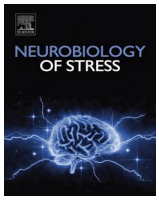
Neurobiology of Stress 30 (2024) 100624

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr



Environmental enrichment attenuates depressive-like behavior in maternal rats by inhibiting neuroinflammation and apoptosis and promoting neuroplasticity

Guopeng Chen [a,1], Yuhui Zhang [a,1], Ruiling Li [a,1], Liuyin Jin [a], Keke Hao [a], Jingtong Rong [a], Hao Duan [a], Yiwei Du [a], Lihua Yao [a], Dan Xiang [a,*], Zhongchun Liu [a,b,**]

[a] Department of Psychiatry, Renmin Hospital of Wuhan University, Wuhan, 430060, China
[b] Taikang Center for Life and Medical Sciences, Wuhan University, Wuhan, 430071, China

ARTICLE INFO

Keywords:
Postpartum depression
Cognitive impairment
Neuroplasticity
Neuroinflammation
Environmental enrichment

ABSTRACT

Gestational stress can exacerbate postpartum depression (PPD), for which treatment options remain limited. Environmental enrichment (EE) may be a therapeutic intervention for neuropsychiatric disorders, including depression, but the specific mechanisms by which EE might impact PPD remain unknown. Here we examined the behavioral, molecular, and cellular impact of EE in a stable PPD model in rats developed through maternal separation (MS). Maternal rats subjected to MS developed depression-like behavior and cognitive dysfunction together with evidence of significant neuroinflammation including microglia activation, neuronal apoptosis, and impaired synaptic plasticity. Expanding the duration of EE to throughout pregnancy and lactation, we observed an EE-associated reversal of MS-induced depressive phenotypes, inhibition of neuroinflammation and neuronal apoptosis, and improvement in synaptic plasticity in maternal rats. Thus, EE effectively alleviates neuroinflammation, neuronal apoptosis, damage to synaptic plasticity, and consequent depression-like behavior in mother rats experiencing MS-induced PPD, paving the way for new preventive and therapeutic strategies for PPD.

1. Introduction

Postpartum depression (PPD) is a serious mental illness characterized by the clinical symptoms of depression, tiredness, insomnia, inappropriate guilt, and excessive attention or indifference to the infant for at least two weeks (Raza and Raza, 2023; Yun et al., 2019). PPD is the most common complication of childbirth, with suicide related to PPD accounting for ~20% of postpartum deaths (Lindahl et al., 2005). Maternal depression can also adversely affect the behavioral, emotional, and cognitive development of infants, who can exhibit lower social participation, less mature regulatory behavior, more negative emotions, and higher cortisol responsiveness (Feldman et al., 2009; Halligan et al., 2007; Zhao and Zhang, 2020). Therefore, it is imperative to understand the underlying neurobiological mechanisms of PPD.

Chronic stress during pregnancy can induce depression and anxiety behaviors in postpartum rats along with maternal nursing defects (Lancaster et al., 2010; Miller, 2002). Continuous maternal separation (MS) is thought to simulate impaired infant-mother relationships associated with PPD, and this model has been used to simulate PPD in rodents (Alves et al., 2020). There are several putative neuroendocrine, epigenetic, and neuroinflammatory biomarkers of patients at high-risk of PPD. For example, reduced oxytocin levels may predict PPD and its severity (Skrundz et al., 2011; Thul et al., 2020), and elevated β-endorphin levels (Yim et al., 2010) and reduced platelet serotonin (Maurer-Spurej et al., 2007), omega-3 (Shapiro et al., 2012), and vitamin D (Robinson et al., 2014) levels have all been associated with an increased risk of PPD. Genome-wide association studies have also identified candidate genes and pathways associated with PPD, many of which have previously been associated with severe depression such as serotonin transporter, tryptophan hydroxylase-2, catechol-O-methyltransferase, monoamine oxidase, and brain-derived neurotrophic factor.

Pregnant women show measurable decreases in cognitive ability

* Corresponding author. Wuhan University, 238 Jiefang Road, Wuhan, 430060, China.
** Corresponding author. Wuhan University, 238 Jiefang Road, Wuhan, 430060, China.
E-mail addresses: xiangdannuli@163.com (D. Xiang), zcliu6@whu.edu.cn (Z. Liu).
[1] These authors contributed equally.

https://doi.org/10.1016/j.ynstr.2024.100624
Received 17 January 2024; Received in revised form 25 February 2024; Accepted 10 March 2024
Available online 11 March 2024

(Henry and Sherwin, 2012). In contrast to severe depression and cognitive impairment, the pathogenesis of postpartum symptoms appears to be more related to psychosocial stress or nerve damage, perhaps as a result of hormonal fluctuations (Bloch et al., 2003; Brummelte and Galea, 2010; Pariante and Lightman, 2008; Becker et al., 2016). The hippocampus plays a central role in dealing with emotion and cognition (Korotkova et al., 2018), and there is now good evidence that the hippocampus is involved in stress responses related to the pathogenesis of postpartum emotional and cognitive dysfunction (Pawluski and Galea, 2007; Baka et al., 2017). According to the synaptic hypothesis of depression (Hajszan, 2020), perinatal stress causes neuroplastic changes in the maternal brain, which may lead to postpartum affective disorders and cognitive impairment (Pawluski et al., 2016). Hippocampal dysfunction in patients with severe depression is associated with reduced hippocampal volume, inhibition of hippocampal neurogenesis, and synaptic loss in adults, and these structural injuries can be prevented or reversed by antidepressant therapy (Hajszan, 2020; Sheline et al., 2003; Duman and Monteggia, 2006). It used to be thought that the number of neurons in the brain was fixed during adulthood, but it has now been confirmed that neurogenesis can still occur in certain brain regions during adulthood (Wu et al., 2020). In particular, neurogenesis is a persistent physiological phenomenon in regions such as the hippocampus and the olfactory bulb (Wu et al., 2020). Neurogenesis may play an important role in processes such as learning, memory and emotion regulation (Murai et al., 2016). Several studies have shown that neurogenesis is associated with improved cognitive function, antidepressant effects, and coping with stress (Murai et al., 2016). Newborn neurons need to form the correct synaptic connections, which is closely related to synaptic plasticity. Several studies suggest that increased neurogenesis may promote neuroplasticity and improve learning and memory functions (Mohammad et al., 2018). The isolation-induced behavioural syndrome is accompanied by reductions in PFC volume and hippocampal synaptic plasticity (Fone and Porkess, 2008). Mitochondrial disease and depression reportedly lead to diminished hippocampal synaptic plasticity and neuronal atrophy, but SNS can alleviates depression-like behavior via improve hippocampal synaptic plasticity (Deng et al., 2022). A single prolonged maternal separation leads to maladaptive changes that persist into adulthood including changes in hippocampal adult neurogenesis and synaptic plasticity (Hu et al., 2020; Oomen et al., 2010).

Neuroinflammation is another neurobiological mechanism implicated in PPD (Troubat et al., 2021; Won and Kim, 2020), and it may play an important role in susceptibility to perinatal mood disorders. Interleukin (IL)-6 and IL-1β levels are positively correlated with depression scores in postpartum women (Cassidy-Bushrow et al., 2012), and elevated IL-6 and TNF-α during delivery are associated with PPD (Boufidou et al., 2009; Sluiter et al., 2020). High levels of IL-1β are also associated with suicidal thoughts during pregnancy (Szpunar et al., 2021). C-X-C motif chemokine 1 (CXCL1) has been reported to be significantly increased in women with PPD (Brann et al., 2020). In general, the levels of many cytokines change after delivery and may therefore act as inflammatory biomarkers of PPD. NLRP3 inflammatory bodies are protein complexes that play an important role in neuroinflammation (Huang et al., 2021) by converting pro-caspase-1 into mature caspase-1, which subsequently mediates the activation of pro-inflammatory cytokines (IL-1β and IL-18) (Zhu et al., 2020), inflammation, and cell death (Huang et al., 2021; Zhu et al., 2018). In PPD mice, glial NLRP3 inflammatory bodies are activated in the hippocampus (Zhu and Tang, 2020), and activation of NF-κB/NLRP3/caspase-1 has also been detected in the hippocampus of PPD rats (Abdul Aziz et al., 2021).

Environmental enrichment (EE) describes a type of environmental manipulation in which the complexity and novelty of the physical and social environment are increased (Leggio et al., 2005; Volkmar and Greenough, 1972). EE has been widely used to study the impact of environmental factors on learning and memory. Since its first description by Hebb in 1949, it has been widely proven to benefit health. Since environmental complexity induces neurogenesis and dendritic complexity in the hippocampus, it may provide a means to study the role of environmental factors in reducing anxiety and depression-like behavior (Pittenger and Duman, 2008). Enriched environments can be viewed not only as an external source of rich stimuli, but also as providing space for individual behaviours that shape the individual's brain plasticity patterns and thus their functioning (Kempermann, 2019). EE can exert powerful effects on neural plasticity, determining a conspicuous enhancement, for instance, of hippocampal synaptic plasticity in adult animals (Sale et al., 2014). EE activates ActA via the NMDAR-$Ca2^{+}$-ActA pathway, which in turn activates the Wnt/βcatenin pathway and regulates synaptic plasticity, playing an important role in learning (Zhang et al., 2021). EE treatment improves maternal sleep deprivation-induced cognitive deficits by offspring histone acetylation and synaptic plasticity markers (Zhang et al., 2023). Conditions of the normal environment did not have any effect on baseline synaptic transmission and presynaptic plasticity, but housing the animals in EE rescued the impairment of LTP induction induced by 2-VO (Bayat et al., 2015). Different environmental conditions after SAH, may affect the miRNA levels associated with synaptic plasticity and microtubule organization in the frontal lobe, and this might have some effects especially on cognitive and motor functions related to this brain area (Ergen et al., 2021). Enriched environments prevent old rats from the aging-dependent impairment of cognition and plasticity. Spatial working memory deficits decrease in enriched rats, in association with an increased neuronal plasticity, as compared with standard reared rats (Arnaiz et al., 2004). EE can reduce the negative effects of stress by acting on the same neural pathway or on different neural pathways at the same time. However, most EE studies focus on offspring, and while a few studies have used EE in PPD, the underlying relationships and mechanisms are not fully understood. It has been reported that EE during and after pregnancy can reverse maternal anxiety and depression-like behavior (Sparling et al., 2020). EE exposure affects the function of the hypothalamus-pituitary axis (HPA) by reducing stress hormones, including corticotropin (ACTH) and corticosterone (Belz et al., 2003), and EE has been shown to activate the oxytocin system in the brains of mice (Rae et al., 2018).

Here we combined behavioral studies with molecular and morphological analyses to study the impact of EE on depression induced by MS in postpartum rats. EE improved depression-like behavior and cognitive function in postpartum rats, and these effects were related to hippocampal neuroinflammation and neuroplasticity. EE significantly downregulated NLRP3 and proinflammatory cytokine expression (e.g., IL-1β and TNF-α), inhibited microglia, and decreased neuronal apoptosis in the hippocampus induced by MS in postpartum rats. The neuroplastic defects and neurological damage induced by MS in rats improved after EE, proposing EE as a treatment for PPD.

2. Materials and methods

2.1. Animals and maternal separation

Twenty-eight nulliparous female Sprague Dawley female rats and 14 male Sprague Dawley rats (6-8-weeks-old) were purchased from the Animal Research Centre of Sanxia University (Yichang, China). All rats were raised in the experimental holding areas (12 h light/dark cycle at 23 ± 1 °C, 50 ± 10% relative humidity, with lights on from 08:00 to 20:00, *ad libitum* access to dry food pellets and water) following WHU ethics protocols (WDRM202300297). Body weight was recorded daily during the experimental period. After one week of acclimatization, male and female rats were mated after combining cages in a 1:2 ratio, and males were removed after checking for vaginal plugs early the next morning to confirm pregnancy.

Maternal separation (MS) took place from PND (post-natal day) 1, according to standard procedures (Deng et al., 2022). In brief, pups were

removed for 4 h between 10:00 and 12:00 and 14:00 and 16:00, after which pups were returned to their home cages with their mother. The litters of control mothers were not removed from their home cages in those periods. Food and water were always available during the experiment. Weaning took place at PND 21, after which all litters were removed for use in other research. All measurements were carried out on these maternal rats.

2.2. Environmental enrichment and groups

The experimental protocol is summarized in (Fig. 1A). The 28 maternal rats were divided into four groups: non-MS with standardized environment group (SE-NC, N = 7); non-MS with environmental enrichment group (EE-NC, N = 6); MS with standardized environment group (SE-MS, N = 7); and MS with environmental enrichment group (EE-MS, N = 8).

Rats in the EE group was placed in transparent ventilated plastic cages measuring 60 × 45 × 35 cm for six weeks for environmental enrichment treatment (Maas et al., 2020). Exercise facilities such as tree holes, platform tunnels, teeter-totters, swings, running wheels, and climbing ladders were placed in the cages to promote locomotor development; floral scented balls, bath salts, and floral bedding were placed in the cages to promote olfactory development; and beads and plush balls of different shapes and colors were placed in the cages to promote visual and tactile development. Water and food were placed in a fixed location and different foods such as melon seeds, peanuts, and dried worms were occasionally given to supplement nutrition. At the same time, we replaced and cleaned all items every four days to achieve the effect of "enriching the environment" (Fig. 1B).

2.3. Behavioral assays

All behavioral tests were performed during the light phase in a temperature- (22–24 °C) and humidity- (40%–60%) controlled room illuminated by eight 32 W fluorescent lights (EPM apparatuses were 7 feet away from the light source; SPT was carried out in boxes where the light source was a single 0.6 W light bulb). All behaviors were carried out between 9 a.m. and 6 p.m. SPT behavior was assessed in soundproof behavioral boxes. All behaviors were measured without the experimenter being present in the room. Behavioral equipment was cleaned with 75% ethanol between individual animals.

Open field test (OFT): The OFT was conducted to measure the effect of EE on general locomotor ability and depression-like and anxiety-related behavior (Orefice et al., 2019). Rats were placed in a custom-made open field chamber (100 × 100 × 40 cm) and their movement recorded and analyzed for 5 min using video-tracking software (Noldus, Wageningen, the Netherlands).

Elevated plus maze (EPM): The EPM test is used to measure anxiety-related behavior in rodents (Cerniauskas et al., 2019). During the test, rats explore a plus-shaped maze (length of each arm: 50 cm). Two arms were closed (wall height: 40 cm) and two arms were open. Rats typically spent time exploring all arms, but spending significantly more time in the closed arms than the open arms indicates anxiety-related behavior. Animals were placed in the EPM for 5 min, their movement recorded via an automated video tracking system (Noldus), and the time spent in open and closed arms calculated. Experimenters were blinded to group allocation and outcome assessment.

Forced swim test (FST): The FST is a behavioral challenge assay that assesses passive coping and despair responses (Cerniauskas et al., 2019). Rats were placed in a transparent glass beaker filled with tap water at 25 °C. The water level in the beaker was high enough so that

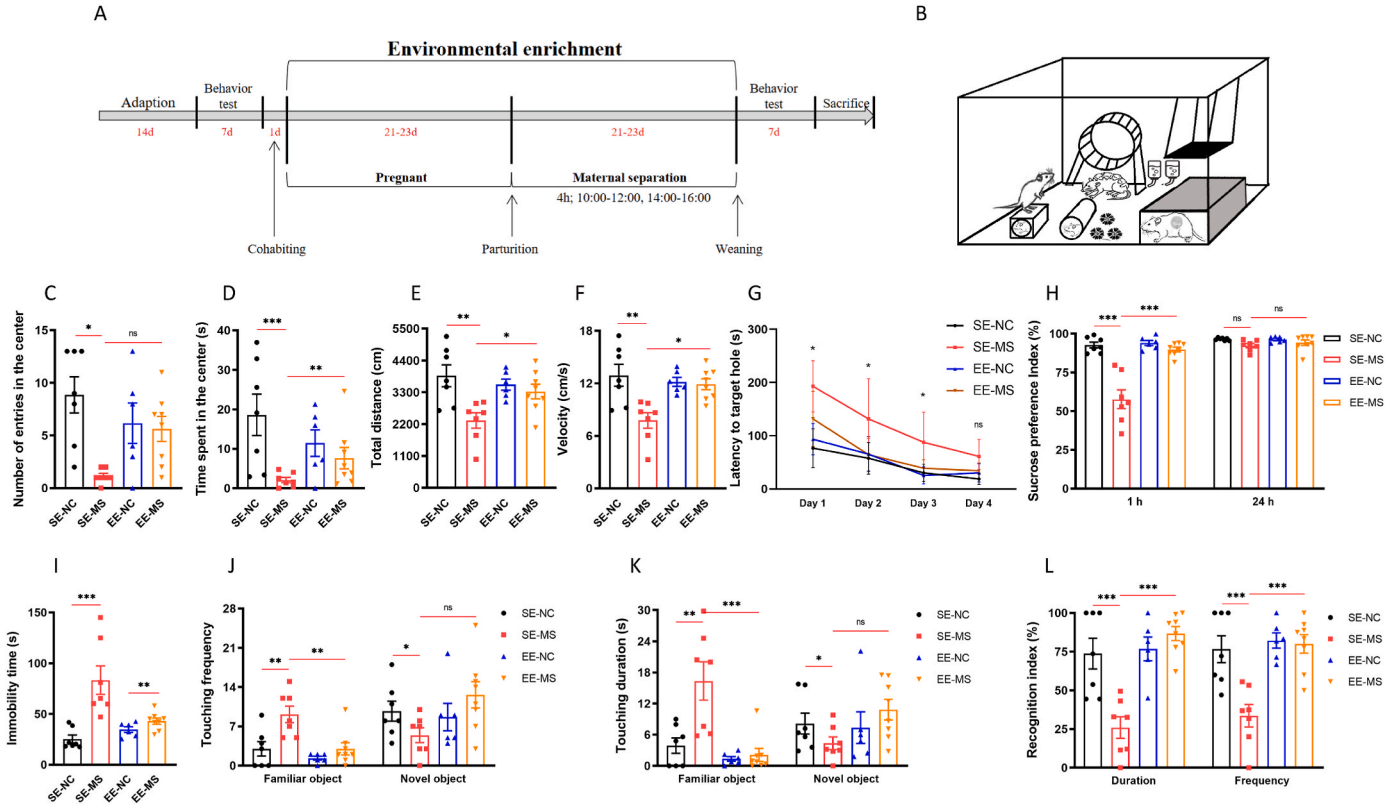


Fig. 1. EE attenuates depression-like behaviors in MS-induced postpartum rats with depression.
(A) Schematic representation of the MS procedure and EE treatments in rats. (B) The environmental enrichment paradigm. (C–F) The open field test. (G) The Barnes maze Test. (H) The sucrose preference test. (I) The forced swimming test. (J–L) The novel object recognition test. All data are expressed as mean ± SEM (n = 6–8 per group). *p < 0.05, **p < 0.01, ***p < 0.001 by two-way ANOVA with Tukey's post-hoc analysis. NS, no significance.

rats could not touch the bottom of the beaker while trying to stay afloat. The behavioral test lasted for 6 min, and rats were recorded on video during the entire session. Typically, at the beginning of the test (first 2 min), rats struggled vigorously but eventually switched to a more passive floating state, so only the last 4 min were analyzed. The time spent struggling was measured by blind scoring of the video after completion of testing. Experimenters were blinded to group allocation and outcome assessment.

Sucrose preference test (SPT): The SPT assesses an animal's preference for a sweet solution (1% w/v sucrose dissolved in water) relative to plain water, and failure to do so is indicative of anhedonia, a core symptom of depression (Cerniauskas et al., 2019). Volume or weight of sucrose or water consumed was measured. Animals were water restricted overnight before the experiment. Bottle side and animal group tested were counterbalanced between each trial. Testing was for 1 h and 24 h, and the percentage of sucrose solution over total consumption was calculated. Experimenters were blinded to group allocation and outcome assessment.

Barnes maze test: We examined spatial memory with the Barnes maze (Carvalho et al., 2019), which was elevated 140 cm above the floor and consisted of 20 holes located evenly at the surface periphery, each 10 cm in diameter. The target box was a hole connecting to a dark chamber, allowing the animal to escape from bright light exposure. The day before the formal experiment, animals were adapted to the target box for 4 min. On the first day, each animal was placed in the center black cube of the maze for 5 s and permitted to explore the maze to find the target box when the cube was removed. Once the animal entered the escape box, it was left there for 30 s; if it failed to find the target box within 3 min, it was taken to the target box and allowed to remain in the target box for 1 min. Each animal underwent two trials during the day with an interval of 4 h. The latency time to reach the target box was recorded. The test was performed over 4 days. The whole process was monitored by a digital camera and a computer system.

New object recognition: Briefly, animals were adapted to the organic plastic experimental facility of 40 × 40 × 40 cm every day and then returned to the cage after 10 min free exploration for three consecutive days. On the fourth day, two identical objects (block-shaped toys) were placed opposite each other on one side of the site. The mice were gently placed in the position of the two objects, with their back to them (familiar stage). After 10 min of exploration, the animal was removed and returned to its cage. Exploration was defined as pointing the nose at an object (distance of <2 cm) and/or touching an object with the nose. Animals showing a preference for objects during the process of familiarity were excluded from the analysis. After 1.5 h, one of the two same objects was replaced by a different object, named the "old" object and the "new" object. The time when the mice explored the two objects was recorded. The new object recognition (NOR) index (%) was calculated as (time to explore new objects/total time to explore two objects: time to explore old objects/total time to explore two objects) × 100%.

2.4. Sample collection

After completing behavioral testing on weaning, animals were sacrificed using 2% pentobarbital (50 mg/kg, i.p.). Hippocampal tissue was taken from 4 to 5 animals in each group and frozen immediately in dry ice and then transferred to −80 °C storage until required for further gene and protein expression analyses. The whole brains of 3–4 rats per group were removed and fixed in 4% paraformaldehyde for subsequent histopathologic analysis (including Golgi-Cox staining) and immunofluorescence analysis.

2.5. Protein extraction and Western blot analyses

Briefly, protein was extracted from hippocampal tissue using RIPA lysis buffer (65 mM Tris-HCl pH 7.5, 150 mM NaCl, 1 mM EDTA, 1% NP-40, 0.5% sodium deoxycholate, and 0.1% SDS) and quantified. Protein samples were separated on 8% or 10% SDS-PAGE gels and transferred to PVDF membranes (IPVH00010; Millipore, Billerica, MA, USA), which were blocked with 5% skimmed milk in TBST. Membranes were incubated with the indicated primary antibodies overnight at 4 °C and then with secondary horseradish peroxidase (HRP)-conjugated antibodies for 1 h at room temperature. Protein expression signals were detected by a ChemiDoc MP Imaging System (Bio-Rad, Hercules, CA, USA). β-actin was used as the equal loading control. All antibodies used in this study are listed in Supplementary Table 1.

2.6. RNA extraction and quantitative PCR analysis

Total RNA was extracted with Trizol. qPCR analysis was performed. mRNA expression levels of target genes were normalized to those of the β-actin-encoding gene *Actb*. The primer pairs used in this study are shown in Supplementary Table 2.

2.7. cDNA library preparation, RNA sequencing, and data processing

Total RNA was extracted from hippocampus samples using TRIzol reagent following the manufacturer's instructions (Thermo Fisher Scientific, Waltham, MA). Sequencing libraries were generated using the MGIEasy RNA Library Prep Kit according to the manufacturer's recommendations (MGI Tech, Shenzhen, China), which involved RNA fragmentation, cDNA synthesis, end repair, adapter ligation, and PCR amplification. The prepared libraries were then sequenced on a MGISEQ-2000 platform, generating 50 bp single-end reads for further analysis.

The raw RNA-seq reads were subjected to quality control using SOAPnuke (v2.0.7) to remove adapter sequences and low-quality reads (with N content >5%). After quality control, the clean reads were aligned to the canine reference genome Cfam1.0 (RefSeq) using hisat2 (v2.1.0). Following alignment, read counts for each gene were calculated using StringTie (v1.3.3b). Subsequently, the limma R package was used to identify differentially expressed genes.

For GSEA, GO or Reactome gene sets (v.5.1) were downloaded from the Molecular Signatures Database (MSigDB) website (https://www.gsea-msigdb.org/gsea/msigdb/). GSEA was performed on normalized expression data using the R package fgsea (v1.20.0). Pathways with a p-value <0.05 were considered significant.

2.8. Histopathologic analysis

TUNEL staining: TUNEL staining was performed on paraffin-embedded sections using the In Situ Cell Death Detection Kit, Fluorescein (ZSGB-Bio, China) according to the manufacturer's instructions. Slides were incubated for 30 min at 37 °C in 20 μg/ml proteinase K working solution, rinsed with PBS, and the area around the sample dried. The slides were then incubated with 50 μl of TUNEL reaction mixture containing terminal deoxynucleotidyl transferase (TdT) for 60 min in a dark, humidified atmosphere at 37 °C. After rinsing three times with PBS, slides were analyzed for positive cells.

Nissl staining: For Nissl staining, sections were stained in Nissl staining solution (cat# C0117, Beyotime, China) for 5 min, washed with double-distilled water, and mounted with Permount. Images were captured under a light microscope. Neurons with visible nuclear and relatively complete cellular morphology were counted using ImageJ software.

Golgi-Cox staining: Golgi-Cox staining was performed using a commercial staining kit (Hito Golgi-Cox OptimStain Kit, Hitobiotec Corp, Kingsport, TN) to characterize potential changes in the density and features of neuronal dendritic spines. The whole brain was soaked in the staining solution at room temperature for 14 days avoiding light according to the instruction manual. Tissues were prepared as 60-μm paraffin sections. Images were captured using a confocal microscope (LSM880, Zeiss, Jena, Germany). 3-D reconstruction was performed

using Imaris software (v.9.0.1, Bitplane AG, Schlieren, Switzerland) to detect categories of dendrite spine, where cells with straight terminal branches with clear resolution of spines and longer than 10 μm were selected for dendritic spine counting and analysis.

2.9. Immunofluorescence staining

For immunofluorescence microscopy, paraffin sections were labeled with primary antibodies overnight, followed by incubation with a suitable fluorophore-conjugated secondary antibody for 1 h. Immunofluorescence images were obtained using a fluorescence microscope with DP2-BSW software (v2.2, Olympus, Tokyo, Japan). All antibodies used in this study are listed in Supplementary Table 3.

2.10. Statistical analysis

All data were analyzed using the appropriate statistical analysis methods with GraphPad Prism 8.0 software (GraphPad Software, San Diego, CA, USA), and the data are expressed as means ± SEM. Student's *t*-test was used to analyze differences between two groups, while two-way ANOVA was applied for multiple comparisons, followed by Tukey's post hoc testing (for data showing homogeneity of variance). For datasets with skewed distributions, nonparametric statistical analysis was performed using the Mann-Whitney *U* test for two groups. A p-value <0.05 was considered statistically significant.

3. Results

3.1. EE attenuates depression-like behavior in MS-induced postpartum rats with depression

After cohabiting and confirming that the parent mother was pregnant the next morning, parent mothers in the EE group were randomly transferred to a rich environment or their normal cages until the end of the experiment (Fig. 1A). Maternal rats showed general depression-like and anxiety-like behavior and cognitive impairment after maternal separation, and EE reversed this change (Fig. 1C-L). Open field testing showed that EE alleviated anxiety-like behavior (Fig. 1C–F) in maternal rats induced by MS, the latter shown by a decrease in activity in the central area, including the number of times entering the central area (Fig. 1C; $F(1, 24) = 6.758$, $p = 0.0157$, SE - MS vs EE - MS, $p = 0.1072$) and the time staying in the central area (Fig. 1D; $F(1, 24) = 8.900$, $p = 0.0065$, SE - MS vs EE - MS, $p < 0.01$). The total activity distance (Fig. 1E; $F(1, 24) = 5.277$, $p = 0.0306$, SE - MS vs EE - MS, $p < 0.05$) and average velocity (Fig. 1F; $F(1, 24) = 7.694$, $p = 0.0106$, SE - MS vs EE - MS, $p < 0.05$) to show activity desire was also significantly lower in the MS group and reversed to control/baseline by EE.

Similarly, using FST to detect despair and SPT to detect a loss of pleasure, FST showed that the immobility time of maternal rats was significantly prolonged by MS and EE reversed this change (Fig. 1I; $F(1, 24) = 10.57$, $p = 0.0034$, SE - MS vs EE - MS, $p < 0.01$). Sucrose preference was tested over 1 h and 24 h and, in the former but not the latter, MS rats showed a significant decrease in sugar preference index, while maternal rats in the EE group had a significant sugar preference (Fig. 1H; 1 h: $F(1, 24) = 20.57$, $p = 0.0001$, SE - MS vs EE - MS, $p < 0.0001$; 24 h: $F(1, 24) = 0.6776$, $p = 0.4185$, SE - MS vs EE - MS, $p = 0.8584$).

We also examined the influence of EE on cognitive function using the Barnes maze test and new object recognition experiment. After four days of Barnes maze testing, maternal rats subjected to MS showed obvious impairment of memory and spatial location recognition, although each group of maternal rats showed a certain degree of learned accuracy (Fig. 1G; day 1: $F(1, 24) = 5.632$, $p = 0.0260$, SE - MS vs EE - MS, $p < 0.05$; day 2: $F(1, 24) = 4.577$, $p = 0.0428$, SE - MS vs EE - MS, $p < 0.05$; day 3: $F(1, 24) = 8.666$, $p = 0.0071$, SE - MS vs EE - MS, $p < 0.05$; day 4: $F(1, 24) = 6.278$, $p = 0.0194$, SE - MS vs EE - MS, $p = 0.0727$). Similarly, the new object recognition experiment showed that the frequency (Fig. 1J; Familiar object: $F(1, 24) = 11.11$, $p = 0.0028$, SE - MS vs EE - MS, $p < 0.01$; Novel object: $F(1, 24) = 4.092$, $p = 0.0544$, SE - MS vs EE - MS, $p = 0.0708$) and time (Fig. 1K; Familiar object: $F(1, 24) = 7.493$, $p = 0.0115$, SE - MS vs EE - MS, $p < 0.001$; Novel object: $F(1, 24) = 2.968$, $p = 0.0978$, SE - MS vs EE - MS, $p = 0.1375$) of exploring novel objects and cognitive index (RI) (Fig. 1L; Duration: $F(1, 24) = 15.23$, $p = 0.0007$, SE - MS vs EE - MS, $p < 0.0001$; Frequency: $F(1, 24) = 8.515$, $p = 0.0075$, SE - MS vs EE - MS, $p < 0.001$) of MS rats decreased significantly, while EE significantly reversed this change.

3.2. Transcriptional profile governed by EE

To further explore the biological mechanisms by which the EE improves depression-like behaviors caused by MS, hippocampal samples from the EE-MS and SE-MS groups were subjected to transcriptome sequencing. Principal component analysis (PCA) revealed distinct separation of EE-MS and SE-MS rats based on gene expression profiles (Fig. 2A).

Screening differentially-expressed genes (DEG) between the EE-MS and SE-MS groups, 104 genes were downregulated and 57 were upregulated (Fig. 2B). Gene Ontology (GO) analysis and Reactome data analysis (Fig. 2C) revealed that neuroinflammation, neuroplasticity, and apoptosis pathway-related processes were significantly related to EE, with neuroinflammation and apoptosis pathway-related processes significantly enriched in the SE-MS group and neuroplasticity-related processes significantly enriched in the EE-MS group. Significant DEGs related to these three biological processes are shown in Fig. 2D–F.

3.3. EE reverses neuroinflammation in the hippocampus

Transcript analysis of hippocampal tissue from maternal rats revealed significantly upregulated inflammation after MS, and neuroinflammation may be an important phenotype of depression-like behavior mediated by MS stimulation. To verify these transcriptome results, qPCR was used to detect common inflammatory markers and inflammatory body NLRP3, IL-1β, TNF-α, and NLRP3 were significantly upregulated after MS modeling, while EE significantly downregulated these markers (Fig. 3I; IL-1β: $F(1, 8) = 69.12$, $p < 0.0001$, SE - MS vs EE - MS, $p < 0.0001$; TNF-α: $F(1, 8) = 20.66$, $p = 0.0019$, SE - MS vs EE - MS, $p < 0.001$; NLRP3: $F(1, 8) = 5.414$, $p = 0.0484$, SE - MS vs EE - MS, $p < 0.05$). Immunofluorescence analysis (Fig. 3A–F; IL-1β: $F(1, 12) = 13.78$, $p = 0.0030$, SE - MS vs EE - MS, $p < 0.001$; TNF-α: $F(1, 12) = 21.23$, $p = 0.0006$, SE - MS vs EE - MS, $p < 0.0001$; NLRP3: $F(1, 12) = 18.08$, $p = 0.0011$, SE - MS vs EE - MS, $p < 0.001$) and western blotting (Fig. 3G and H; IL-1β: $F(1, 8) = 43.39$, $p < 0.0002$, SE - MS vs EE - MS, $p < 0.05$; TNF-α: $F(1, 8) = 69.18$, $p < 0.0001$, SE - MS vs EE - MS, $p < 0.0001$; NLRP3: $F(1, 8) = 773.8$, $p < 0.0001$, SE - MS vs EE - MS, $p < 0.0001$) confirmed transcript-level changes at the protein level. Furthermore, microglia are recognized as the most important phagocytes in the central nervous system, mediating inflammatory activation and phagocytosis in the brain. Quantification of IBA1, a microglia marker, showed that maternal rats treated with MS showed microglial activation that was mitigated by EE (Fig. 3G and H; IBA1: $F(1, 8) = 7.069$, $p = 0.0289$, SE - MS vs EE - MS, $p < 0.05$). It is possible that microglia and NLRP3 mediate neuroinflammation.

3.4. EE improves neuronal apoptosis and neurogenesis induced by MS

The renewal and neurogenesis of cerebral neurons are essential to CNS function (Lim et al., 2016). To examine whether EE reverses the effects of MS on parental rats by affecting neuronal apoptosis and neurogenesis, we measured key apoptotic proteins by immunofluorescence (Fig. 4A–D; TUNEL: $F(1, 12) = 18.34$, $P < 0.0011$, SE - MS vs EE - MS, $p < 0.001$; NeuN: $F(1, 11) = 10.09$, $p = 0.0088$, SE - MS vs EE - MS, $p < 0.05$) and western blotting (Fig. 4G and H; Caspase 9: $F(1, 8) = 2069$, $p < 0.0001$, SE - MS vs EE - MS, $p < 0.0001$; Caspase 3: $F(1, 8) = 566.8$, p

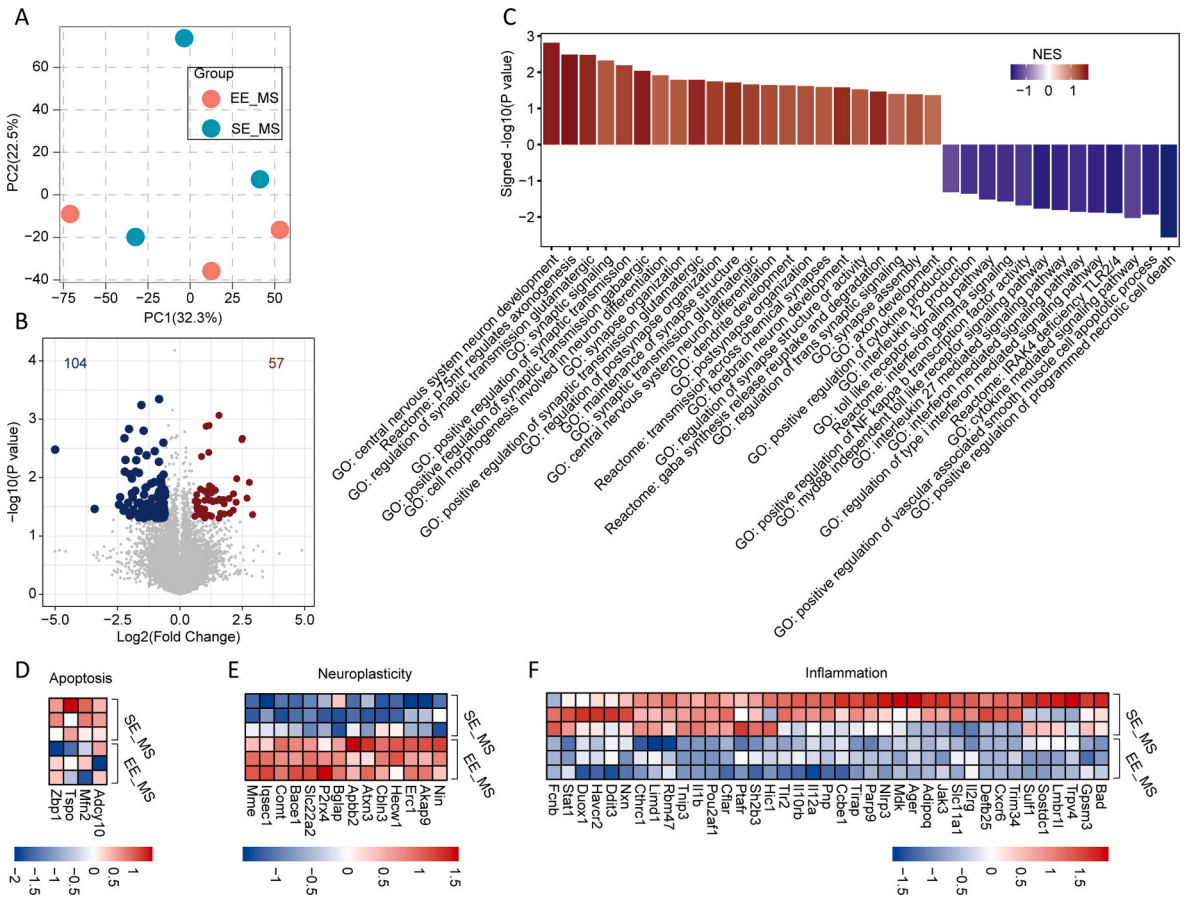


Fig. 2. Transcriptional profiles governed by EE.
(A) Principal component analysis (PCA) of the EE-MS and SE-MS groups. (B) Volcano plot of the EE-MS and SE-MS groups generated by screening two groups of differential expressed genes (DEG). (C) Gene Ontology (GO) and Reactome data analysis. (D) Heatmap used to visualize significant apoptosis-related DEGs. (E) Heatmap used to visualize significant neuroplasticity-related DEGs. (F) Heatmap used to visualize significant neuroinflammation-related DEGs.

< 0.0001, SE - MS vs EE - MS, $p < 0.0001$; bax: $F(1, 8) = 297.0$, $p < 0.0001$, SE - MS vs EE - MS, $p < 0.0001$; bcl-2: $F(1, 8) = 181.6$, $p < 0.0001$, SE - MS vs EE - MS, $p < 0.0001$). Caspase3/9 and Bax increased significantly after MS modeling, suggesting increased apoptotic activity associated with a decrease and loss of neurons, while EE decreased expression of these markers, indicating that apoptosis was significantly inhibited after EE to protect neurons. Consistent with these pro-apoptotic molecules, as an inhibitor of apoptosis, BCL-2 (B-cell lymphoma 2) was inhibited after MS modeling and its activity was restored after EE. Nissl staining is commonly used to detect the state and activity of neurons, and we found that there was significant neuronal loss after the establishment of MS and preservation of hippocampal neurogenesis (Fig. 4E and F; $F(1, 12) = 11.97$, $p = 0.0047$, SE - MS vs EE - MS, $p < 0.01$) in maternal rats experiencing EE.

3.5. EE diminishes impaired synaptic plasticity induced by MS

Depression is often accompanied by synaptic impairment, which may be the structural basis of cognitive impairment in patients with depression (Carrard et al., 2018). To further study whether EE regulates impaired synaptic function after MS modeling, we detected the pre-synaptic membrane marker GAP43, synaptic vesicle molecule SYN, and postsynaptic membrane marker PSD95. MS significantly downregulated synaptic structural molecules related to cognitive impairment, while EE upregulated these molecules to restore cognitive function. Measuring indicators of neuronal function and central system state such as BDNF and c-fos, EE also prevented their downregulation caused by MS, as verified by immunofluorescence (Fig. 5A–F; GAP43: $F(1, 12) = 29.51$, $p = 0.0002$, SE - MS vs EE - MS, $p < 0.05$; PSD95: $F(1, 12) = 11.12$, $p = 0.0059$, SE - MS vs EE - MS, $p < 0.01$; BDNF: $F(1, 12) = 14.00$, $p = 0.0028$, SE - MS vs EE - MS, $p < 0.001$), qPCR (Fig. 5I; GAP43: $F(1, 8) = 9.422$, $p = 0.0154$, SE - MS vs EE - MS, $p < 0.05$; SYN: $F(1, 8) = 8.710$, $p = 0.0184$, SE - MS vs EE - MS, $p < 0.05$; PSD95: $F(1, 8) = 27.89$, $p = 0.0007$, SE - MS vs EE - MS, $p < 0.001$; BDNF: $F(1, 8) = 7.644$, $p = 0.0245$, SE - MS vs EE - MS, $p < 0.05$), and western blotting (Fig. 5G and H; GAP43: $F(1, 8) = 17.55$, $P = 0.0030$, SE - MS vs EE - MS, $p < 0.001$; SYN: $F(1, 8) = 10.33$, $p = 0.0123$, SE - MS vs EE - MS, $p < 0.05$; PSD95: $F(1, 8) = 9.291$, $p = 0.0159$, SE - MS vs EE - MS, $p < 0.01$; BDNF: $F(1, 8) = 11.08$, $p = 0.0104$, SE - MS vs EE - MS, $p < 0.05$; c-Fos: $F(1, 8) = 8.555$, $p = 0.0191$, SE - MS vs EE - MS, $p < 0.01$).

3.6. EE improves the regeneration of dendritic spines induced by MS

Finally, we examined synapse ultrastructure. It is well known that dendrites are not only involved in the formation of synapses, but also a key structure connecting neurons to neurons and neurons to glial cells. To examine whether EE affected the maintenance and loss of dendritic spines, we used Golgi staining to clearly show the ultrastructure of dendrites and dendritic spines. Synaptic density decreased significantly after MS exposure (Fig. 6A and B; Spine density: $F(1, 12) = 33.66$, $p < 0.0001$, SE - MS vs EE - MS, $p < 0.01$), and EE significantly reversed this decrease in the number of dendrite spines.

4. Discussion

Here we used the classical MS model as a rat model of PPD. In our

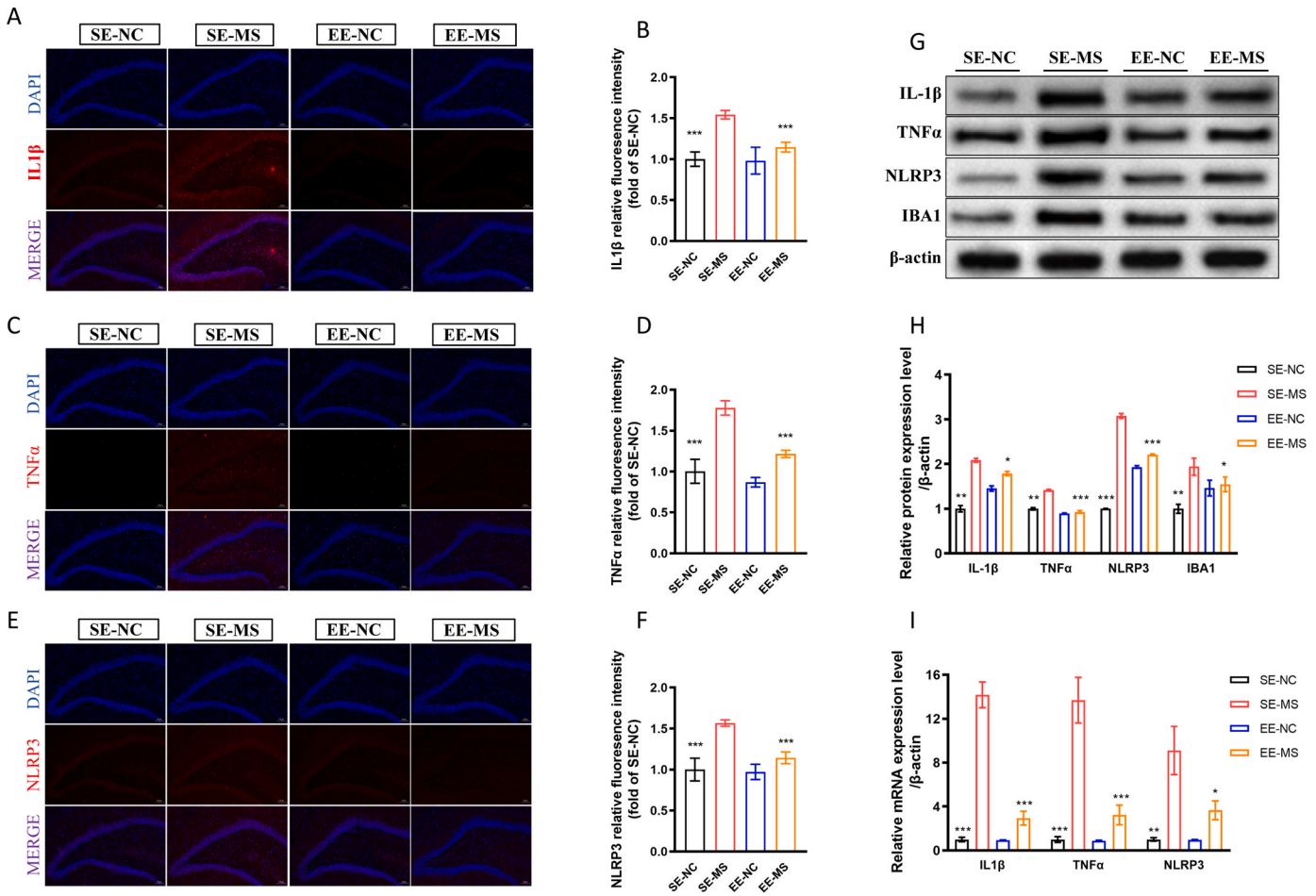


Fig. 3. EE reverses neuroinflammation levels in the hippocampus.
(A–B) Representative immunostaining for IL-1β in the hippocampal DG subregion and its quantitative analysis. Scale bars, 100 μm. (C–D) Representative immunostaining for TNFα in the hippocampal DG subregion and its quantitative analysis. Scale bars, 100 μm. (E–F) Representative immunostaining for NLRP3 in the hippocampal DG subregion and its quantitative analysis. Scale bars, 100 μm. (G–H). Representative western blots of IL1β, TNFα, NLRP3, and IBA1 in the hippocampal region and graphs showing relative protein expression. β-actin was the loading control. (I) Graphs showing relative mRNA expression of IL-1β, TNFα, and NLRP3. mRNA expression levels were normalized to those of β-actin in the qPCR assay. All data are presented as the means ± SEM (n = 3–4 per group). *p < 0.05, **p < 0.01, ***p < 0.001 versus the SE-MS group by two-way ANOVA with Tukey's post-hoc analysis. NS, no significance.

behavioral experiments, and consistent with our hypothesis, we found that MS also increased anxiety and depression-like behavior in postpartum dams. The finding that stress causes anxiety and depression-like behavior in postpartum mothers is consistent with previous findings (Salari et al., 2016; Smith et al., 2004). Sucrose preference experiment was used to reflect the lack of pleasure in maternal separation-induced postpartum depression in maternal rats, One issue that needs to be clarified is that sucrose preference was tested over 1-h and 24-h, but showed disparities between them. Depressive states may lead to alterations in the function of the reward system in rats (Fox et al., 2020). Over a short period of time, this alteration may have made the rats less responsive to rewarding stimuli and therefore did not show a clear preference for sugar water. However, over extended periods of time, even in the depressed state, rats began to experience the rewarding nature of sugar water and therefore showed a clear preference for sugar water in the prolonged experiments. The depressive state may lead to alterations in the rat's neurotransmitter system, such as dopamine and serotonin (McDevitt et al., 2011). For a short period of time, this biological alteration may make it difficult for rats to fully experience the sense of reward from sugar water. However, over time, rats adapt to this state and show a preference for sugar water. The depressed state made the rats more anxious and restless, resulting in a weaker response to novel stimuli and an inability to show a positive response to sugar water, which may have inhibited the expression of a preference for sugar water (McDevitt et al., 2011). However, over time, depressed rats gradually adapted to the difference in taste between plain and sugar water, thereby showing a clear preference for sugar water in the prolonged experiment. At the same time, consistent with our hypothesis, EE during pregnancy and postpartum repaired the behavioral and biological changes induced by MS in the hippocampus.

EE is mainly used in the context of early-life adversity, and it is thought that early EE can help reverse the serious emotional and psychological problems caused by early life adversity, perhaps through epigenetic mechanisms (Swartz et al., 2017). It is well known that environmental factors interact with biological and genetic factors to influence the development and health of organisms. Environmental Enhancement (EE), a proven paradigm of positive environmental manipulation, has been shown to have beneficial effects on the brain and behaviour (Dandi et al., 2023). An enriched environment leads to important changes in brain structure and function by altering gene expression and protein levels, changing neurotransmitter systems and other brain chemicals, and altering the structure of neurons and the brain as a whole. Enriched environments have been shown to modify behaviour and have a protective effect on seizure development (Kotloski and Sutula, 2015). It has been previously reported that EE improves CUMS-induced depressive-like behaviour and cognitive performance

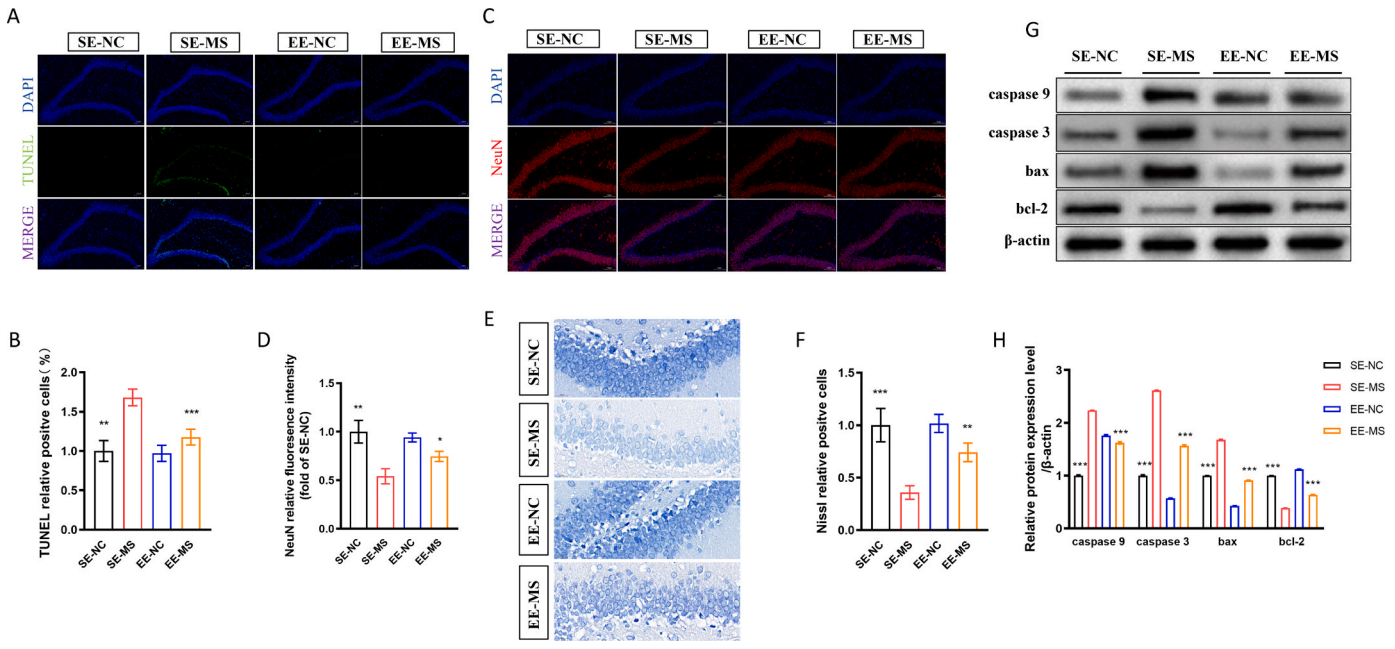


Fig. 4. EE improves neuronal apoptosis and neurogenesis induced by MS.
(A–B) Representative images of TUNEL staining in the hippocampal DG subregion and its quantitative analysis. Scale bars, 100 μm. (C–D) Representative immunostaining for NeuN in the hippocampal DG subregion and its quantitative analysis. Scale bars, 100 μm. (E–F) Nissl staining in the hippocampal DG subregion and its quantitative analysis. Scale bars, 100 μm. (G–H) Representative western blots of caspase 9, caspase 3, Bax, and Bcl-2 in the hippocampal region and graphs showing relative protein expression. β-actin was the loading control. All data are presented as means ± SEM (n = 3–4 per group). *p < 0.05, **p < 0.01, ***p < 0.001 versus the SE-MS group by two-way ANOVA with Tukey's post-hoc analysis. NS, no significance.

and increases neuronal dendritic spine density by regulating the miR-92a-3p/KLF2 pathway and inhibiting neuronal apoptosis (Ji and Zhao, 2023). Prenatal stress-induced learning and memory deficits in offspring can be corrected by enrichment of the environment by a mechanism related to reduced plasma corticosterone and increased hippocampal IGF-2 and Arc in offspring rats as a result of chronic maternal stress during pregnancy (Guan et al., 2021). EE provides evidence for neuroprotective effects in depression and cognitive deficits through activation of the SIRT1/microRNA-134 pathway (Shen et al., 2019). Effects of short environmental enrichment on early–life adversity induced cognitive alternations in adolescent rats (Joushi et al., 2021). enrichment can normalize chronic restraint stress-induced reduction in Bdnf, and can prevent acute restraint stress-induced increase in Egr1 (Cordner et al., 2021). Environmental enrichment decreases chronic psychosocial stress-impaired extinction and reinstatement of ethanol conditioned place preference in male mice (Bahi and Dreyer, 2020). The application of EE in sensitive periods of maternal development may affect mothers in several different ways. For example, EE may improve contact with cubs within the improved living environment. Mothers experiencing pregnancy and the postpartum period undergo significant neuroendocrine and behavioral changes caused by changes in maternal physiological and environmental needs (Bukhari et al., 2019). Some researchers believe that the maternal experience itself is a rich experience due to the interaction between endocrine changes and the need to take care of the young (Feldman, 2020). Although there is a clear positive relationship between neuroendocrine changes during pregnancy and the development of maternal behavior, the influence of EE on maternal behavior is unclear. We exposed female rats to EE during pregnancy and postpartum lactation and studied changes in hippocampal adult neurogenesis, neuroinflammation, and neuroplasticity. Interestingly, a rich environment prevented hippocampal neuronal inflammation and apoptosis associated with MS pressure, stimulating cell proliferation and the formation of new neurons.

Neuroinflammation plays an important role in overcoming stress in the brain (Cobourne-Duval et al., 2018; Wang et al., 2013). Transcriptome analysis showed that there was significantly less inflammatory signal in the hippocampus of EE rats than in MS rats. EE may improve non-specific neural responses in the hippocampus. We also observed downregulation of many neurokines in the EE group, including IL-1β, TNF-α, and NLRP3 (NLR family, pyrrolidine domain 3) inflammatory body complex. NLRP3 is an intracellular polyprotein complex that participates in many innate immune processes related to infection, inflammation, and autoimmunity (Mehto et al., 2019). These signals or stress exposures may be key factors in PPD. As the main immune cells in the brain, microglia play a role in responding to brain stress, and microglial activation is a typical phenotype of brain inflammation (Voet et al., 2018). Our results suggest that the improvement in depression-like behavior of maternal rats after EE exposure may be related to a decrease in the neuroinflammatory response of NLRP3 inflammatory bodies and cytokines.

Patients with clinical PPD often have both cognitive impairment and depressive symptoms (Gelaye et al., 2016). In our experiment, compared with the MS model, EE significantly improved cognitive function. Cognitive impairment is usually a sign of decreased synaptic function (Spinelli et al., 2017). Proinflammatory cytokine IL-1β can directly act on neurons or activate microglia through the blood-brain barrier, thus altering synaptic plasticity (Wang et al., 2018; Miller and Raison, 2016). On the other hand, the neurotoxic effect of neuroinflammation can lead to synaptic remodeling, indicating that neuroplasticity also plays an important role in the pathophysiology and antidepressant function of depression (Wang et al., 2018). It has been reported that high levels of inflammatory molecules reduce various neuroplasticity markers. Indeed, NLRP3 and mature IL-1β play an important role in synaptic plasticity and cognitive function (Miller and Raison, 2016). Adult neurogenesis is a lifelong process in the brains of healthy adult mammals (Shani-Narkiss et al., 2020). The hippocampus is an important brain area responsible for advanced functions such as memory and cognition. Reproductive experience, pregnancy, and lactation affect a woman's physiological and endocrine system (Bridges, 2016; Shingo et al., 2003; Tomizawa et al., 2003). Reproductive hormones produced during

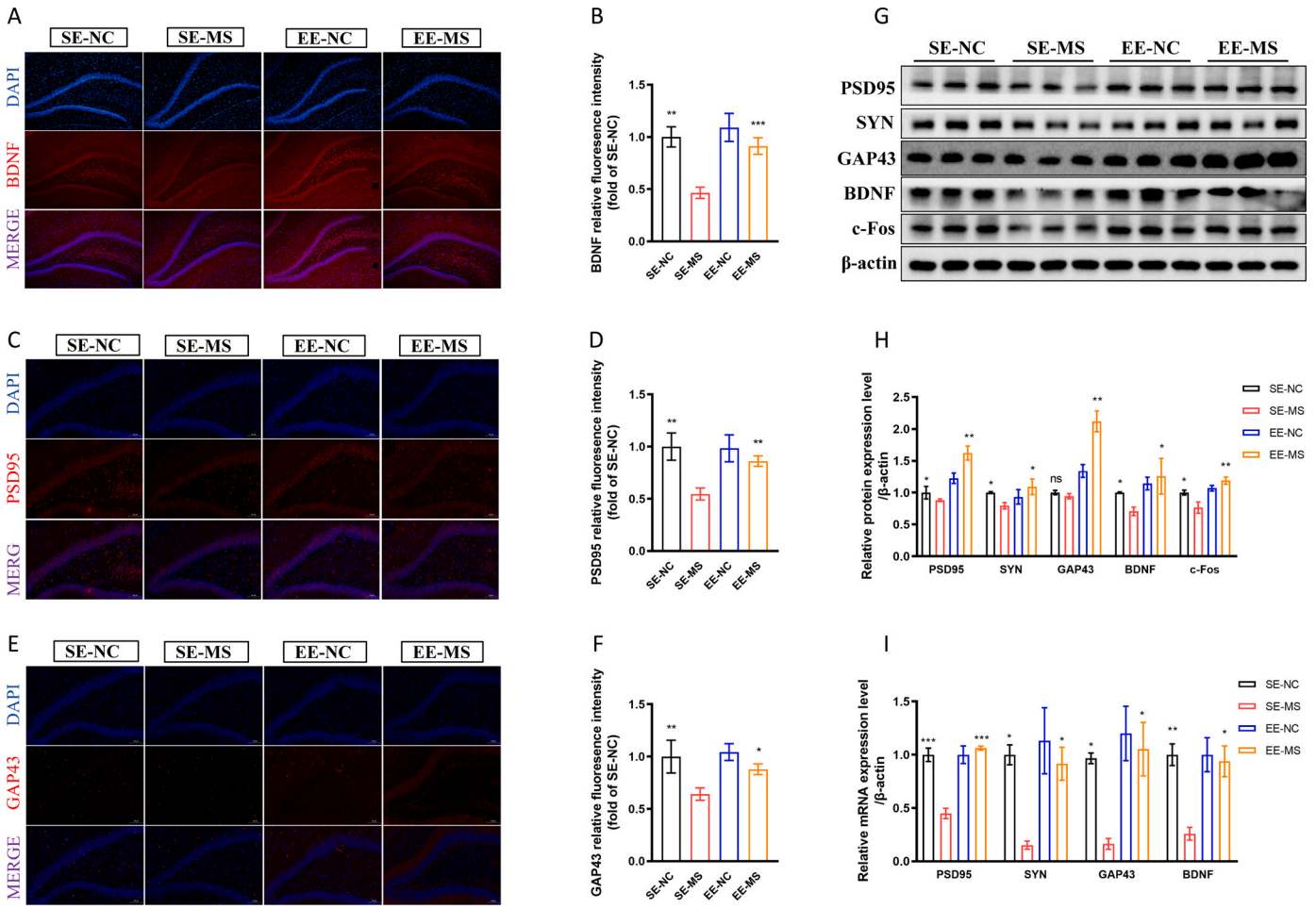


Fig. 5. EE reduces impaired synaptic plasticity induced by MS.
(A–B) Representative immunostaining for BDNF in the hippocampal DG subregion and its quantitative analysis. Scale bars, 100 μm. (C–D) Representative immunostaining for PSD95 in the hippocampal DG subregion and its quantitative analysis. Scale bars, 100 μm. (E–F) Representative immunostaining for GAP43 in the hippocampal DG subregion and its quantitative analysis. Scale bars, 100 μm. (G–H). Representative western blots of PSD95, SYN, GAP43, BDNF, and c-fos in the hippocampal region and graphs showing relative protein expression. β-actin was the loading control. (I) Graphs showing relative mRNA expression of PSD95, SYN, GAP43, and BDNF. mRNA expression levels were normalized to β-actin. All data are presented as means ± SEM (n = 3–4 per group). *p < 0.05, **p < 0.01, ***p < 0.001 versus the SE-MS group by two-way ANOVA with Tukey's post-hoc analysis. NS, no significance.

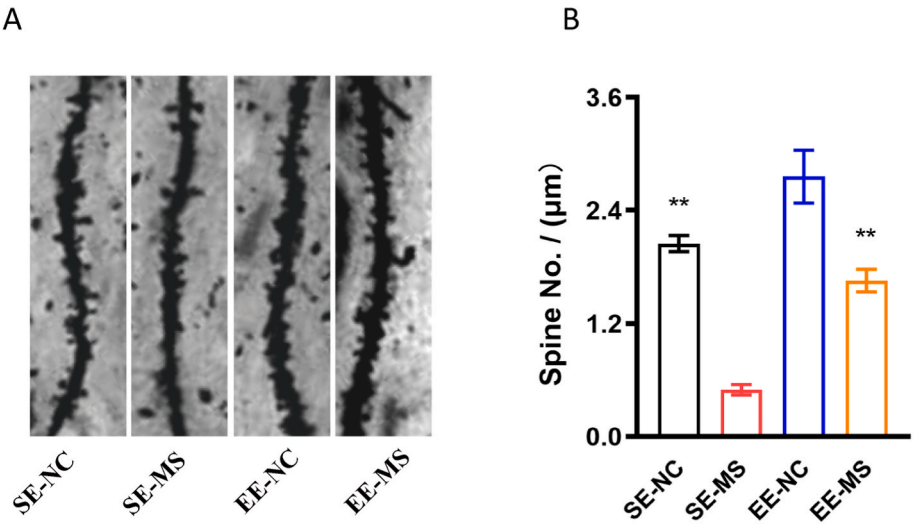


Fig. 6. EE improves the regeneration of dendritic spines induced by MS.
(A) Representative Golgi-Cox staining of hippocampal neurons. (B) Spine density results from Golgi staining (**p < 0.01 versus the SE-MS group by two-way ANOVA with Tukey's post-hoc analysis. NS, no significance.; n = 4 in each group).

pregnancy and the postpartum period are known to alter neurogenesis and dendritic morphology (Shingo et al., 2003; Prange-Kiel and Rune, 2006). Cognitive defects after the reproductive experience have been reported in both humans and mice (Henry and Sherwin, 2012; Cui et al., 2014), although the results are inconclusive and contradictory. Previous studies have shown that EE can have a beneficial effect on hippocampal neurogenesis in adults (Hu et al., 2010; Kempermann et al., 1997), and it has also been shown to increase the number of new granulosa cells in the dentate gyrus (Kempermann et al., 1997, 1998). Susceptibility to environmental stimuli, such as EE, may increase serotonin, thereby increasing neuronal plasticity. In this study, we observed that EE reversed MS-induced downregulations in synaptic function and several specific indicators of synaptic plasticity including PSD95, SYN, and GAP43, which play an important role in cognitive function. In addition, by analyzing the structure of dendritic spines, we detected a higher density of dendritic spines in the EE than in the MS group, all suggesting that EE can improve cognitive function.

A range of interventions, including psychotherapy/counselling and antidepressant medication, are often tested clinically in women with PPD. The evidence for the efficacy of psychological interventions is strong. Several antidepressants, including paroxetine, sertraline and nortriptyline, have been identified as the most effective antidepressants for breastfeeding women. There is evidence that preventive interventions are effective, but the observed effects are small (O'Hara and McCabe, 2013; Stewart and Vigod, 2019). Treatment options available to obstetricians include sedative antipsychotics such as olanzapine or haloperidol, which can be used in conjunction with benzodiazepines such as lorazepam (Treatment and Management of Mental, 2023).

Our experiments had some limitations. EE is an experimental construct, and it may have considerable heterogeneity in practice, although the start time and duration of the rich environment were imposed on the maternal rats in our experiments, lasting from the day of pregnancy to the day of weaning, followed by behavioral testing. Sudden entry into EE may trigger stress. Shortening the enrichment time may lead to different results, which can be considered in future studies. During EE, excessive stimulation induced by changing items every four days may have excessive psychological burden, in turn leading to abnormal behavior.

The pathophysiology of PPD is complex and incompletely understood, and postpartum depression is a relatively complex clinical disorder and that no single model can simulate the full pathological etiology of the disorder, especially with regard to female hormone-related regulatory mechanisms and neuropsychiatric disorders. The chosen model (MS) mirrors some (but not all) aspects of PPD and that the study might therefore provide some clues on the biology of PPD and how to treat it. And we have not stratified the animals for susceptibility and depression. As an intervention, EE is complicated by laboratory factors such as the size of the cage, the number of animals, the choice of items in the enriched environment, and the frequency of item replacement. We didnot distinguish among the three aspects of the EE paradigm in this study: gestational EE, postpartum EE, and gestational combined postpartum EE, to highlight the advantages of gestational combined postpartum EE. Our research shows that EE might be beneficial for PPD, and that the holistic care of pregnant women is of value.

5. Conclusion

In conclusion, EE has a significant positive impact on MS-induced PPD by inhibiting neuroinflammation and apoptosis and promoting neuroplasticity. These observations may provide new insights into the mechanisms of postpartum depression.

Novelty and Significance

1. Current MS models are mainly used to simulate early life stress in offspring, and here we extend the influence of MS to successfully simulate maternal postpartum depression.
2. PPD may be caused by stress-induced neuroinflammation and neuroplastic disorders mediated by NLRP3, and EE can reverse these changes, indicating the importance of the environment and social support during pregnancy and lactation.
3. Our study provides new avenues for the prevention and treatment of PPD.
4. The environment-rich intervention cycle included the whole pregnancy and lactation period, providing clues on the impact of the intervention.

Funding

This work was supported by grants from the National Natural Science Foundation of China (grant number: U21A20364, 82201677), the Fundamental Research Funds for the Central Universities (grant number: 2042021kf0096).

CRediT authorship contribution statement

Guopeng Chen: Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Yuhui Zhang:** Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Ruiling Li:** Formal analysis, Data curation. **Liuyin Jin:** Software, Methodology, Investigation, Data curation. **Keke Hao:** Software, Methodology, Investigation, Data curation. **Jingtong Rong:** Formal analysis, Data curation. **Hao Duan:** Formal analysis, Data curation. **Yiwei Du:** Formal analysis, Data curation. **Lihua Yao:** Resources, Project administration. **Dan Xiang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Zhongchun Liu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2024.100624.

References

Abdul Aziz, N.U., Chiroma, S.M., Mohd Moklas, M.A., Adenan, M.I., Ismail, A., Basir, R., Ali, R.M., Hidayat Bin Baharuldin, M.T., 2021. Menhaden fish oil attenuates postpartum depression in rat model via inhibition of NLRP3-inflammasome driven inflammatory pathway. J Tradit Complement Med 11 (5), 419–426.

Alves, R.L., Portugal, C.C., Summavielle, T., Barbosa, F., Magalhaes, A., 2020. Maternal separation effects on mother rodents' behaviour: a systematic review. Neurosci. Biobehav. Rev. 117, 98–109.

Arnaiz, S.L., D'Amico, G., Paglia, N., Arismendi, M., Basso, N., del Rosario Lores Arnaiz, M., 2004. Enriched environment, nitric oxide production and synaptic plasticity prevent the aging-dependent impairment of spatial cognition. Mol Aspects Med 25 (1–2), 91–101.

Bahi, A., Dreyer, J.L., 2020. Environmental enrichment decreases chronic psychosocial stress-impaired extinction and reinstatement of ethanol conditioned place preference in C57BL/6 male mice. Psychopharmacology (Berl) 237 (3), 707–721.

Baka, J., Csakvari, E., Huzian, O., Dobos, N., Siklos, L., Leranth, C., MacLusky, N.J., Duman, R.S., Hajszan, T., 2017. Stress induces equivalent remodeling of hippocampal spine synapses in a simulated postpartum environment and in a female rat model of major depression. Neuroscience 343, 384–397.
Bayat, M., Sharifi, M.D., Haghani, M., Shabani, M., 2015. Enriched environment improves synaptic plasticity and cognitive deficiency in chronic cerebral hypoperfused rats. Brain Res. Bull. 119 (Pt A), 34–40.
Becker, M., Weinberger, T., Chandy, A., Schmukler, S., 2016. Depression during pregnancy and postpartum. Curr Psychiatry Rep 18 (3), 32.
Belz, E.E., Kennell, J.S., Czambel, R.K., Rubin, R.T., Rhodes, M.E., 2003. Environmental enrichment lowers stress-responsive hormones in singly housed male and female rats. Pharmacol. Biochem. Behav. 76 (3–4), 481–486.
Bloch, M., Daly, R.C., Rubinow, D.R., 2003. Endocrine factors in the etiology of postpartum depression. Compr Psychiatry 44 (3), 234–246.
Boufidou, F., Lambrinoudaki, I., Argeitis, J., Zervas, I.M., Pliatsika, P., Leonardou, A.A., Petropoulos, G., Hasiakos, D., Papadias, K., Nikolaou, C., 2009. CSF and plasma cytokines at delivery and postpartum mood disturbances. J. Affect. Disord. 115 (1–2), 287–292.
Brann, E., Fransson, E., White, R.A., Papadopoulos, F.C., Edvinsson, A., Kamali-Moghaddam, M., Cunningham, J.L., Sundstrom-Poromaa, I., Skalkidou, A., 2020. Inflammatory markers in women with postpartum depressive symptoms. J. Neurosci. Res. 98 (7), 1309–1321.
Bridges, R.S., 2016. Long-term alterations in neural and endocrine processes induced by motherhood in mammals. Horm. Behav. 77, 193–203.
Brummelte, S., Galea, L.A., 2010. Depression during pregnancy and postpartum: contribution of stress and ovarian hormones. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 34 (5), 766–776.
Bukhari, S.A., Saul, M.C., James, N., Bensky, M.K., Stein, L.R., Trapp, R., Bell, A.M., 2019. Neurogenomic insights into paternal care and its relation to territorial aggression. Nat. Commun. 10 (1), 4437.
Carrard, A., Elsayed, M., Margineanu, M., Boury-Jamot, B., Fragniere, L., Meylan, E.M., Petit, J.M., Fiumelli, H., Magistretti, P.J., Martin, J.L., 2018. Peripheral administration of lactate produces antidepressant-like effects. Mol Psychiatry 23 (2), 392–399.
Carvalho, K., Faivre, E., Pietrowski, M.J., Marques, X., Gomez-Murcia, V., Deleau, A., Huin, V., Hansen, J.N., Kozlov, S., Danis, C., Temido-Ferreira, M., Coelho, J.E., Meriaux, C., Eddarkaoui, S., Gras, S.L., Dumoulin, M., Cellai, L., Neuro, C.E.B.B.B., Landrieu, I., Chern, Y., Hamdane, M., Buee, L., Boutillier, A.L., Levi, S., Halle, A., Lopes, L.V., Blum, D., 2019. Exacerbation of C1q dysregulation, synaptic loss and memory deficits in tau pathology linked to neuronal adenosine A2A receptor. Brain 142 (11), 3636–3654.
Cassidy-Bushrow, A.E., Peters, R.M., Johnson, D.A., Templin, T.N., 2012. Association of depressive symptoms with inflammatory biomarkers among pregnant African-American women. J. Reprod. Immunol. 94 (2), 202–209.
Cerniauskas, I., Winterer, J., de Jong, J.W., Lukacsovich, D., Yang, H., Khan, F., Peck, J. R., Obayashi, S.K., Lilascharoen, V., Lim, B.K., Foldy, C., Lammel, S., 2019. Chronic stress induces activity, synaptic, and transcriptional remodeling of the lateral habenula associated with deficits in motivated behaviors. Neuron 104 (5), 899–915 e8.
Cobourne-Duval, M.K., Taka, E., Mendonca, P., Soliman, K.F.A., 2018. Thymoquinone increases the expression of neuroprotective proteins while decreasing the expression of pro-inflammatory cytokines and the gene expression NFkappaB pathway signaling targets in LPS/IFNgamma -activated BV-2 microglia cells. J. Neuroimmunol. 320, 87–97.
Cordner, Z.A., Marshall-Thomas, I., Boersma, G.J., Lee, R.S., Potash, J.B., Tamashiro, K.L. K., 2021. Fluoxetine and environmental enrichment similarly reverse chronic social stress-related depression- and anxiety-like behavior, but have differential effects on amygdala gene expression. Neurobiol Stress 15, 100392.
Cui, J., Jothishankar, B., He, P., Staufenbiel, M., Shen, Y., Li, R., 2014. Amyloid precursor protein mutation disrupts reproductive experience-enhanced normal cognitive development in a mouse model of Alzheimer's disease. Mol. Neurobiol. 49 (1), 103–112.
Dandi, E., Spandou, E., Dalla, C., Tata, D.A., 2023. Tauhe neuroprotective role of environmental enrichment against behavioral, morphological, neuroendocrine and molecular changes following chronic unpredictable mild stress: a systematic review. Eur. J. Neurosci. 58 (4), 3003–3025.
Deng, D., Cui, Y., Gan, S., Xie, Z., Cui, S., Cao, K., Wang, S., Shi, G., Yang, L., Bai, S., Shi, Y., Liu, Z., Zhao, J., Zhang, R., 2022. Sinisan alleviates depression-like behaviors by regulating mitochondrial function and synaptic plasticity in maternal separation rats. Phytomedicine 106, 154395.
Duman, R.S., Monteggia, L.M., 2006. A neurotrophic model for stress-related mood disorders. Biol Psychiatry 59 (12), 1116–1127.
Ergen, F.B., Cosan, D.T., Kandemir, T., Dag, I., Mutlu, F., Cosan, T.E., 2021. An enriched environment leads to increased synaptic plasticity-associated miRNA levels after experimental subarachnoid hemorrhage. J. Stroke Cerebrovasc. Dis. 30 (6), 105766.
Feldman, R., 2020. What is resilience: an affiliative neuroscience approach. World Psychiatr. 19 (2), 132–150.
Feldman, R., Granat, A., Pariente, C., Kanety, H., Kuint, J., Gilboa-Schechtman, E., 2009. Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. J. Am. Acad. Child Adolesc. Psychiatry 48 (9), 919–927.
Fone, K.C., Porkess, M.V., 2008. Behavioural and neurochemical effects of post-weaning social isolation in rodents-relevance to developmental neuropsychiatric disorders. Neurosci. Biobehav. Rev. 32 (6), 1087–1102.
Fox, M.E., Chandra, R., Menken, M.S., Larkin, E.J., Nam, H., Engeln, M., Francis, T.C., Lobo, M.K., 2020. Dendritic remodeling of D1 neurons by RhoA/Rho-kinase mediates depression-like behavior. Mol Psychiatry 25 (5), 1022–1034.
Gelaye, B., Rondon, M.B., Araya, R., Williams, M.A., 2016. Epidemiology of maternal depression, risk factors, and child outcomes in low-income and middle-income countries. Lancet Psychiatr. 3 (10), 973–982.
Guan, S.Z., Fu, Y.J., Zhao, F., Liu, H.Y., Chen, X.H., Qi, F.Q., Liu, Z.H., Ng, T.B., 2021. The mechanism of enriched environment repairing the learning and memory impairment in offspring of prenatal stress by regulating the expression of activity-regulated cytoskeletal-associated and insulin-like growth factor-2 in hippocampus. Environ. Health Prev. Med. 26 (1), 8.
Hajszan, T., 2020. Stress and remodeling of hippocampal spine synapses. Vitam Horm 114, 257–279.
Halligan, S.L., Murray, L., Martins, C., Cooper, P.J., 2007. Maternal depression and psychiatric outcomes in adolescent offspring: a 13-year longitudinal study. J. Affect. Disord. 97 (1–3), 145–154.
Henry, J.F., Sherwin, B.B., 2012. Hormones and cognitive functioning during late pregnancy and postpartum: a longitudinal study. Behav. Neurosci. 126 (1), 73–85.
Hu, Y.S., Xu, P., Pigino, G., Brady, S.T., Larson, J., Lazarov, O., 2010. Complex environment experience rescues impaired neurogenesis, enhances synaptic plasticity, and attenuates neuropathology in familial Alzheimer's disease-linked APPswe/PS1DeltaE9 mice. FASEB J 24 (6), 1667–1681.
Hu, P., Maita, I., Phan, M.L., Gu, E., Kwok, C., Dieterich, A., Gergues, M.M., Yohn, C.N., Wang, Y., Zhou, J.N., Qi, X.R., Swaab, D.F., Pang, Z.P., Lucassen, P.J., Roepke, T.A., Samuels, B.A., 2020. Early-life stress alters affective behaviors in adult mice through persistent activation of CRH-BDNF signaling in the oval bed nucleus of the stria terminalis. Transl. Psychiatry 10 (1), 396.
Huang, Y., Xu, W., Zhou, R., 2021. NLRP3 inflammasome activation and cell death. Cell. Mol. Immunol. 18 (9), 2114–2127.
Ji, X., Zhao, Z., 2023. Exposure to enriched environment ameliorated chronic unpredictable mild stress-induced depression-like symptoms in rats via regulating the miR-92a-3p/kruppel-like factor 2 (KLF2) pathway. Brain Res. Bull. 195, 14–24.
Joushi, S., Esmaeilpour, K., Masoumi-Ardakani, Y., Esmaeili-Mahani, S., Sheibani, V., 2021. Effects of short environmental enrichment on early-life adversity induced cognitive alternations in adolescent rats. J. Neurosci. Res. 99 (12), 3373–3391.
Kempermann, G., 2019. Environmental enrichment, new neurons and the neurobiology of individuality. Nat. Rev. Neurosci. 20 (4), 235–245.
Kempermann, G., Kuhn, H.G., Gage, F.H., 1997. More hippocampal neurons in adult mice living in an enriched environment. Nature 386 (6624), 493–495.
Kempermann, G., Kuhn, H.G., Gage, F.H., 1998. Experience-induced neurogenesis in the senescent dentate gyrus. J. Neurosci. 18 (9), 3206–3212.
Korotkova, T., Ponomarenko, A., Monaghan, C.K., Poulter, S.L., Cacucci, F., Wills, T., Hasselmo, M.E., Lever, C., 2018. Reconciling the different faces of hippocampal theta: the role of theta oscillations in cognitive, emotional and innate behaviors. Neurosci. Biobehav. Rev. 85, 65–80.
Kotloski, R.J., Sutula, T.P., 2015. Environmental enrichment: evidence for an unexpected therapeutic influence. Exp. Neurol. 264, 121–126.
Lancaster, C.A., Gold, K.J., Flynn, H.A., Yoo, H., Marcus, S.M., Davis, M.M., 2010. Risk factors for depressive symptoms during pregnancy: a systematic review. Am. J. Obstet. Gynecol. 202 (1), 5–14.
Leggio, M.G., Mandolesi, L., Federico, F., Spirito, F., Ricci, B., Gelfo, F., Petrosini, L., 2005. Environmental enrichment promotes improved spatial abilities and enhanced dendritic growth in the rat. Behav. Brain Res. 163 (1), 78–90.
Lim, J.H., Stafford, B.K., Nguyen, P.L., Lien, B.V., Wang, C., Zukor, K., He, Z., Huberman, A.D., 2016. Neural activity promotes long-distance, target-specific regeneration of adult retinal axons. Nat. Neurosci. 19 (8), 1073–1084.
Lindahl, V., Pearson, J.L., Colpe, L., 2005. Prevalence of suicidality during pregnancy and the postpartum. Arch Womens Ment Health 8 (2), 77–87.
Maas, D.A., Eijsink, V.D., Spoelder, M., van Hulten, J.A., De Weerd, P., Homberg, J.R., Valles, A., Nait-Oumesmar, B., Martens, G.J.M., 2020. Interneuron hypomyelination is associated with cognitive inflexibility in a rat model of schizophrenia. Nat. Commun. 11 (1), 2329.
Maurer-Spurej, E., Pittendreigh, C., Misri, S., 2007. Platelet serotonin levels support depression scores for women with postpartum depression. J. Psychiatry Neurosci. 32 (1), 23–29.
McDevitt, R.A., Hiroi, R., Mackenzie, S.M., Robin, N.C., Cohn, A., Kim, J.J., Neumaier, J. F., 2011. Serotonin 1B autoreceptors originating in the caudal dorsal raphe nucleus reduce expression of fear and depression-like behavior. Biol Psychiatry 69 (8), 780–787.
Mehto, S., Jena, K.K., Nath, P., Chauhan, S., Kolapalli, S.P., Das, S.K., Sahoo, P.K., Jain, A., Taylor, G.A., Chauhan, S., 2019. The crohn's disease risk factor IRGM limits NLRP3 inflammasome activation by impeding its assembly and by mediating its selective autophagy. Mol Cell 73 (3), 429–445 e7.
Miller, L.J., 2002. Postpartum depression. JAMA 287 (6), 762–765.
Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16 (1), 22–34.
Mohammad, H., Marchisella, F., Ortega-Martinez, S., Hollos, P., Eerola, K., Komulainen, E., Kulesskaya, N., Freemantle, E., Fagerholm, V., Savontaus, E., Rauvala, H., Peterson, B.D., van Praag, H., Coffey, E.T., 2018. JNK1 controls adult hippocampal neurogenesis and imposes cell-autonomous control of anxiety behaviour from the neurogenic niche. Mol Psychiatry 23 (2), 362–374.
Murai, K., Sun, G., Ye, P., Tian, E., Yang, S., Cui, Q., Sun, G., Trinh, D., Sun, O., Hong, T., Wen, Z., Kalkum, M., Riggs, A.D., Song, H., Ming, G.L., Shi, Y., 2016. The TLX-miR-219 cascade regulates neural stem cell proliferation in neurodevelopment and schizophrenia iPSC model. Nat. Commun. 7, 10965.

O'Hara, M.W., McCabe, J.E., 2013. Postpartum depression: current status and future directions. Annu. Rev. Clin. Psychol. 9, 379–407.
Oomen, C.A., Soeters, H., Audureau, N., Vermunt, L., van Hasselt, F.N., Manders, E.M., Joels, M., Lucassen, P.J., Krugers, H., 2010. Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress conditions in adulthood. J. Neurosci. 30 (19), 6635–6645.
Orefice, L.L., Mosko, J.R., Morency, D.T., Wells, M.F., Tasnim, A., Mozeika, S.M., Ye, M., Chirila, A.M., Emanuel, A.J., Rankin, G., Fame, R.M., Lehtinen, M.K., Feng, G., Ginty, D.D., 2019. Targeting peripheral somatosensory neurons to improve tactile-related phenotypes in ASD models. Cell 178 (4), 867–886 e24.
Pariante, C.M., Lightman, S.L., 2008. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 31 (9), 464–468.
Pawluski, J.L., Galea, L.A., 2007. Reproductive experience alters hippocampal neurogenesis during the postpartum period in the dam. Neuroscience 149 (1), 53–67.
Pawluski, J.L., Lambert, K.G., Kinsley, C.H., 2016. Neuroplasticity in the maternal hippocampus: relation to cognition and effects of repeated stress. Horm. Behav. 77, 86–97.
Pittenger, C., Duman, R.S., 2008. Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology 33 (1), 88–109.
Prange-Kiel, J., Rune, G.M., 2006. Direct and indirect effects of estrogen on rat hippocampus. Neuroscience 138 (3), 765–772.
Rae, M., Zanos, P., Georgiou, P., Chivers, P., Bailey, A., Camarini, R., 2018. Environmental enrichment enhances conditioned place preference to ethanol via an oxytocinergic-dependent mechanism in male mice. Neuropharmacology 138, 267–274.
Raza, S.K., Raza, S., 2023. Postpartum Psychosis, StatPearls, Treasure Island (FL) Ineligible Companies. Disclosure: Syed Raza Declares No Relevant Financial Relationships with Ineligible Companies.
Robinson, M., Whitehouse, A.J., Newnham, J.P., Gorman, S., Jacoby, P., Holt, B.J., Serralha, M., Tearne, J.E., Holt, P.G., Hart, P.H., Kusel, M.M., 2014. Low maternal serum vitamin D during pregnancy and the risk for postpartum depression symptoms. Arch Womens Ment Health 17 (3), 213–219.
Salari, A.A., Fatehi-Gharehlar, L., Motayagheni, N., Homberg, J.R., 2016. Fluoxetine normalizes the effects of prenatal maternal stress on depression- and anxiety-like behaviors in mouse dams and male offspring. Behav. Brain Res. 311, 354–367.
Sale, A., Berardi, N., Maffei, L., 2014. Environment and brain plasticity: towards an endogenous pharmacotherapy. Physiol. Rev. 94 (1), 189–234.
Shani-Narkiss, H., Vinograd, A., Landau, I.D., Tasaka, G., Yayon, N., Terletsky, S., Groysman, M., Maor, I., Sompolinsky, H., Mizrahi, A., 2020. Young adult-born neurons improve odor coding by mitral cells. Nat. Commun. 11 (1), 5867.
Shapiro, G.D., Fraser, W.D., Seguin, J.R., 2012. Emerging risk factors for postpartum depression: serotonin transporter genotype and omega-3 fatty acid status. Can J Psychiatry 57 (11), 704–712.
Sheline, Y.I., Gado, M.H., Kraemer, H.C., 2003. Untreated depression and hippocampal volume loss. Am J Psychiatry 160 (8), 1516–1518.
Shen, J., Li, Y., Qu, C., Xu, L., Sun, H., Zhang, J., 2019. The enriched environment ameliorates chronic unpredictable mild stress-induced depressive-like behaviors and cognitive impairment by activating the SIRT1/miR-134 signaling pathway in hippocampus. J. Affect. Disord. 248, 81–90.
Shingo, T., Gregg, C., Enwere, E., Fujikawa, H., Hassam, R., Geary, C., Cross, J.C., Weiss, S., 2003. Pregnancy-stimulated neurogenesis in the adult female forebrain mediated by prolactin. Science 299 (5603), 117–120.
Skrundz, M., Bolten, M., Nast, I., Hellhammer, D.H., Meinlschmidt, G., 2011. Plasma oxytocin concentration during pregnancy is associated with development of postpartum depression. Neuropsychopharmacology 36 (9), 1886–1893.
Sluiter, F., Incollingo Rodriguez, A.C., Nephew, B.C., Cali, R., Murgatroyd, C., Santos Jr., H.P., 2020. Pregnancy associated epigenetic markers of inflammation predict depression and anxiety symptoms in response to discrimination. Neurobiol Stress 13, 100273.
Smith, J.W., Seckl, J.R., Evans, A.T., Costall, B., Smythe, J.W., 2004. Gestational stress induces post-partum depression-like behaviour and alters maternal care in rats. Psychoneuroendocrinology 29 (2), 227–244.
Sparling, J.E., Barbeau, K., Boileau, K., Konkle, A.T.M., 2020. Environmental enrichment and its influence on rodent offspring and maternal behaviours, a scoping style review of indices of depression and anxiety. Pharmacol. Biochem. Behav. 197, 172997.
Spinelli, M., Fusco, S., Mainardi, M., Scala, F., Natale, F., Lapenta, R., Mattera, A., Rinaudo, M., Li Puma, D.D., Ripoli, C., Grassi, A., D'Ascenzo, M., Grassi, C., 2017. Brain insulin resistance impairs hippocampal synaptic plasticity and memory by increasing GluA1 palmitoylation through FoxO3a. Nat. Commun. 8 (1), 2009.
Stewart, D.E., Vigod, S.N., 2019. Postpartum depression: pathophysiology, treatment, and emerging therapeutics. Annu. Rev. Med. 70, 183–196.
Swartz, J.R., Hariri, A.R., Williamson, D.E., 2017. An epigenetic mechanism links socioeconomic status to changes in depression-related brain function in high-risk adolescents. Mol Psychiatry 22 (2), 209–214.
Szpunar, M.J., Malaktaris, A., Baca, S.A., Hauger, R.L., Lang, A.J., 2021. Are alterations in estradiol, cortisol, and inflammatory cytokines associated with depression during pregnancy and postpartum? An exploratory study. Brain Behav Immun Health 16, 100309.
Thul, T.A., Corwin, E.J., Carlson, N.S., Brennan, P.A., Young, L.J., 2020. Oxytocin and postpartum depression: a systematic review. Psychoneuroendocrinology 120, 104793.
Tomizawa, K., Iga, N., Lu, Y.F., Moriwaki, A., Matsushita, M., Li, S.T., Miyamoto, O., Itano, T., Matsui, H., 2003. Oxytocin improves long-lasting spatial memory during motherhood through MAP kinase cascade. Nat. Neurosci. 6 (4), 384–390.
Treatment and management of mental health conditions during pregnancy and postpartum: ACOG clinical practice guideline No. 5. Obstet. Gynecol. 141 (6), 2023, 1262–1288. Contributions).
Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B., Brizard, B., El Hage, W., Surget, A., Belzung, C., Camus, V., 2021. Neuroinflammation and depression: a review. Eur. J. Neurosci. 53 (1), 151–171.
Voet, S., Mc Guire, C., Hagemeyer, N., Martens, A., Schroeder, A., Wieghofer, P., Daems, C., Staszewski, O., Vande Walle, L., Jordao, M.J.C., Sze, M., Vikkula, H.K., Demeestere, D., Van Imschoot, G., Scott, C.L., Hoste, E., Goncalves, A., Guilliams, M., Lippens, S., Libert, C., Vandenbroucke, R.E., Kim, K.W., Jung, S., Callaerts-Vegh, Z., Callaerts, P., de Wit, J., Lamkanfi, M., Prinz, M., van Loo, G., 2018. A20 critically controls microglia activation and inhibits inflammasome-dependent neuroinflammation. Nat. Commun. 9 (1), 2036.
Volkmar, F.R., Greenough, W.T., 1972. Rearing complexity affects branching of dendrites in the visual cortex of the rat. Science 176 (4042), 1445–1447.
Wang, J., Yang, Z., Liu, C., Zhao, Y., Chen, Y., 2013. Activated microglia provide a neuroprotective role by balancing glial cell-line derived neurotrophic factor and tumor necrosis factor-alpha secretion after subacute cerebral ischemia. Int. J. Mol. Med. 31 (1), 172–178.
Wang, J., Hodes, G.E., Zhang, H., Zhang, S., Zhao, W., Golden, S.A., Bi, W., Menard, C., Kana, V., Leboeuf, M., Xie, M., Bregman, D., Pfau, M.L., Flanigan, M.E., Esteban-Fernandez, A., Yemul, S., Sharma, A., Ho, L., Dixon, R., Merad, M., Han, M.H., Russo, S.J., Pasinetti, G.M., 2018. Epigenetic modulation of inflammation and synaptic plasticity promotes resilience against stress in mice. Nat. Commun. 9 (1), 477.
Won, E., Kim, Y.K., 2020. Neuroinflammation-associated alterations of the brain as potential neural biomarkers in anxiety disorders. Int. J. Mol. Sci. 21 (18).
Wu, A., Yu, B., Chen, Q., Matthews, G.A., Lu, C., Campbell, E., Tye, K.M., Komiyama, T., 2020. Context-dependent plasticity of adult-born neurons regulated by cortical feedback. Sci. Adv. 6 (42).
Yim, I.S., Glynn, L.M., Schetter, C.D., Hobel, C.J., Chicz-Demet, A., Sandman, C.A., 2010. Prenatal beta-endorphin as an early predictor of postpartum depressive symptoms in euthymic women. J. Affect. Disord. 125 (1–3), 128–133.
Yun, H., Park, E.S., Choi, S., Shin, B., Yu, J., Yu, J., Amarasekara, D.S., Kim, S., Lee, N., Choi, J.S., Choi, Y., Rho, J., 2019. TDAG51 is a crucial regulator of maternal care and depressive-like behavior after parturition. PLoS Genet. 15 (6), e1008214.
Zhang, X., Shi, X., Wang, J., Xu, Z., He, J., 2021. Enriched environment remedies cognitive dysfunctions and synaptic plasticity through NMDAR-Ca(2+)-Activin A circuit in chronic cerebral hypoperfusion rats. Aging (Albany NY) 13 (16), 20748–20761.
Zhang, Y.M., Wei, R.M., Ni, M.Z., Wu, Q.T., Li, Y., Ge, Y.J., Kong, X.Y., Li, X.Y., Chen, G. H., 2023. An enriched environment improves maternal sleep deprivation-induced cognitive deficits and synaptic plasticity via hippocampal histone acetylation. Brain Behav 13 (6), e3018.
Zhao, X.H., Zhang, Z.H., 2020. Risk factors for postpartum depression: an evidence-based systematic review of systematic reviews and meta-analyses. Asian J Psychiatr 53, 102353.
Zhu, J., Tang, J., 2020. LncRNA Gm14205 induces astrocytic NLRP3 inflammasome activation via inhibiting oxytocin receptor in postpartum depression. Biosci. Rep. 40 (8).
Zhu, J., Hu, Z., Han, X., Wang, D., Jiang, Q., Ding, J., Xiao, M., Wang, C., Lu, M., Hu, G., 2018. Dopamine D2 receptor restricts astrocytic NLRP3 inflammasome activation via enhancing the interaction of beta-arrestin2 and NLRP3. Cell Death Differ. 25 (11), 2037–2049.
Zhu, J., Sun, T., Zhang, J., Liu, Y., Wang, D., Zhu, H., Yao, H., Ding, J., Hu, G., Lu, M., 2020. Drd2 biased agonist prevents neurodegeneration against NLRP3 inflammasome in Parkinson's disease model via a beta-arrestin2-biased mechanism. Brain Behav. Immun. 90, 259–271.