

Early life adversity influences brain development through neuroendocrine, immune, and microbiota-related mechanisms: A review

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The early life experiences have an important impact on the development of the brain and behavior and early life adversities (ELA) may affect several biological systems including the hypothalamic-pituitary-adrenal (HPA) axis, neurotransmitter and immune signaling systems, and microbiota composition. Dysregulation of these systems may result in an altered stress reactivity in both early life and the adulthood periods leading to maladaptive responses to the environmental stimuli. The activation of certain neuropeptides, including oxytocin, stimulation of the HPA axis, and increased glucocorticoid levels, may also play an important role in the early adaptive processes. In terms of brain maturation, ELA can directly or indirectly elicit structural changes in neurite growth, neurogenesis, neuronal connectivities, and signaling processes, which may contribute to the production of the long-term behavioral changes associated with an increased risk of the neuropsychiatric disorders' development in later periods of the life. In this review, we summarize the effect of ELA on the HPA axis function, stress-related hormonal balance, immune responses, and the gut microbiome indicating how these changes may affect the brain function and behavior in the early stages of the life and adulthood. We also provide insight into animal studies revealing the responses of corticotropin-releasing hormone, urocortins, and corticosterone in various neural circuits in response to ELA evoked by maternal separation and limited bedding paradigms.

Keywords: early-life adversity, hypothalamic-pituitary-adrenal axis, oxytocin, microbiota, immune system

The early life adversity (ELA) refers to an exposure to a wide range of early negative experiences including abuse, neglect, household dysfunction, and other psychosocial or biological stressors that can impair the emotional, psychological, and behavioral functioning and increase the risk of adverse health outcomes across the lifespan (Duffy et al. 2018; Nelson et al. 2025). Although the effects of ELA on brain development have been widely studied, the underlying cellular and endocrine mechanisms

are only partially understood. Several studies have shown that sustained changes in glucocorticoid release and receptor levels during the perinatal and postnatal periods may impair the neuronal differentiation and synaptogenesis in many brain regions including the hippocampus and the prefrontal cortex (PFC) increasing the risk of anxiety, depression, and schizophrenia development (Lupien et al. 2009; Chen and Baram 2016; Anza et al. 2025). It is also known that ELA regulates the expression and activity of

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stress-related peptides including corticotropin-releasing hormone (CRH) and urocortins, which modulate both the hypothalamic-pituitary-adrenal axis (HPA) responsiveness and behavioral outcomes during critical periods of the development (Wang et al. 2012). One of the key components involved in the regulation of the HPA axis with important consequences for emotional and social behavior is oxytocin, a hypothalamic neuropeptide, which mediates mother-offspring interactions. Alterations in oxytocin signaling have been observed in rodents and primates long after ELA stimuli, such as maternal separation or sensory deprivation (Jin et al. 2021; Municchi et al. 2025). Moreover, it has been well established that changes in oxytocin production and release may profoundly affect the brain maturation during specific developmental periods (Marlin and Froemke 2017).

In addition to neuroendocrine factors, brain development may also be influenced by peripheral immune cells and gut microbiome composition, both of which are affected by ELA (Cong et al. 2015; Cunningham et al. 2022). Immune components including macrophages and complement proteins participate in the neurite growth and synaptic pruning, which are essential processes for the proper maturation of neural networks and are influenced by the endocrine signaling (Wang et al. 2025). The gut microbiome shapes neurodevelopment through microbiota-gut-brain signaling pathways that influence HPA axis maturation, neuroinflammation, and neurotrophic factor expression (Kar et al. 2022; Wang et al. 2023a; Li et al. 2026).

This review summarizes the current knowledge of ELA effect on the stress-related hormonal systems particularly oxytocin and the HPA axis function, immune responses, and the microbiota, and indicates how these alterations may collectively affect the brain function and behavior (Figure 1).

HPA axis development and ELA

Stressors vary in their physical and psychological demands eliciting stressor-specific responses that engage multiple physiological systems. However, the HPA axis is a central stress circuit responding to different kinds of stressors (Koss and Gunar 2018). When fully matured, HPA activation mobilizes the physical and psychological resources in response to stress and regulates the key homeostatic systems including metabolic, cardiovascular, immune, reproductive, and central nervous systems (Howland et al. 2017). It is known that the early postnatal period is

characterized by a stress hyporesponsive period in rodents, during which the basal glucocorticoid levels are relatively low and stress-induced corticosterone (CORT) response is markedly attenuated (Levine et al. 2001). The stress hyporesponsive developmental period represents a key window in early-life neuroendocrine system maturation with important implications for the long-term regulation of the HPA axis and the development of a stress resilience (Schmidt 2025). The stress hyporesponsive period in rodents spans postnatal days 4–14 and is characterized by an attenuated glucocorticoid response, whereas in humans, a direct equivalent is unclear and a functional analogue of reduced cortisol reactivity emerges approximately 0–6 months during the early infancy (Howland 2023). This period is considered particularly sensitive to ELA, which is hypothesized to induce hyperactivity of the HPA axis characterized by elevated serum levels of glucocorticoids, i.e. humans, CORT in rodents, accompanied by impaired negative feedback regulation of the HPA axis (Smith and Pollak 2020; Alcantara-Alonso et al. 2024). Maternal care is a key determinant of the integrity of this hyporesponsive period and proper HPA axis maturation, with studies demonstrating developmental differences in glucocorticoid receptor (GR) expression and feedback sensitivity during this period (Liu et al. 1997). High levels of maternal licking and grooming are associated with an enhanced hippocampal GR expression and improved negative feedback regulation of the HPA axis in adulthood (Meaney and Szyf 2005).

A recent study (O'Neill et al. 2025) has emphasized the need to standardize the early-life stress protocols in experimental settings and reports that the postnatal period between postnatal days 6 to 10 is associated with elevated CORT levels in mice exposed to stress compared with controls. Therefore, experimental models commonly used to study the consequences of ELA include maternal separation and limited bedding during the early developmental stages. The maternal separation model is also clinically relevant, as it reflects the conditions of early parental deprivation neglecting or disrupting the caregiver–infant bonding (Zhang et al. 2024). Lajud et al. (2012) have shown that periodic maternal separation did not alter basal CORT levels at postnatal days 3, 6, 9, or 12, but did enhance the CORT response to acute maternal separation stress. However, in adulthood, the stressed animals exhibited increased basal HPA axis activity without a difference in net stress-induced CORT release between control and maternal stressed animals (Lajud et al. 2012). Another study has

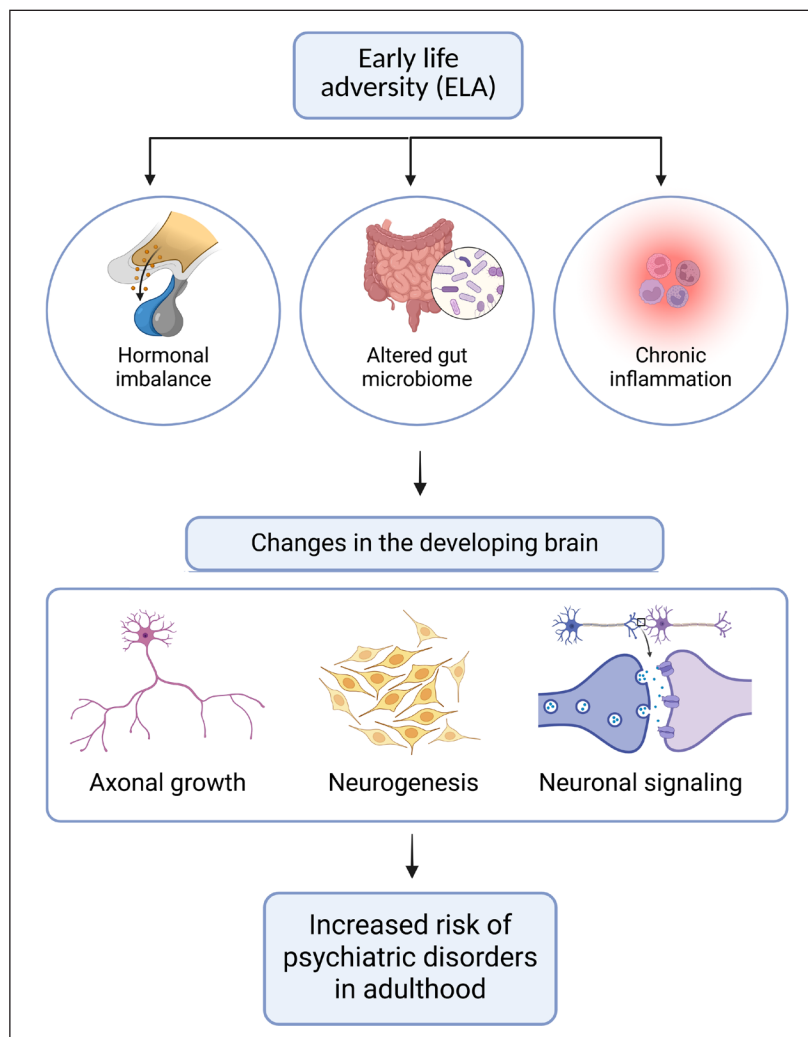


Figure 1. Effects of early-life adversity on neuroendocrine, immune, and microbiota systems induced by maternal separation or limited bedding, which leads to dysregulation of stress-related hormonal systems, alterations in the gut microbiome, and chronic inflammatory activation. These changes impair the key neurodevelopmental processes including axonal growth, neurogenesis, and neuronal signaling. It provides mechanistic insight into the early-life adversity contribution to the increased vulnerability to psychiatric disorders later in the human life.

reported that ELA elicited a greater CORT response to acute stress in males, but not in females even though females were already higher at baseline (Garvin et al. 2026). Other studies have also claimed that maternal separation induces immediate alterations in stress reactivity during the early development, while leading to persistent dysregulation of the HPA axis in adulthood (Jiang et al. 2025). This concept is essential for understanding of both the short- and long-term effects of stress on the brain plasticity and adaptive mechanisms even in the later stages of the life.

CRH signaling and HPA axis dysregulation in ELA

The functioning of the HPA axis is primarily directed by CRH from the hypothalamic paraventricular nucleus (PVN) and some other higher-order limbic and cortical structures including the PFC, the hippocampus, and the amygdala (Herman and Cullinan 1997). As mentioned above, ELA activates the HPA axis and also exerts long-term effects on its regulation with CRH representing one of the principal

regulatory factors involved in this process. In a model of periodic maternal separation, the hippocampal CRH expression was increased at postnatal days 9–15 and the hypothalamic CRH from postnatal days 12–21. It is important to note that the same study has shown that maternal separation increased the hippocampal and the hypothalamic CRH expression in pups, but only transiently, whereas this increase persisted in the hypothalamus of adult animals (Roque et al. 2022). Not only elevated levels of CRH and pro-opiomelanocortin (POMC) in the hypothalamus, but also higher levels of CRH receptors (CRHR1 and CRHR2) and lower levels of the GRs NR3C1 in the hippocampus have been shown (de Almeida Magalhaes et al. 2017). The crucial role of CRHR1 signaling in promoting the negative effects of ELA on cognitive functions has also been demonstrated in conditional forebrain CRF1 knock-out mice, which were protected from the negative effects of early life stress (Wang et al. 2011). Following the stress exposure, pups with fragmented maternal care showed reduced dendritic outgrowth and spine formations in the hippocampal CA3 pyramidal neurons along with decreased the hippocampal levels of synapse-related proteins (Liao et al. 2014). The nectin-3, an adhesion molecule involved in axodendritic interactions and stabilization of synaptic contacts, also downregulated in hippocampal neurons of ELA animals is likely to be mediated by CRH–CRHR1 signaling (Wang et al. 2013). In this context, it is important to note that several studies have shown that ELA alters long-term potentiation in developing the hippocampal circuits with effects that vary across the developmental stages and between the genders (Derks et al. 2016; Jappy et al. 2025).

Long-term consequences of ELA on CRH signaling and behavior

The ELA influences the neurodevelopment by inducing a range of neurobiological and behavioral changes. While these changes may lead to short-term adaptive advantages in high-risk or threatening environments, they are often maladaptive in normative contexts. Consequently, such alterations are associated with an increased risk of chronic physical health conditions, psychiatric disorders, and engagement in health-risk behaviors across the lifespan (Duffy et al. 2018). Exposure to ELA induces endocrine and metabolic alterations in adulthood that increase food intake and promote overweight in rats (Alcantara-Alonso et al. 2017). CRH together with urocortins (Ucn1 - 3) is known to induce anorexic effects through

CRHR2 receptor activation. However, maternal separation exposed animals in adulthood showed increased feeding and weight gain despite increased CRH, Ucn2, and CRHR2 mRNA expression in the hypothalamic PVN. This discrepancy is likely due to CRHR2 resistance to Ucn2 effects and impaired receptor function in maternal separation animals, which are thought to be caused by chronic stimulation by CRH or Ucn2 induced by early-life stress (Alcantara-Alonso et al. 2017).

In adulthood, rats exposed to ELA exhibit disrupted sleep-wake behavior. One study points to changed dendritic structure, spine loss, and elevated CRH–CRHR1 signaling in the accumbens nucleus (NAc), which play a critical role in maternal separation-induced disrupted sleep architecture (Wang et al. 2023b). NAc in connection with the basolateral amygdala (BLA) also contributes to alterations in reward-related behaviors of ELA-exposed mice. In males, ELA induced anhedonia-like behavior, whereas in females, it enhanced reward motivation indicating sex-dependent alterations in reward circuitry. Notably, the CRH+/ γ-aminobutyric acid (GABA) BLA-NAc projections involved in reward behaviors differ structurally and functionally between males and females, suggesting a potential mechanism underlying the pronounced sex-dependent effects of ELA on reward behavior (Taniguchi et al. 2026). CRH plays a pivotal role in regulating behavioral responses mediated by the extended amygdala, a complex neural network that includes the bed nucleus of the stria terminalis (BNST) and the central nucleus of the amygdala. CRH signaling between the amygdala and BNST has been implicated in increased ethanol consumption associated with maternal stress. Moreover, the interaction between maternal stress and ethanol intake appears to be sex-dependent, with females showing greater vulnerability (Bonetti Bertagna et al. 2026). Impairments in learning and memory emerging later in life as consequences of ELA are associated with alterations in hippocampal neuron structure and connectivity leading to progressive deficits in long-term potentiation (LTP) and spatial memory function, which worsen with age. Blocking of the hippocampal CRHR1 has been proven to prevent the ELA-induced memory and LTP deficits (Short et al. 2020). Memory deficits are supposed to be ameliorated by blocking CRHR1, which mediates CRH-induced dendritic spine and synapse loss by disrupting the actin cytoskeleton within spines (Short et al. 2020).

Alterations in anxiety-like and social behaviors in chronically maternally separated mice are associated

with reduced GR mRNA expression in the brain particularly in the amygdala. Restoration of GR expression reversed these behavioral abnormalities (Taylor and Kokiko-Cochran 2024). Moreover, in male mice exposed to fragmented maternal care, increased freezing behavior in a conditioned threat paradigm was attenuated by pharmacological blockade of GRs further implicating GR signaling in stress-induced behavioral dysregulation (Arnett et al. 2015).

Role of oxytocin in early brain development and ELA

The developmental changes of oxytocin and oxytocin receptor (OXTR) may interact with the HPA axis shaping long-term stress regulation and emotional behavior. Oxytocin is a neuropeptide produced primarily in the PVN and the hypothalamic supraoptic nuclei (SON) and released both peripherally and centrally, where it acts as a neuro-modulator (Bakos et al. 2016; Aulinas and Lawson 2025). Beyond its classical roles in parturition and lactation, oxytocin is involved in the regulation of the stress response and social behavior (Jezova et al. 1995; Jurek and Neumann 2018). During early brain development, the oxytocin system undergoes dynamic maturation characterized by region-specific changes in OXTR expression and activity-dependent plasticity (Marlin and Froemke 2017; Rokicki et al. 2022; Li et al. 2025). There are also indications that OXTR expression is developmentally regulated with levels rising during the prenatal period and peaking in early childhood (Rokicki et al. 2022).

Oxytocin is critically involved in mediating the maternal effects. For example, Hiller et al. (2011) have demonstrated that changes in oxytocin expression occur in parallel with alterations in CRH levels during the peripartum period and in response to overcrowding stress. It has also been shown that oxytocin inhibits hypothalamic CRH neurons via OXTR-dependent mechanisms blunting stress-induced CORT release (Pati et al. 2020). Thus, oxytocin may help regulate excessive HPA axis activation particularly during sensitive developmental periods. It is also becoming increasingly clear that oxytocin plays a role in shaping the development of certain brain structures and may also influence stress reactivity later in the life. For example, neonatal oxytocin administration alters neurotrophic factor expression and produces long-term changes in memory performance (Havranek et al. 2015; Bukatova et al. 2023). Conversely, ELA paradigms

such as maternal separation have been shown to reduce central oxytocin expression and OXTR binding in limbic regions, which may be associated with altered HPA axis responses and increased anxiety-like behavior in adulthood (Lukas et al. 2010; Onaka and Takayanagi 2021). These findings suggest that disruptions in oxytocin signaling during critical periods may influence the balance between stress vulnerability and resilience. Moreover, oxytocin modulates GABAergic and dopaminergic neurotransmission, thereby influencing the maturation of social and reward circuits that are also sensitive to glucocorticoid exposure (Marlin and Froemke 2017). As discussed above, ELA leads to complex neuroplastic alterations in the brain with oxytocin likely contributing to these processes across several neural circuits. Thus, the effects of ELA primarily maternal separation and limited bedding on neuroendocrine markers across development show region-specific alterations in stress-related hormones, including CRH, POMC and oxytocin (Table 1).

ELA-induced immune system dysregulation and its impact on brain development

One of the significant contributors to the development of the nervous system during early postnatal life is the immune system and its components. Beyond host defense and regulation of the immune response, immune mechanisms influence brain development by regulating neurogenesis, axonal growth, neuronal migration, synaptogenesis and synaptic pruning, myelination, circuit plasticity, as well as regulation of the brain microenvironment (Bilbo and Schwarz 2012; Catale et al. 2022; Wang et al. 2025). Given this close interplay between the immune and nervous systems, alterations in the immune function, especially in early life, may directly influence nervous system processes and profoundly impact physical and mental health (Beurel and Nemeroff 2024; Wang et al. 2025).

It has been suggested that greater vulnerability of individuals to psychopathology as a result of ELA is caused by the presence of inflammation, which impacts neuro-immune interactions, while ELA's effect on inflammation and immune system reactivity may be lifelong (Catale et al. 2022). Although the association between inflammation and ELA appears to be a complex and lacks clearly elucidated underlying mechanisms, it likely involves priming of peripheral immune cells (e.g., monocytes, macrophages) induced by adverse early-life experiences, which initiates and sustains inflammation. These immune cells produce

Table 1

The effects of early life adversity (ELA) on neuroendocrine markers across development show region-specific alterations in stress-related hormones

Hormone	Effect	ELA model/species	Brain region/plasma	Age	Reference
CRH	=	Limited bedding/mouse	PVN	adult	Wang et al. 2012
			central amygdala		
	↑	Maternal separation/rat	PVN	P71	Alcantara-Alonso et al. 2024
	=		amygdala		
	=		hippocampus		
	=	Limited bedding/rat	amygdala	P71	Alcantara-Alonso et al. 2024
	↑		hippocampus		
	↑		PVN		
	↑	Maternal separation/rat	hypothalamus	P6, P12, P15	Roque et al. 2022
	↑		hippocampus		
	↑	Maternal separation/mouse	hypothalamus	P21	de Almeida Magalhaes et al. 2017
Corticosterone	↑	Maternal separation/rat	plasma	P71	Alcantara-Alonso et al. 2024
	=	Limited bedding/rat			
Cortisol	↑	Maternal separation/rat	plasma	adult	Lajud et al. 2012
	↑			P21	Roque et al. 2022
	=	Maternal separation/mouse	plasma	P45	Bonetti Bertagna et al. 2026
OXT	↓	Maternal separation/rat	hypothalamus	adult	Roque et al. 2022
POMC	↑	Maternal separation/mouse	hypothalamus	P21	de Almeida Magalhaes et al. 2017
Ucn2	↑	Maternal separation/rat	PVN	P71	Alcantara-Alonso et al. 2017

Abbreviations: CRH – corticotropin-releasing hormone; OXT – oxytocin; P – postnatal days; POMC – pro-opiomelanocortin; PVN – the paraventricular nucleus of the hypothalamus; Ucn2 – urocortin 2.

higher levels of typical markers of inflammation, such as white blood cell count, circulating pro-inflammatory cytokine levels (e.g., interleukins IL-6 and IL-1 β ; tumor necrosis factor - TNF) and the acute phase molecule C-reactive protein (CRP) that was found in maltreated children or in adolescents exposed to adverse childhood experiences, as well as oxidative stress molecules found in patients with panic disorder who suffered childhood trauma (Surtees et al. 2003; Azad et al. 2012; Slopen et al. 2013; Baumeister et al. 2016; Elwenspoek et al. 2017; Kuhlman et al. 2020; Quagliato and Nardi 2022). Although at physiological levels, IL-6, TNF- α , transforming growth factor- β (TGF- β), and IL-33 support synaptic plasticity, synaptic scaling, and microglial homeostasis, their chronic elevation disrupts long-term potentiation, dendritic spine density, and excitation–inhibition balance while promoting microglial overactivation (Stellwagen and Malenka 2006; Garay and McAllister 2010).

Besides monocytes and macrophages, other peripheral immune cells also seem to be involved. For example, it has been shown that the number of Th17 and regulatory T cells was increased and NK cell numbers decreased in the high liability group with childhood trauma (Elwenspoek et al. 2017; Counotte et al. 2018; Beurel and Nemeroff 2024). Low NK cell activity was also associated with childhood trauma in both adolescents with depression or conduct disorder (Birmaher et al. 1994). Moreover, Th17 cells promote susceptibility to depression after stress and affect neuronal circuits in autism (Beurel et al. 2022).

In addition to dysregulation of the peripheral immune system, ELA has been associated with alterations in immune components in the central nervous system (CNS) including microglia, astrocytes, and peripheral immune cell populations that reside at the brain interfaces whose cell densities and morphology were influenced across several brain regions (e.g. in the hippocampus, striatum, NAc, PFC,

amygdala or hypothalamus) after early-life stress (Jorgensen et al. 2025). These immune cells produce a wide range of signaling molecules including cytokines, chemokines, complement proteins, and trophic factors as well as their receptors, which contribute to processes associated with neurodevelopment (Wang et al. 2025) and which levels were also altered after ELA. For example, in rats, it was found that early-life infection with *E. coli* leads to long-term sensitization/priming of microglia within the brain (Bland et al. 2010; Bilbo and Schwarz 2012). Also in astrocytes, mitochondrial oxidative phosphorylation dysfunction is associated with a disrupted lipid homeostasis in the brain leading to synaptic loss, neuroinflammation, demyelination, and cognitive impairment. Such mitochondrial dysfunction within reactive astrogliosis represents a potential central mechanism underlying neurodegenerative diseases (Habib et al. 2020).

Overall, the above-mentioned findings indicate that ELA may impair neuro-immune interactions essential for neurodevelopment with effects that may persist well beyond the developmental period and contribute to heightened susceptibility to cognitive, emotional, and psychiatric disorders later in the life.

ELA-associated dysbiosis and its effects on brain development

Increasing evidence indicates that the early-life microbiota contributes to brain development through the microbiota-gut-brain axis, a bidirectional communication system involving neural, immune, endocrine, and metabolic pathways (Cryan et al. 2019; Wang et al. 2023a). ELA may disrupt this system and influence neurodevelopmental outcomes (Morais et al. 2021). Several microbial taxa have been associated with neurodevelopment in infancy. Higher abundance of *Bacteroides* and *Bifidobacterium* has frequently been linked to more favorable cognitive and behavioral development in humans (Carlson et al. 2018). These genera are common in the infant gut and are involved in the metabolism of human milk oligosaccharides contributing to the production of short-chain fatty acids (SCFAs) and essential micronutrients that support host metabolism and immune maturation (Wang et al. 2023a). SCFAs have also been shown to modulate immune responses, maintain blood-brain barrier integrity, influence neuronal signaling processes including neurotransmitter release, synaptic plasticity, and learning-related mechanisms (Stilling et al. 2016; Dalile et al. 2019), as well as microglial maturation and may promote proliferation of neural

precursor cells (Erny et al. 2015; Cryan et al. 2019). Other microbial taxa including *Lachnospiraceae*, *Streptococcus*, and *Faecalibacterium*, have shown more variable associations with neurodevelopmental outcomes (Carlson et al. 2018).

ELA may alter the composition and diversity of gut microbiota, a condition commonly referred to as dysbiosis. Stress-induced physiological changes, such as altered gut motility, intestinal permeability, and mucosal immunity modify the intestinal environment and influence microbial communities (Beurel and Nemeroff 2024). Experimental models of maternal separation and early stress demonstrate decreased levels of beneficial genera such as *Bifidobacterium* and *Lactobacillus* and increased abundance of potentially pro-inflammatory bacteria (Foster et al. 2017; Callaghan et al. 2020). These immune signals influence microglial activation and neuro-inflammatory processes in the developing brain, which are crucial regulators of synaptic pruning and neural circuit formation (Erny et al. 2015). Chronic low-grade inflammation during development may therefore contribute to long-term changes in cognition, emotional regulation, and behavior.

Experimental and human studies suggest that individuals exposed to ELA show measurable alterations in gut microbial profiles and associated metabolic pathways linked to brain functional connectivity, neural circuit modulation, and emotional regulation (Coley et al. 2021). Immune signaling generated in the gut may influence brain function by interacting with microglia, the resident immune cells of the CNS responsible for synaptic pruning and neural circuit refinement during development (Erny et al. 2015; Cryan et al. 2019). ELA-associated dysbiosis characterized by a reduction in SCFA-producing taxa such as *Clostridia* and *Bifidobacterium* and an expansion of pro-inflammatory microbes including *Proteobacteria* and segmented filamentous bacteria may skew immune differentiation toward pro-inflammatory Th17 cells, while reducing regulatory T cells, thereby promoting systemic and neuroinflammatory signaling pathways that may influence neurodevelopment (Wang et al. 2024; Zhang et al. 2024).

Neuropeptides and endocrine signals are integral to bidirectional communication within the microbiota-gut-brain axis, thereby contributing to the mediation of ELA-induced effects on neurodevelopment. Early disruptions of the gut microbiome may alter HPA signaling and stress-hormone regulation, influencing neuroimmune development and brain maturation (Wang et al. 2023a; Schneider et al.

2024). Neuropeptides such as oxytocin are also involved, as certain gut microbes (e.g., *Lactobacillus reuteri*) may stimulate oxytocinergic pathways that regulate social behavior, stress resilience, and neural development (Varian et al. 2023). Additionally, microbial metabolites and early gut inflammation may influence endocrine and sex-hormone signaling, further shaping neurodevelopmental outcomes and behavioral responses to stress (Sullivan et al. 2025).

Conclusion and future orientation

ELA affects several neuroendocrine parameters during both early development and adulthood. A critical feature of these alterations is the reactivity of the HPA axis to environmental stimuli, which may become dysregulated leading to exaggerated or maladaptive stress responses. Structural changes in the brain also appear to be an important component of ELA-related adaptations including alterations in neurite growth, dendritic arborization, and connectivity within the neural circuits. In addition, the neuroendocrine components including neuropeptides like oxytocin as well as steroid hormones cortisol and CORT play an important role in adaptive changes in the brain during the early stages of development.

The complex interactions between the early immune alterations and the changes in microbiota represent an additional level of regulation that remains to be insufficiently understood due to the

considerable variability represented across different studies and experimental models. Although recent studies indicate potential sex differences in the consequences of ELA, accumulating evidence suggests that context-dependent factors and the specific nature and timing of stress exposure may play a more significant role in shaping HPA-axis reactivity. The individuals appear to differ markedly in their sensitivity to ELA highlighting the importance of investigating mechanisms of resilience, which may explain why a subset of individuals shows relative resistance to the long-term effects of the early adversity.

Future studies should prioritize the identification of sex-specific mechanisms, critical developmental windows, and the biological basis of resilience following ELA. Established experimental rodent models, such as maternal separation and limited bedding, offer valuable and well-defined frameworks for the elucidation of these processes.

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References

- Alcantara-Alonso V, Amaya MI, Matamoros-Trejo G, de Gortari P. Altered functionality of the corticotrophin-releasing hormone receptor-2 in the hypothalamic paraventricular nucleus of hyperphagic maternally separated rats. *Neuropeptides* 63, 75–82, 2017.
- Alcantara-Alonso V, Garcia-Luna C, Soberanes-Chavez P, Estrada-Camarena E, de Gortari P. Two adverse early life events induce differential changes in brain CRH and serotonin systems in rats along with hyperphagia and depression. *J Integr Neurosci* 23, 41, 2024.
- Anza S, Heistermann M, Ostner J, Schulke O. Early prenatal but not postnatal glucocorticoid exposure is associated with enhanced HPA axis activity into adulthood in a wild primate. *Proc Biol Sci* 292, 20242418, 2025.
- Arnett MG, Pan MS, Doak W, Cyr PE, Muglia LM, Muglia LJ. The role of glucocorticoid receptor-dependent activity in the amygdala central nucleus and reversibility of early-life stress programmed behavior. *Transl Psychiatry* 5, e542, 2015.
- Aulinas A, Lawson EA. The oxytocin system and implications for oxytocin deficiency in hypothalamic-pituitary disease. *Endocr Rev* 46, 518–548, 2025.
- Azad MB, Lissitsyn Y, Miller GE, Becker AB, HayGlass KT, Kozyrskyj AL. Influence of socioeconomic status trajectories on innate immune responsiveness in children. *PLoS One* 7, e38669, 2012.
- Bakos J, Zatkova M, Bacova Z, Ostatnikova D. The role of hypothalamic neuropeptides in neurogenesis and neuritogenesis. *Neural Plast* 2016, 3276383, 2016.
- Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor- α . *Mol Psychiatry* 21, 642–649, 2016.

- Beurel E, Medina-Rodriguez EM, Jope RS. Targeting the adaptive immune system in depression: focus on T helper 17 cells. *Pharmacol Rev* 74, 373–386, 2022.
- Beurel E, Nemeroff CB. Early life adversity, microbiome, and inflammatory responses. *Biomolecules* 14, 802, 2024.
- Bilbo SD, Schwarz JM. The immune system and developmental programming of brain and behavior. *Front Neuroendocrinol* 33, 267–286, 2012.
- Birmaher B, Rabin BS, Garcia MR, Jain U, Whiteside TL, Williamson DE, al-Shabbout M, Nelson BC, Dahl RE, Ryan ND. Cellular immunity in depressed, conduct disorder, and normal adolescents: role of adverse life events. *J Am Acad Child Adolesc Psychiatry*, 33, 671–678, 1994.
- Bland ST, Beckley JT, Young S, Tsang V, Watkins LR, Maier SF, Bilbo SD. Enduring consequences of early-life infection on glial and neural cell genesis within cognitive regions of the brain. *Brain Behav Immun* 24, 329–338, 2010.
- Bonetti Bertagna N, Favoretto CA, Rodolpho BT, Righi T, Loss CM, Morais IBM, Vrechi TAM, Erustes AG, Pereira GJS, Miguel TT, Cruz FC. The impact of maternal separation stress on the CRFergic system in the extended amygdala and its relevance to acute stress-induced ethanol consumption in mice. *Alcohol* 130, 40–56, 2026.
- Bukatova S, Reichova A, Bacova Z, Bakos J. Neonatal oxytocin treatment alters levels of precursor and mature BDNF forms and modifies the expression of neuronal markers in the male rat hippocampus. *Neuropeptides* 102, 102384, 2023.
- Callaghan BL, Fields A, Gee DG, Gabard-Durnam L, Caldera C, Humphreys KL, Goff B, Flannery J, Telzer EH, Shapiro M, Tottenham N. Mind and gut: Associations between mood and gastrointestinal distress in children exposed to adversity. *Dev Psychopathol* 32, 309–328, 2020.
- Carlson AL, Xia K, Azcarate-Peril MA, Goldman BD, Ahn M, Styner MA, Thompson AL, Geng X, Gilmore JH, Knickmeyer RC. Infant gut microbiome associated with cognitive development. *Biol Psychiatry* 83, 148–159, 2018.
- Catale C, Carola V, Viscomi MT. Early life stress-induced neuroinflammation and neurological disorders: a novel perspective for research. *Neural Regen Res* 17, 1971–1972, 2022.
- Chen Y, Baram TZ. Toward understanding how early-life stress reprograms cognitive and emotional brain networks. *Neuropsychopharmacology* 41, 197–206, 2016.
- Coley EJJ, Mayer EA, Osadchiy V, Chen Z, Subramanyam V, Zhang Y, Hsiao EY, Gao K, Bhatt R, Dong T, Vora P, Naliboff B, Jacobs JP, Gupta A. Early life adversity predicts brain-gut alterations associated with increased stress and mood. *Neurobiol Stress* 15, 100348, 2021.
- Cong X, Henderson WA, Graf J, McGrath JM. Early life experience and gut microbiome: the brain-gut-microbiota signaling system. *Adv Neonatal Care* 15, 314–323, quiz E1-2, 2015.
- Counotte J, Drexhage HA, Wijkhuijs JM, Pot-Kolder R, Bergink V, Hoek HW, Veling W. Th17/T regulator cell balance and NK cell numbers in relation to psychosis liability and social stress reactivity. *Brain Behav Immun* 69, 408–417, 2018.
- Cryan JF, O’Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV, Guzzetta KE, Jaggar M, Long-Smith CM, Lyte JM, Martin JA, Molinero-Perez A, Moloney G, Morelli E, Morillas E, O’Connor R, Cruz-Pereira JS, Peterson VL, Rea K, Ritz NL, Sherwin E, Spichak S, Teichman EM, van de Wouw M, Ventura-Silva AP, Wallace-Fitzsimons SE, Hyland N, Clarke G, Dinan TG. The microbiota-gut-brain axis. *Physiol Rev* 99, 1877–2013, 2019.
- Cunningham K, Mengelkoch S, Gassen J, Hill SE. Early life adversity, inflammation, and immune function: An initial test of adaptive response models of immunological programming. *Dev Psychopathol* 34, 539–555, 2022.
- Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat Rev Gastroenterol Hepatol* 16, 461–478, 2019.
- de Almeida Magalhaes T, Correia D, de Carvalho LM, Damasceno S, Brunialti Godard AL. Maternal separation affects expression of stress response genes and increases vulnerability to ethanol consumption. *Brain Behav* 8, e00841, 2017.
- Derks NA, Krugers HJ, Hoogenraad CC, Joels M, Sarabdjitsingh RA. Effects of early life stress on synaptic plasticity in the developing hippocampus of male and female Rats. *PLoS One* 11, e0164551, 2016.
- Duffy KA, McLaughlin KA, Green PA. Early life adversity and health-risk behaviors: proposed psychological and neural mechanisms. *Ann N Y Acad Sci*, 1428, 151–169, 2018.
- Elwenspoek MMC, Hengesch X, Leenen FAD, Schrittz A, Sias K, Schaan VK, Meriaux SB, Schmitz S, Bonnemberger F, Schachinger H, Voge C, Turner JD, Muller CP. Proinflammatory T cell status associated with early life adversity. *J Immunol* 199, 4046–4055, 2017.

- Erny D, Hrabé de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, Keren-Shaul H, Muhlakoiv T, Jakobshagen K, Buch T, Schwierzeck V, Utermohlen O, Chun E, Garrett WS, McCoy KD, Diefenbach A, Staeheli P, Stecher B, Amit I, Prinz M. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci* 18, 965–977, 2015.
- Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiol Stress* 7, 124–136, 2017.
- Garay PA, McAllister AK. Novel roles for immune molecules in neural development: implications for neurodevelopmental disorders. *Front Synaptic Neurosci* 2, 136, 2010.
- Garvin MM, Kar U, Kooiker CL, Bolton JL. Deletion of the microglial phagocytic receptor MerTK mimics early-life adversity-induced changes in synapses and behavior in male mice. *Brain Behav Immun* 133, 106246, 2026.
- Habib N, McCabe C, Medina S, Varshavsky M, Kitsberg D, Dvir-Szternfeld R, Green G, Dionne D, Nguyen L, Marshall JL, Chen F, Zhang F, Kaplan T, Regev A, Schwartz M. Disease-associated astrocytes in Alzheimer's disease and aging. *Nat Neurosci* 23, 701–706, 2020.
- Havranek T, Zatkova M, Lestanova Z, Bacova Z, Mravec B, Hodosy J, Strbak V, Bakos J. Intracerebroventricular oxytocin administration in rats enhances object recognition and increases expression of neurotrophins, microtubule-associated protein 2, and synapsin I. *J Neurosci Res* 93, 893–901, 2015.
- Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci* 20, 78–84, 1997.
- Hillner KM, Reber SO, Neumann ID, Slaterry DA. Exposure to chronic pregnancy stress reverses peripartum-associated adaptations: implications for postpartum anxiety and mood disorders. *Endocrinology* 152, 3930–3940, 2011.
- Howland MA, Sandman CA, Glynn LM. Developmental origins of the human hypothalamic-pituitary-adrenal axis. *Expert Rev Endocrinol Metab* 12, 321–339, 2017.
- Howland MA. Recalibration of the stress response system over adult development: Is there a perinatal recalibration period? *Dev Psychopathol* 35, 2315–2337, 2023.
- Jappy D, Sokolov R, Dobryakova Y, Krut V, Maltseva K, Fedulina A, Smirnov I, Rozov A. Early-life stress differentially affects CA3 synaptic inputs converging on apical and basal dendrites of CA1 pyramidal neurons. *Front Neural Circuits* 19, 1533791, 2025.
- Jezova D, Skultetyova I, Tokarev DI, Bakos P, Vigas M. Vasopressin and oxytocin in stress. *Ann N Y Acad Sci*, 771, 192–203, 1995.
- Jiang L, Xue L, Jurueña MF. The impact of early life stress on the hypothalamic-pituitary-adrenal axis in unipolar major depression: A systematic review. *Psychoneuroendocrinology* 181, 107607, 2025.
- Jin Y, Song D, Yan Y, Quan Z, Qing H. The role of oxytocin in early-life-stress-related neuropsychiatric disorders. *Int J Mol Sci* 24, 10430, 2023.
- Jorgensen CC, Thone-Reineke C, Moscovice LR, Gimsa U. Critical biological systems linking early-life stress to later-life outcomes: A systematic review of animal models. *Neurosci Biobehav Rev* 179, 106425, 2025.
- Jurek B, Neumann ID. The oxytocin receptor: from intracellular signaling to behavior. *Physiol Rev* 98, 1805–1908, 2018.
- Kar F, Hacıoglu C, Kar E, Donmez DB, Kanbak G. Probiotics ameliorates LPS induced neuroinflammation injury on A β 1–42, APP, γ - β secretase and BDNF levels in maternal gut microbiota and fetal neurodevelopment processes. *Metab Brain Dis* 37, 1387–1399, 2022.
- Koss KJ, Gunnar MR. Annual Research Review: Early adversity, the hypothalamic-pituitary-adrenocortical axis, and child psychopathology. *J Child Psychol Psychiatry* 59, 327–346, 2018.
- Kuhlman KR, Horn SR, Chiang JJ, Bower JE. Early life adversity exposure and circulating markers of inflammation in children and adolescents: A systematic review and meta-analysis. *Brain Behav Immun* 86, 30–42, 2020.
- Lajud N, Roque A, Cajero M, Gutierrez-Ospina G, Torner L. Periodic maternal separation decreases hippocampal neurogenesis without affecting basal corticosterone during the stress hyporesponsive period, but alters HPA axis and coping behavior in adulthood. *Psychoneuroendocrinology* 37, 410–420, 2012.
- Levine S. Primary social relationships influence the development of the hypothalamic-pituitary-adrenal axis in the rat. *Physiol Behav* 73, 255–260, 2001.
- Li H, Li Y, Wang T, Li S, Liu H, Ning S, Shen W, Zhao Z, Wu H. Spatiotemporal mapping of the oxytocin receptor at single-cell resolution in the postnatally developing mouse brain. *Neurosci Bull* 41, 224–242, 2025.
- Li Y, Li T, Zhang Y, Wang Y, Wu G, Tan Y. Microbial metabolites in the gut-brain axis: their impact on depression pathophysiology and treatment. *Neuroscience* 593, 1–7, 2026.

- Liao XM, Yang XD, Jia J, Li JT, Xie XM, Su YA, Schmidt MV, Si TM, Wang XD. Blockade of corticotropin-releasing hormone receptor 1 attenuates early-life stress-induced synaptic abnormalities in the neonatal hippocampus. *Hippocampus* 24, 528–540, 2014.
- Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky PM, Meaney MJ. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science* 277, 1659–1662, 1997.
- Lukas M, Bredewold R, Neumann ID, Veenema AH. Maternal separation interferes with developmental changes in brain vasopressin and oxytocin receptor binding in male rats. *Neuropharmacology* 58, 78–87, 2010.
- Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci* 10, 434–445, 2009.
- Marlin BJ, Froemke RC. Oxytocin modulation of neural circuits for social behavior. *Dev Neurobiol* 77, 169–189, 2017.
- Meaney MJ, Szyf M. Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues Clin Neurosci* 7, 103–123, 2005.
- Morais LH, Schreiber HL 4th, Mazmanian SK. The gut microbiota-brain axis in behaviour and brain disorders. *Nat Rev Microbiol* 19, 241–255, 2021.
- Municchi D, Mancini C, Nutarelli S, Tiberi M, D'Addario SL, Chila G, Passeri A, Massa G, Di Segni M, Babicola L, Canterini S, Lo Iacono L, Cifani C, Cabib S, Renzi M, Chiurciu V, Viscomi MT, Ventura R. The oxytocin system mediates behavioral and neurobiological alterations associated with early adversity. *Mol Psychiatry* 2025 Dec 28, Epub ahead of print.
- Nelson CA, Sullivan EF, Valdes V. Early adversity alters brain architecture and increases susceptibility to mental health disorders. *Nat Rev Neurosci* 26, 642–656, 2025.
- Onaka T, Takayanagi Y. The oxytocin system and early-life experience-dependent plastic changes. *J Neuroendocrinol* 33, e13049, 2021.
- O'Neill OS, Terstege DJ, Gill AK, Edge-Partington M, Ramkumar R, Epp JR, Sargin D. An open-source and highly adaptable rodent limited bedding and nesting apparatus for chronic early life stress. *eNeuro* 12, ENEURO.0081–25.2025, 2025.
- Pati D, Harden SW, Sheng W, Kelly KB, de Kloet AD, Krause EG, Frazier CJ. Endogenous oxytocin inhibits hypothalamic corticotrophin-releasing hormone neurones following acute hypernatraemia. *J Neuroendocrinol* 32, e12839, 2020.
- Quagliato LA, Nardi AE. Cytokine profile in drug-naive panic disorder patients. *Transl Psychiatry* 12, 75, 2022.
- Rokicki J, Kaufmann T, de Lange AG, van der Meer D, Bahrami S, Sartorius AM, Haukvik UK, Steen NE, Schwarz E, Stein DJ, Nærland T, Andreassen OA, Westlye LT, Quintana DS. Oxytocin receptor expression patterns in the human brain across development. *Neuropsychopharmacology* 47, 1550–1560, 2022.
- Roque A, Valles Mendez KM, Ruiz R, Pineda E, Lajud N. Early life stress induces a transient increase in hippocampal corticotropin-releasing hormone in rat neonates that precedes the effects on hypothalamic neuropeptides. *Eur J Neurosci* 55, 2108–2121, 2022.
- Schmidt MV. From “Gig” to Genes: The enduring legacy of Seymour Levine in developmental stress neurobiology. *Neurobiol Stress* 40, 100772, 2025.
- Schneider E, O'Riordan KJ, Clarke G, Cryan JF. Feeding gut microbes to nourish the brain: unravelling the diet-microbiota-gut-brain axis. *Nat Metab* 6, 1454–1478, 2024.
- Short AK, Maras PM, Pham AL, Ivy AS, Baram TZ. Blocking CRH receptors in adults mitigates age-related memory impairments provoked by early-life adversity. *Neuropsychopharmacology* 45, 515–523, 2020.
- Slopen N, Kubzansky LD, McLaughlin KA, Koenen KC. Childhood adversity and inflammatory processes in youth: a prospective study. *Psychoneuroendocrinology* 38, 188–200, 2013.
- Smith KE, Pollak SD. Early life stress and development: potential mechanisms for adverse outcomes. *J Neurodev Disord* 12, 34, 2020.
- Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF- α . *Nature* 440, 1054–1059, 2006.
- Stilling RM, van de Wouw M, Clarke G, Stanton C, Dinan TG, Cryan JF. The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis? *Neurochem Int* 99, 110–132, 2016.
- Sullivan O, Sie C, Ng KM, Cotton S, Rosete C, Hamden JE, Singh AP, Lee K, Choudhary J, Kim J, Yu H, Clayton CA, Carranza Garcia NA, Voznyuk K, Deng BD, Plett N, Arora S, Ghezzi H, Huan T, Soma KK, Yu JJ, Tropini C, Ciernia AV. Early-life gut inflammation drives sex-dependent shifts in the microbiome-endocrine-brain axis. *Brain Behav Immun* 125, 117–139, 2025.
- Surtees P, Wainwright N, Day N, Brayne C, Luben R, Khaw KT. Adverse experience in childhood as a developmental risk factor for altered immune status in adulthood. *Int J Behav Med* 10, 251–268, 2003.

- Taniguchi L, Goodpaster CM, Chen Y, de Carvalho GB, Birnie MT, Paul A, Chiang A, Chen LY, Baram TZ, DeNardo LA. Sex and stress govern the function and innervation of a basolateral amygdala to nucleus accumbens corticotropin-releasing hormone/GABA-expressing projection. *J Neurosci* 46, e1239252025, 2026.
- Taylor MA, Kokiko-Cochran ON. Context is key: glucocorticoid receptor and corticosteroid therapeutics in outcomes after traumatic brain injury. *Front Cell Neurosci* 18, 1351685, 2024.
- Varian BJ, Weber KT, Erdman SE. Oxytocin and the microbiome. *Compr Psychoneuroendocrinol* 16, 100205, 2023.
- Wang XD, Rammes G, Kraev I, Wolf M, Liebl C, Scharf SH, Rice CJ, Wurst W, Holsboer F, Deussing JM, Baram TZ, Stewart MG, Muller MB, Schmidt MV. Forebrain CRF₁ modulates early-life stress-programmed cognitive deficits. *J Neurosci* 31, 13625–13634, 2011.
- Wang XD, Labermaier C, Holsboer F, Wurst W, Deussing JM, Muller MB, Schmidt MV. Early-life stress-induced anxiety-related behavior in adult mice partially requires forebrain corticotropin-releasing hormone receptor 1. *Eur J Neurosci* 36, 2360–2367, 2012.
- Wang XD, Su YA, Wagner KV, Avrabos C, Scharf SH, Hartmann J, Wolf M, Liebl C, Kuhne C, Wurst W, Holsboer F, Eder M, Deussing JM, Muller MB, Schmidt MV. Nectin-3 links CRHR1 signaling to stress-induced memory deficits and spine loss. *Nat Neurosci* 16, 706–713, 2013.
- Wang Q, Yang Q, Liu X. The microbiota-gut-brain axis and neurodevelopmental disorders. *Protein Cell* 14, 762–775, 2023a.
- Wang T, Ma YN, Zhang CC, Liu X, Sun YX, Wang HL, Wang H, Zhong YH, Su YA, Li JT, Si TM. The nucleus accumbens CRH-CRHR1 system mediates early-life stress-induced sleep disturbance and dendritic atrophy in the adult mouse. *Neurosci Bull* 39, 41–56, 2023b.
- Wang J, Hou Y, Mu L, Yang M, Ai X. Gut microbiota contributes to the intestinal and extraintestinal immune homeostasis by balancing Th17/Treg cells. *Int Immunopharmacol* 143, 113570, 2024.
- Wang C, He T, Jie Qin J, Jiao J, Ji F. The roles of immune factors in neurodevelopment. *Front Cell Neurosci* 19, 1451889, 2025.
- Zhang Y, Wang S, Hei M. Maternal separation as early-life stress: Mechanisms of neuropsychiatric disorders and inspiration for neonatal care. *Brain Res Bull* 217, 111058, 2024.