative abundance distribution diagram of species at phylum and genus levels. The results showed that the species composition of MS model and CUMS model were similar. At the phylum level, the abundance of *Bacteroidetes* in control group was higher than that in stress model, while the abundance of *Firmicutes* and *proteobacteria* was lower than that in stress model. At the genus level, the abundance of *Muribaculaceae* and *Alistipes* was higher in control group, while that of *Lactobacillus* was lower in control group.

3.5.4. Significant species differences

Barplot difference analysis shows microorganisms that differ significantly at the phylum and genus levels (P < 0.05, Fig. 6A and B). The results showed that there were significant differences in *Bacteroidetes*, *Firmicutes* and *Proteobacteria* in phylum. The relative abundance of *Lactobacillus*, *Desulfovibrio* and *Mucispirillum* in stress model was significantly higher than that in control group. The relative abundance of *Bacteroidetes* was significantly lower than that of control group.

In LEfSe (LDA Effect Size) analysis (Fig. 6C), each node represents a species classification at this level. The higher the abundance of this species, the larger the node is. The node color yellow means that the species has no significant difference in the comparison group; if the node color is red, it means that the species has significant difference in the comparison group, and the species has a higher abundance in the red group, and so on for other colors. The results showed significant differences in species at different levels in control, MS and CUMS models. It can be seen that the abundance of *Bacteroides* in control group was significantly higher than that in stress model at different classification levels. The relative abundance of *Lactobacillus*, *Robinsoniella*, *Erysipelatoclostridium* and *Clostridioides* in MS model was significantly higher than that in other groups. The relative abundance of *Empedobacter*, *Mucispirillum* and *Deferribacteres* in CUMS model was significantly higher than that in other groups.

4. Discussion

At present, there are a variety of PPD modeling methods. Different PPD models have both advantages and disadvantages. Their PPD indicators are evaluated differently. This can reveal the heterogeneity of clinical PPD and it is also instructive for the treatment of clinical PPD with different phenotypes. However, no scholar has made a specific and detailed evaluation on this. Therefore, two different stress models are selected in this study, which are the MS model and the CUMS model. MS has strong specificity in PPD, and CUMS is one of the most appropriate models for the study of depression [12]. The two were compared from three aspects of behavioral indicators, physiological indicators and intestinal flora, providing reference for future PPD model selection.

Animal models of behavior do not necessarily model a specific psychiatric illness but rather specific symptoms and no single model can capture all of the symptoms [14]. We also want to reveal different phenotypes of clinical PPD. Based on this point, we compared the depressive behaviors of MS model and CUMS model. We found that the average body weight of pups in CUMS model decreased more obvious, suggesting that the feeding behavior of CUMS dams was reduced and depression-like behavior appeared, but there was no significant difference in the body weight of dams. A possible explanation for this might be that clinical can be observed in some patients with depression anorexia, weight loss; But there are also patients with gluttony and weight gain.

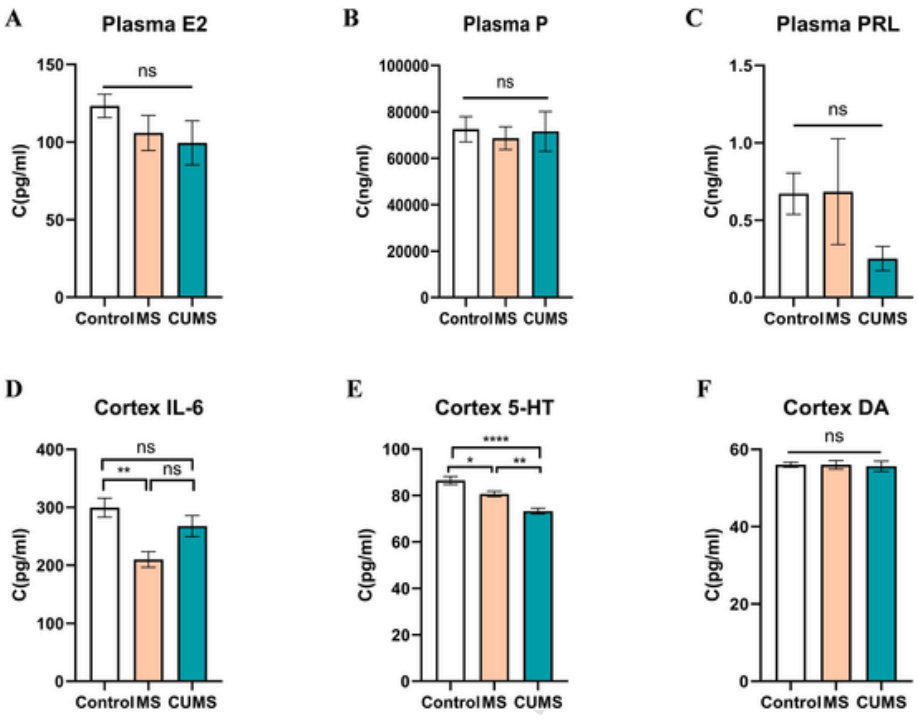

Fig. 3. MS and CUMS induced related substances changes in plasma and cortex determined by ELISA. (A) No significant difference existed in E2 level ($n = 6$). (B) No significant difference existed in P level ($n = 6$). (C) No significant difference existed in PRL level ($n = 4$). (D) IL-6 level in cortex tissue ($n = 6$). (E) 5-HT level in cortex tissue ($n = 6$). (F) No significant difference existed in DA level in cortex tissue ($n = 6$). Data is expressed as the mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$, ns means non-significant.

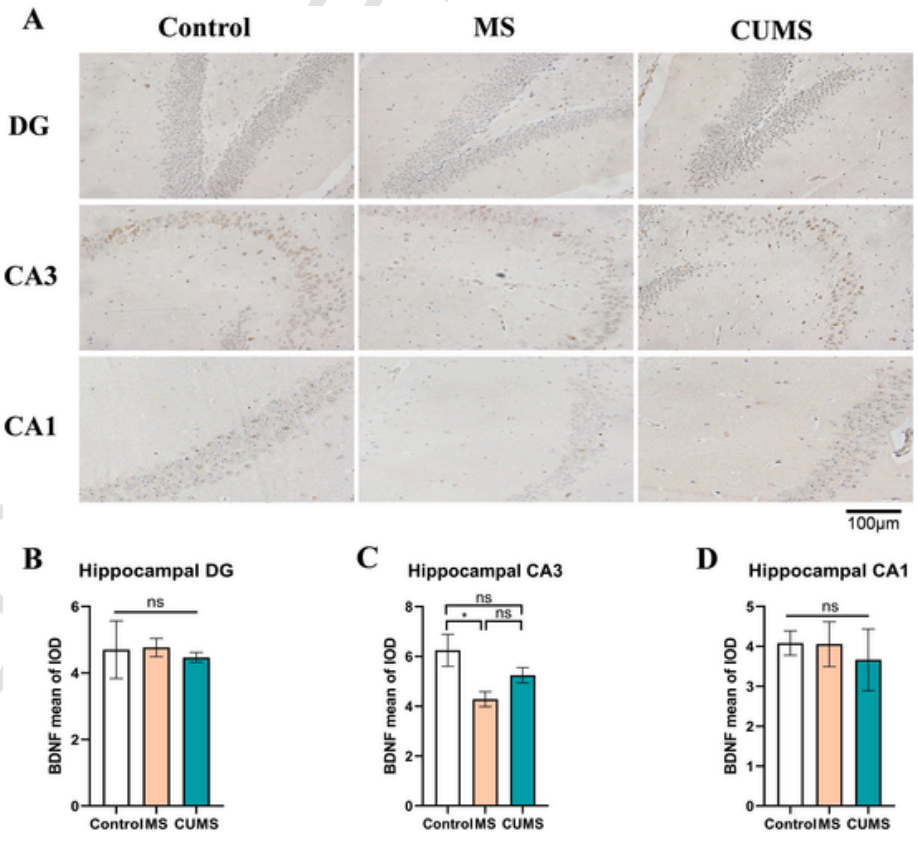

Fig. 4. Number of BDNF-positive cells in the hippocampal sub-regions DG, CA3 and CA1 of normal and stress mice. Representative images of BDNF (A) of the hippocampal sub-regions DG, CA3 and CA1 in the three experimental groups. Scale bar: 100 μm (200 ×). Quantitative determination of hippocampal BDNF content in the DG (B), CA3 (C), CA1 (D) was performed. IOD: integral optical density. Data is expressed as the mean ± SEM, $n = 3$, $^{*}P < 0.05$, ns means non-significant.

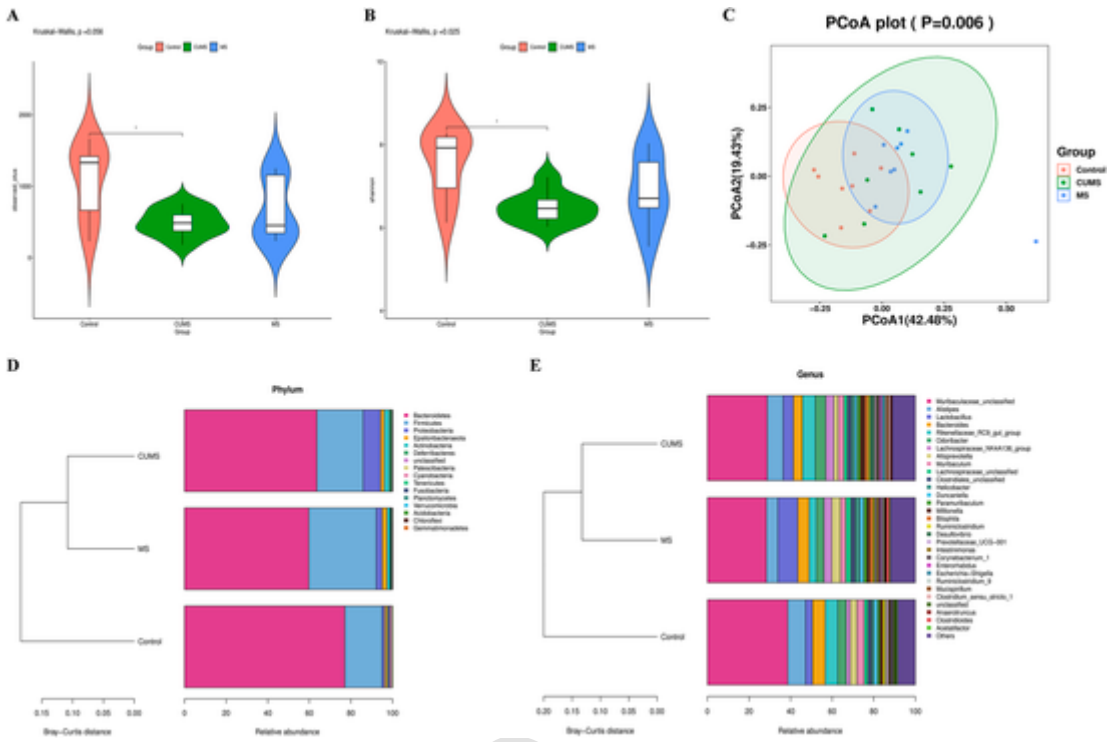

Fig. 5. α-diversity, β-diversity and Species analyses of gut microbiota. (A) Observed_species index (n = 8). (B) Shannon index (n = 8). (C) PCoA analysis of gut bacteria data (n = 8). (D) Cluster graph analysis of phylum level (n = 8). (E) Cluster graph analysis of genus level (n = 8). *P < 0.05.

Therefore, changes in maternal body weight cannot be used as a measure of the success of depression models [13]. The sucrose preference index in CUMS model decreased more obviously. This indicates that the CUMS model is more obvious in anhedonia. In FST and TST, MS model and CUMS model performed differently. The MS model showed longer immobility time in FST and the CUMS model showed longer immobility time in TST. There was no difference in the stay time in the closed arm area between the two groups, which suggested that BALB/C mice were meek and timid, and were more in a state of avoidance and anxiety in the new environment [14,18].

Immune system and cytokines are involved in the development of PPD [19–21]. NLRP3 inflammasome deficiency improved depression-like behavior in mice, and *Caspase1* and *Nlrp3* mRNA levels increased in the blood cells of depressed patients [6]. It suggests that PPD may also be related to inflammation. So we measured the indicators. QPCR results showed that relative *Il1b, Il6, Tnfa, Caspase1* and *Nlrp3* mRNA expression showed no statistical difference in the hippocampus, while relative *Il6* and *Tnfa* mRNA expression decreased in the cortex of the stress model. ELISA results also showed that IL-6 level was decreased in the cortex of stressed dams, especially in the MS model. Although these results differ from some published studies, there are also conflicting reports of inflammatory changes associated with PPD and the limited number of reports makes it difficult to determine a role of neuroinflammation in the underlying neurobiology of PPD [22]. We speculate that neuroinflammation-related cytokines in stressed dams were in a state of feedback regulation on postpartum day 25, and the body initiated the anti-inflammatory response in vivo, so that the inflammatory factors decreased sharply.

Previous studies have shown decreased 5-HT, DA and BDNF levels in patients with PPD [23,24]. The relative *Bdnf* mRNA expression showed no significant difference between cortex and hippocampus. However, immunohistochemical staining results of hippocampus showed that the expression of BDNF significantly decreased in the MS model and slightly decreased in the CUMS model. This study has been unable to demonstrate the changes of DA in the cortex. The level of 5-HT in the cortex showed a downward trend in the stress model and CUMS model decreased significantly.

The plasma levels of estradiol, progesterone and prolactin were determined in this study, since changes in the levels of reproductive hormones are also a risk factor for PPD [2,25]. The results showed that estradiol and prolactin had a decreasing trend in the stress model, but the decrease was more obvious in the CUMS model. One interesting finding is that progesterone levels are particularly high after delivery. We diluted the plasma to 5000-10,000 times during measurement. It is possible that this result may have been skewed by excessive dilution ratio.

The HPA axis is an important part of the neuroendocrine system, involved in controlling responses to stress and regulating many physical activities. Increased stress increases the secretion of related hormones [26]. We were surprised to find that the mRNA expressions of *Crh* and *Crhr1* in CUMS model were significantly increased in the hypothalamus than MS model. We hypothesized that CUMS might cause dams to feel more stressed.

It is becoming increasingly recognized that the gut microbiome can play a role in depression-related mood disorders. In the 16S sequencing results, the α diversity of stress models were lower than that of control group, while the β diversity was not different. Through the distance clustering tree structure analysis, the bacterial community structure of the stress model was similar. One unanticipated result was that *Lactobacillus* increased in the model group. *Lactobacillus* is generally considered a beneficial bacteria and its abundance decreased in the depression model group [5,27,28]. Of course, some scholars also showed that *Lactobacillus* increased in the stress model group [29,30]. A low ratio of *Firmicutes* to *Bacteroidetes* (F/B ratio)is considered a normal, healthy state of the intestinal microbiome [29]. In our study, the F/B ratio increased in the model group, indicating that the intestinal microbiome composition of the model group was developing in a bad direction. Internationally, there are some differences in the abundance and diversity of intestinal microbiome in models of depression or postpartum depression [31–35]. Intestinal microbiome is affected by many aspects. First, different strains and ages of model mice may lead to differences in in-

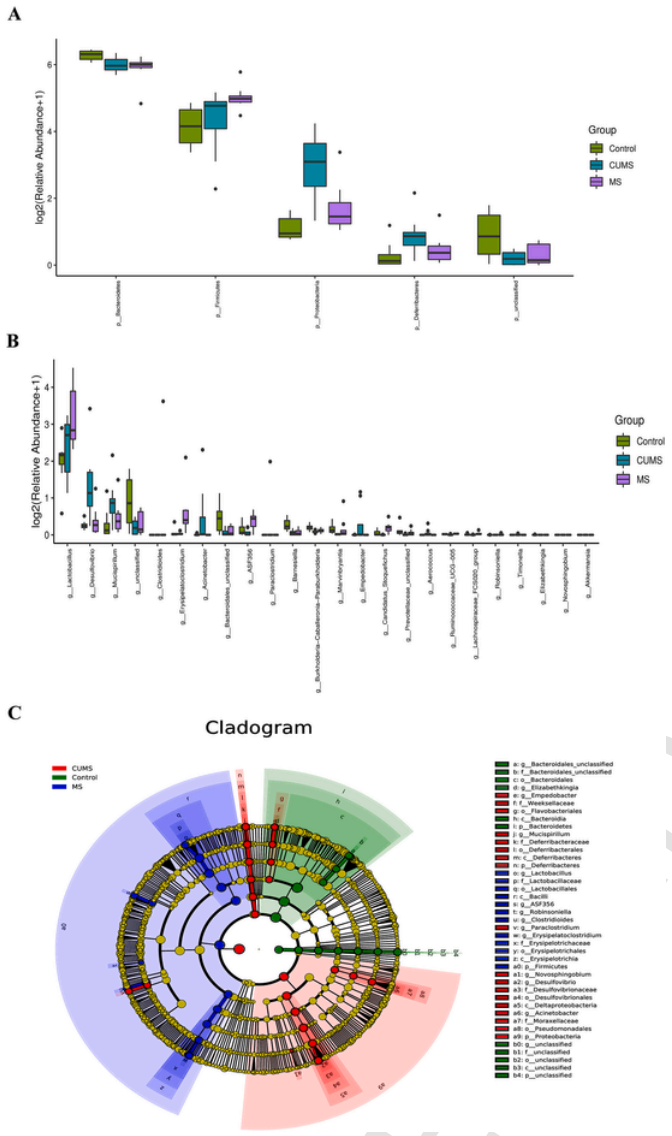

Fig. 6. Analysis of significant difference of gut microbiota. (A) Barplot difference analysis of phylum level (n = 8). (B) Barplot difference analysis of genus level (n = 8). (C) LEfSe difference analysis (n = 8).

testinal microbiome [36]; Second, feeding environment of model mice, including diet, climate, temperature and humidity, will also affect changes in intestinal microbiome; Finally, different modeling methods are adopted. The type, intensity and duration of stressors also lead to different changes in animal physiology and intestinal microbiome [33,37,38].

Our study provides the first evidence to our knowledge that these two models had some different depressive behavioral, hippocampal BDNF changes, cortical 5-HT changes, HPA axis changes and intestinal microbiome changes except for some common features. They all showed depression-like behavior, but CUMS model had more obvious anhedonia in SPT and longer immobile time in TST, while MS model had longer immobile time in FST. CUMS model had the lowest cortical 5-HT content, while MS model had the lowest hippocampal BDNF expression. CUMS model displayed a higher hypothalamus-related mRNA expression (*Crh*, *Crhr1*) than MS model. In general, MS model and CUMS model have different performance in behavior and physiology. The CUMS model showed more obvious parameter changes, which may be more suitable for PPD induced by various social environmental factors.

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Author contribution statement

Yan Zhang, Menghua Liu, Li Zhang, and Wei Zou designed the experiments. Yan Zhang performed most of the experiments, analyzed the results, and wrote manuscripts. Birui Shi performed the experiments, and manuscript revisions; Menghua Liu, Li Zhang and Wei Zou revised the manuscripts. All authors contributed and have approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrc.2022.09.063.

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