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Review

Emerging role of microglia in the developing dopaminergic system: Perturbation by early life stress

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Abstract

Early life stress correlates with a higher prevalence of neurological disorders, including autism, attention-deficit/hyperactivity disorder, schizophrenia, depression, and Parkinson's disease. These conditions, primarily involving abnormal development and damage of the dopaminergic system, pose significant public health challenges. Microglia, as the primary immune cells in the brain, are crucial in regulating neuronal circuit development and survival. From the embryonic stage to adulthood, microglia exhibit stage-specific gene expression profiles, transcriptome characteristics, and functional phenotypes, enhancing the susceptibility to early life stress. However, the role of microglia in mediating dopaminergic system disorders under early life stress conditions remains poorly understood. This review presents an up-to-date overview of preclinical studies elucidating the impact of early life stress on microglia, leading to dopaminergic system disorders, along with the underlying mechanisms and therapeutic potential for neurodegenerative and neurodevelopmental conditions. Impaired microglial activity damages dopaminergic neurons by diminishing neurotrophic support (e.g., insulin-like growth factor-1) and hinders dopaminergic axon growth through defective phagocytosis and synaptic pruning. Furthermore, blunted microglial immunoreactivity suppresses striatal dopaminergic circuit development and reduces neuronal transmission. Furthermore, inflammation and oxidative stress induced by activated microglia can directly damage dopaminergic neurons, inhibiting dopamine synthesis, reuptake, and receptor activity. Enhanced microglial phagocytosis inhibits dopamine axon extension. These long-lasting effects of microglial perturbations may be driven by early life stress–induced epigenetic reprogramming of microglia. Indirectly, early life stress may influence microglial function through various pathways, such as astrocytic activation, the hypothalamic–pituitary–adrenal axis, the gut–brain axis, and maternal immune signaling. Finally, various therapeutic strategies and molecular mechanisms for targeting microglia to restore the dopaminergic system were summarized and discussed. These strategies include classical antidepressants and antipsychotics, antibiotics and anti-inflammatory agents, and herbal-derived medicine. Further investigations combining pharmacological interventions and genetic strategies are essential to elucidate the causal role of microglial phenotypic and functional perturbations in the dopaminergic system disrupted by early life stress.

Key Words: Chinese herbal drugs; dopamine; early life stress; epigenetics; gut-brain axis; hypothalamo–pituitary–adrenal axis; innate immune memory; microglia; neuroinflammation; Parkinson disease; phagocytosis; reward

Introduction

Early life stress (ELS), encompassing neglect, abuse, physical illness, and substance abuse during critical developmental stages, increases susceptibility to mental disorders in adolescence and adulthood (LeMoult et al., 2020). Common manifestations of ELS include maternal separation, social stress, infection, alcohol exposure, and toxicant exposure (Calanni and Rosenstein, 2024; Lee and Jung, 2024). The World Health Organization reports that 75% of children aged 2–4 years experience physical or emotional abuse from caregivers (Olino et al., 2022). ELS, related to chronic comorbidities, potentially perpetuates trauma across generations, compounding clinical, social, and economic consequences. Stress during early developmental stages, particularly the prenatal and postnatal period, disrupts normal brain development, affecting neurogenesis, axonal growth, neural circuit formation, and synaptic pruning (van Dyck and Morrow, 2017; Cattane et al., 2022). The consequences of ELS manifest in complex alterations observed in reward processing during adolescence and adulthood, characterized by diminished responses to reward anticipation and heightened responses to reward receipt. These long-lasting effects significantly increase the risk of attention-deficit hyperactivity disorder (ADHD), substance abuse, suicidal behaviors, and susceptibility to neurological disorders (St Clair et al., 2015; Nicolaides et al., 2023).

In the mesencephalon, dopaminergic (DA) circuits, characterized by tyrosine hydroxylase (TH) at DA axon terminals, convert tyrosine into dopamine and are essential for controlling reward processing, motivation, cognition, and long-term memory formation (Lee and Jung, 2024). ELS disrupts the DA system, resulting in neuronal damage and impairments in synthesis, transmission, reuptake, and receptor function (Sasagawa et al., 2017; Marino et al., 2022). These alterations are particularly evident in the functional connectivity between the substantia nigra (SN), striatum, prefrontal cortex (PFC), nucleus accumbens (NAc), and ventral tegmental area (VTA) (Park et al., 2021; Catale et al., 2022). The potential mechanisms

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through which ELS affects the DA system remain unclear. Clinical evidence suggests that ELS induces peripheral and central inflammation, with elevated pro-inflammatory cytokines identified as key factors contributing to various adverse conditions (Nusslock and Miller, 2016).

Microglia, the primary immune cells in the brain, are crucial in central nervous system (CNS) development and are sensitive to internal and external environmental stimuli (Johnson and Kaffman, 2018; Faust et al., 2021; Feng et al., 2024). From the embryonic stage to adulthood, microglia undergo significant morphological changes, including increased branching and shifts in immunophenotypic profiles. These changes facilitate synaptic pruning and phagocytosis, which are crucial for brain development (Paolicelli et al., 2011). Understanding these influences is essential, as microglia and the DA system are central mediators of behavioral abnormalities induced by ELS (Johnson and Kaffman, 2018). Recent studies show that perinatal stress can have adaptive and maladaptive long-term effects on microglia and the DA system (Paolicelli and Ferretti, 2017; Lumertz et al., 2022). The specific types, timing, and duration of ELS result in heterogeneous responses (Levis et al., 2022; Sanchez and Bangasser, 2022). For example, maternal immune activation (MIA) blunts microglial immunoreactivity in the striatum, except in the hippocampus (Schaafsma et al., 2017). Maternal separation (MS) decreases DA transmission in the hippocampus while enhancing it in other limbic pathways (Hamdan et al., 2022). Additionally, prenatal infections increase DA circuit activation in the mesolimbic system, while DA transmission is abnormally suppressed in the mesocortical system (Luchicchi et al., 2016).

Various neurological disorders, including neurodevelopmental and neurodegenerative diseases, have been associated with ELS-induced disruptions in the DA system. For example, MIA can induce neurodevelopmental disorders such as autism, schizophrenia, and ADHD in offspring, all related to complex changes in the DA system (Luchicchi et al., 2016; Perez-Palomar et al., 2023). Maternal and neonatal immune challenges increase pro-inflammatory factors and oxidative stress, damaging DA neurons in the SN and contributing to Parkinson's disease (PD) in adult offspring (Fan et al., 2011; Izvolskaia et al., 2018). Perinatal stressors, such as MS and prenatal restraint stress, result in early DA neuron loss and increased susceptibility to PD (Baier et al., 2012; He et al., 2020; Ren et al., 2022). These findings suggest that ELS-induced damage to the DA system contributes to the onset of neurological disorders. Given the role of microglia in mediating inflammatory injury, oxidative stress, and neuronal circuit formation (Tesco and Lomoio, 2022), exploring their involvement in this context is essential. However, research on how ELS affects microglial functions, particularly in the DA system and associated behavioral abnormalities, remains limited (Catale et al., 2022). Therefore, this review aims to synthesize findings on ELS effects on microglial function and the DA system, examining microglial dysregulation in the DA system development under ELS conditions and exploring potential causal mechanisms in pathogenesis. Understanding this mechanism could lead to identifying ELS pathogenetic features and establishing new therapeutic strategies for neurodevelopmental and neurodegenerative diseases via targeting microglia to restore the DA system.

Search Strategy

In this narrative review, articles were retrieved from PubMed, Scopus, and Web of Science, updated to July 2024. Most references were published within the past 5 years. The following keywords were used to identify relevant research: "early life stress," "adverse childhood experience," "early adversity," "prenatal stress," "maternal immune activation," "dopamine," "dopaminergic system," "tyrosine hydroxylase," "transmission," "transporter," "microglia," "substantia nigra," "striatum," "ventral tegmental area," "nucleus accumbens," "prefrontal cortex," "hippocampus," and "amygdala." Studies directly addressing ELS and its effect on microglia or the DA system were included. **Figure 1** presents the timeline and milestone events.

Microglial Developmental and Functional Characteristics

Microglia follow a unique developmental trajectory. At embryonic day 8.5 (E8.5), erythro-myeloid progenitors (EMPs) proliferate rapidly in the yolk sac, with a subset maturing into microglial precursors. Between days E9.5 and E10.5, these precursors migrate to the fetal brain, which remains accessible until the blood–brain barrier (BBB) forms around E13.5 to E14.5 (Masuda et al., 2019). This migration distinguishes CNS microglia from hematopoietic stem cells derived from the fetal liver and bone marrow (Cook and Prinz, 2022). Once in the brain, these precursors disperse widely and differentiate into functional microglia, influenced by their intrinsic activity and the brain microenvironment (Yaqubi et al., 2023). Matcovitch-Natan et al. (2016) identified three microglia developmental stages beyond the yolk sac phase—early (E10.5–E14), pre (E14–P9), and adult (from 2–3 weeks post-birth onward), based on stage-specific gene expression profiles. This categorization highlights their heterogeneous functions. The transitions between these phases are orchestrated by complex transcriptomic changes. Furthermore, developing microglia are vulnerable to genetic and environmental disturbances during these stages (Paolicelli and Ferretti, 2017; Masuda et al., 2019). **Figure 2** summarizes microglia emergence and maturation, including key transcription factors and functional gene markers relevant to cell lineage commitment and developmental phenotypes.

As resident macrophages in the brain parenchyma, microglia share similarities with peripheral macrophages. Under normal conditions, microglia predominantly remain in a quiescent state, maintained in part by signaling from neurons and astrocytes (Baxter et al., 2021). In response to tissue damage, pathogens, or other pathological challenges, microglia rapidly alter their morphology and phenotypic function to initiate defensive responses (Geirsdottir et al., 2020). Activated microglia are currently classified into two main phenotypes: classical (M1) and alternative (M2) activation (Fan et al., 2024; Li et al., 2024; Yang et al., 2024). M1 phenotypes are characterized by elevated levels of inflammatory mediators, including pro-inflammatory cytokines, reactive oxygen and nitrogen species, purinergic receptors, and chemokines (Teng et al., 2024). In contrast, the M2 phenotype exerts anti-inflammatory effects by releasing IL-4, IL-10, and TGF-β, promoting neuroprotection and tissue repair (Fang et al., 2023). The imbalance between these phenotypes can result in neural damage (Kwon and Koh, 2020; Guo et al., 2022). Beyond their immediate role in innate immunity, research on ELS highlights the significance of innate immune memory in modifying long-term microglial function (Carloni et al., 2021). After initial priming, microglia can exhibit a stronger (trained) or weaker (tolerant) response to secondary stressors (Netea et al., 2020). Primed microglia in a pro-inflammatory state can be neurotoxic, while microglial tolerance can confer neuroprotective effects (Haley et al., 2019). Beyond their immunological roles, microglia also influence neuronal function through neurotrophic support (Komori et al., 2024) and promote neural circuit maturation through phagocytosis and synaptic pruning (Wolf et al., 2017). These diverse functions position microglia as key regulators in maintaining optimal neuronal function in the CNS.

Microglia Vulnerability to Early Life Stress-Induced Perturbations

Prenatal stressors

Microglia are essential for CNS development, contributing to synaptic pruning, neurogenesis, synaptic plasticity modulation, neural circuit formation, and myelination (Paolicelli et al., 2011; Wang et al., 2022a). Disruptions in microglial development during embryonic and postnatal stages can significantly impair CNS development, leading to behavioral abnormalities. ELS plays a crucial role in disrupting microglial activity. It typically occurs from the fetal stage to prepuberty and it can be divided into prenatal and postnatal stages, with the postnatal phase further subdivided into the lactation (postnatal days 1 to 21, PND1-PND21) and the prepubertal stage (4–6 weeks) (Wang et al., 2017a; Zhang et al., 2019). In rodent models, most postpartum stress occurs during lactation (Orso et al., 2023; Smail and Lenz, 2024). ELS can be classified into behavioral stressors, environmental factors, and infections. **Figure 3** illustrates specific paradigms of ELS. Gómez-González and Escobar et al. (2010) were the first to examine the effect of prenatal behavioral stressors on microglia in offspring. Their findings indicate that forced swimming during pregnancy increases microglial branching in the basal ganglia and PFC of pups at PND1. Studies on prenatal restraint stress show increased microglial activation and elevated pro-inflammatory cytokine expression in the hippocampus of adult offspring (Davis et al., 2022; Hisada et al., 2023). Collectively, these findings highlight the effect of ELS on microglial activity and its subsequent effects on CNS development.

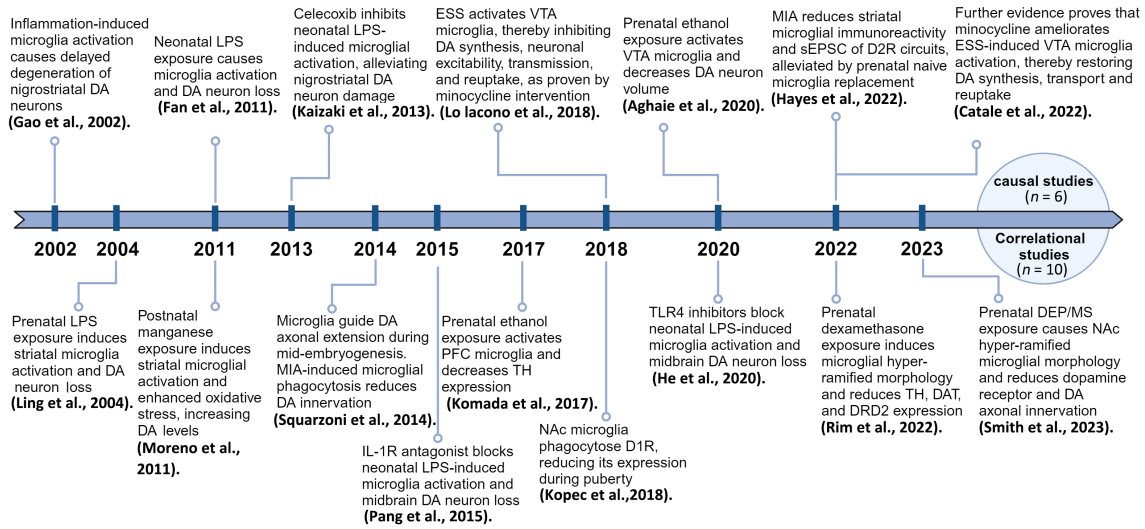

Figure 1 | **Timeline and milestone events highlighting the emerging role of microglia in mediating ELS-induced DA system disorders.**
Created with BioRender.com. D1R: Dopamine D1 receptor; D2R: dopamine D2 receptor; DA: dopamine; DAT: dopamine transporter; DEP: diesel exhaust particles; ELS: early life stress; ESS: early social stress; IL-1R: interleukin-1 receptor; LPS: lipopolysaccharide; MS: maternal stress; NAc: nucleus accumbens; PFC: prefrontal cortex; sEPSC: spontaneous excitatory postsynaptic current; TH: tyrosine hydroxylase; TLR4: Toll-like receptor 4; VTA: ventral tegmental area.

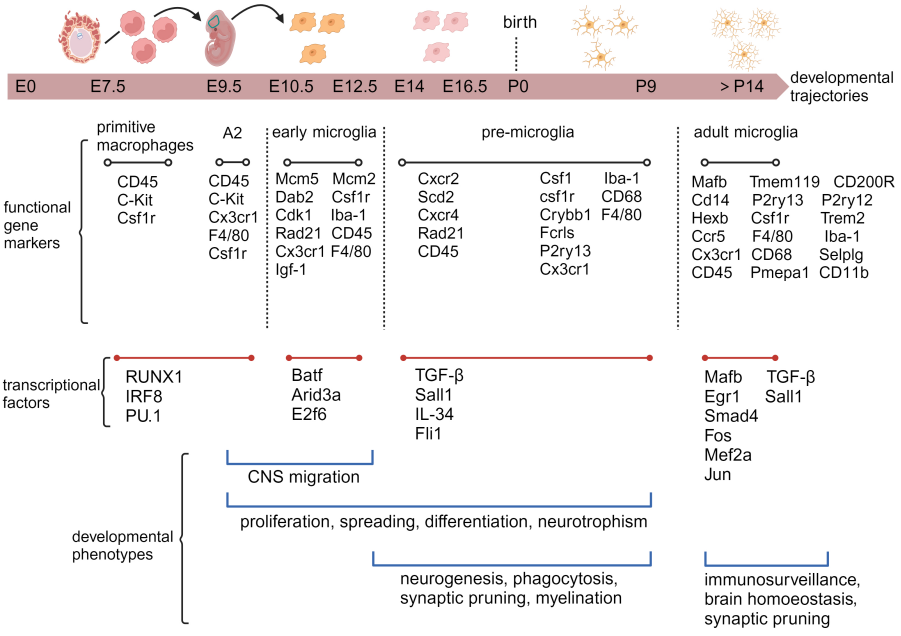

Figure 2 | **Developmental trajectories of microglia in rodents from embryonic stage to adulthood.**
Microglia originate from erythro-myeloid progenitors in the yolk sac and migrate into the fetal brain at E9.5. Once in the brain, early microglia develop under the influence of their intrinsic activities and the surrounding microenvironment. They undergo a series of sequential developmental transformations, ultimately maturing into adult microglia within 2 to 3 weeks after birth. At each stage, microglia exhibit unique functional phenotypes and gene expression markers, with their morphology and function being regulated by specific transcription factor. Created with BioRender.com. Arid3a: AT-rich interactive domain-containing protein 3A; Batf: basic leucine zipper transcription factor, ATF-like; Ccr5: C–C chemokine receptor type 5; CD11b: cluster of differentiation 11b; CD200R: CD200 Receptor; CD45: cluster of differentiation 45; CD68: cluster of differentiation 68; Cdk1: cyclin-dependent kinase 1; C-Kit: tyrosine-protein kinase kit; CNS: central nervous system; Crybb1: beta-crystallin beta b1; Csf1r: colony stimulating factor 1 receptor; Cx3cr1: C–X3–C chemokine receptor type 1; Cxcr2: C–X–C motif chemokine receptor 2; CXCR4: C–X–C chemokine receptor type 4; Dab2: disabled homolog 2; E: embryonic day; E2f6: e2f transcription factor 6; Egr1: early growth response 1; F4/80: macrophage-specific glycoprotein; Fcrls: fc receptor-like molecules; Fli1: Friend leukemia integration 1; Fos: fbj osteosarcoma oncogene; Hexb: hexosaminidase B; Iba-1: ionized calcium-binding adapter molecule 1; Igf-1: insulin-like growth factor 1; IL-1β: interleukin-1beta; IL-34: interleukin 34; Irf8: interferon regulatory factor 8; Jun: Jun proto-oncogene; Mafb: v-maf musculoaponeurotic fibrosarcoma oncogene homolog B; Mcm2: minichromosome maintenance complex component 2; Mcm5: minichromosome maintenance complex component 5; Mef2a: myocyte-specific enhancer factor 2a; P: postnatal day; P2ry12: purinergic receptor P2y12; P2ry13: purinergic receptor P2y13; Pmepa1: prostate transmembrane androgen-inducible protein 1; PU.1: spleen focus forming virus proviral integration oncogene; Rad21: Rad21 cohesin complex component; Runx1: runt-related transcription factor 1; Sall1: Spalt-like transcription factor 1; Scd2: stearoyl-CoA desaturase 2; Selplg: selectin P ligand; Smad4: mothers against decapentaplegic homolog 4; Tgf-β: transforming growth factor beta; Tmem119: transmembrane protein 119; Tmem13: transmembrane protein 13; Trem2: triggering receptor expressed on myeloid cells 2.

Epidemiological studies increasingly link MIA with an elevated risk of neurodevelopmental disorders in offspring (Aguilar-Valles et al., 2020; Weber-Stadlbauer et al., 2021). Clinical observations indicate that MIA significantly enhances microglial activation, leading to aberrant phagocytic activity (Han et al., 2021). Similar microglial abnormalities have been observed in MIA rodent models. For instance, prenatal exposure to lipopolysaccharide (LPS) or polyinosinic-polycytidylic acid (poly I:C) correlates with increased microglial density, M1-type activation, and neuroinflammation in the PFC, hippocampus, and VTA (Giovanoli et al., 2016; Zhao et al., 2019; Santoni et al., 2023). MIA impairs BBB function in offspring, allowing peripheral immune cells and cytokines to infiltrate the brain and further activate microglia (Zhao et al., 2022). In contrast, a recent study reveals that MIA reduces microglial immunoreactivity throughout the brain, except in the hippocampus (Schaafsma et al., 2017). A study by Mattei et al. (2017) shows that prenatal exposure to poly I:C alters the hippocampal microglia transcriptome, resulting in reduced phagocytosis, decreased cell migration, and impaired immunoreactivity. Additionally, maternal obesity, another form of MIA, induces complex alterations in microglial inflammation and oxidative stress, characterized by a combination of upregulated and downregulated genes (Batorsky et al., 2024), along with decreased Cx3Cr1 expression, a gene involved in synaptic pruning (Bordeleau et al., 2020). Collectively, these findings highlight the intricate effects of prenatal stress on microglial immune responses and transcriptomes in offspring. Variations in experimental paradigms (e.g., poly I:C *versus* maternal obesity) and MIA model intensity may contribute to these differences.

The molecular mechanisms by which prenatal stress induces lasting changes in microglial transcriptome and immune responses remain partially understood (Yeh and Ikezu, 2019). Epigenetic reprogramming induces innate immune memory in microglia (Wendeln et al., 2018), potentially explaining the long-term

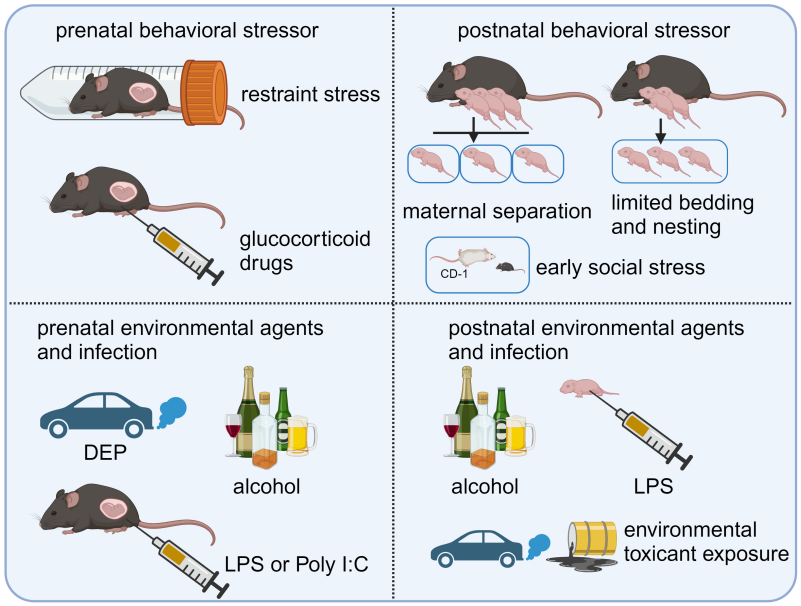

Figure 3 | **Commonly used models for depicting early life stress.**
Early life stress can be classified into prenatal and postnatal categories, including behavioral stressors, environmental events, and infections, depending on the type and timing of the stress. Prenatal behavioral stressors mainly include restraint stress and glucocorticoid exposure. Prenatal environmental events and infections encompass exposure to diesel exhaust particles, alcohol exposure, and maternal immune activation. Early postnatal stressors include maternal separation, limited bedding and nesting, and early social stress. Postnatal environmental events and infections include alcohol exposure, LPS infections, and environmental toxicant exposure. Created with BioRender.com. DEP: Diesel exhaust particles; LPS: lipopolysaccharide; Poly I:C: polyinosinic acid-polycytidylic acid.

effects of ELS. Key epigenetic factors currently being investigated include histone modification, DNA methylation, chromatin remodeling, and microRNAs (Han et al., 2021). For example, Vogel Ciernia et al. (2018) demonstrate that maternal allergic asthma primes offspring microglia. MsigDB enrichment gene analysis in microglia differentially methylated regions primarily involves immune pathways such as IL-6, IRAK6-mediated NF-κB, JAK-STAT, IL-4, and TNF signaling. These transcriptional alterations and differential epigenomic markers significantly overlap with abnormal genes related to ASD (Vogel Ciernia et al., 2018). Microglial immunoreactivity blunted by MIA is associated with chromatin remodeling. While chromatin regions in microglia specifically become more open, immune-related transcription factors improbably bind to these regions (Hayes et al., 2022). Microglia ablation through CSF1R inhibitors reversed this blunted immunoreactivity; however, whether this transcriptomic and immune response reset involves epigenetic erasure remains unclear. Additionally, late gestational exposure to LPS decreases miR-146 and miR-126 expression, which promotes long-term microglial inflammatory responses (Carloni et al., 2016). Thus, it is proposed that MIA mediates long-term transcriptomic and immune reactivity changes in microglia by reprogramming their epigenetic signature.

Early postnatal stressors

Compared with the gestational period, postnatal microglia mature rapidly, transitioning from a primitive state to a more specialized morphology, enhancing their responsiveness to early environmental stressors. Research shows that MS, maternal deprivation (MD), and maternal sleep deprivation induce microglial activation (Saavedra et al., 2021; Mi et al., 2022; Orso et al., 2023; Wang et al., 2023b). MS elevates microglial density in the hippocampus at PND14 (Delpech et al., 2016), an effect persisting into adulthood (Banqueri et al., 2019). MS blunts LPS-induced hippocampal microglial activation in juvenile female rats but intensifies the LPS-triggered reduction in dendritic complexity of newly formed neurons. This may be attributed to MS-induced modulation of cytokine expression, which decreases LPS-stimulated IL-6 and TNF-α levels while increasing IL-1β levels (Nicolas et al., 2022). Pleiotropic cytokines, such as IL-6, can exert pro-survival effects under specific conditions (Zhu et al., 2023). Conversely, limited bedding and nesting (LBN) conditions reduce hippocampal microglial proliferation, impairing microglial phagocytosis and neurotrophic effects, as indicated by reduced CD68 phagosome staining and lower levels of microglia-derived nerve growth factor (Reemst et al., 2022; Dayananda et al., 2023). LBN-induced impairment of microglial phagocytosis is restored at PND33, suggesting that postnatal stress temporarily affects microglial function in a self-healing manner. This temporal aspect is crucial for timing in pharmaceutical development and therapeutic interventions (Ahmed et al., 2024).

Postnatal exposure to bacterial or viral infections triggers a robust microglial response characterized by increased soma size and decreased ramification (Vidal-Itriago et al., 2022). This response facilitates the clearance of pathogens and their damaged cellular debris through improved phagocytosis. However, excessive inflammation and heightened phagocytic activity can impair neuronal development and synapse formation. For instance, exposure to LPS during the first 2 postnatal weeks significantly increases microglial activation in the hippocampus (Saavedra et al., 2021; Wu et al., 2022b), PFC (Berkiks et al., 2019), and midbrain (Theoharides and Kavalioti, 2019). LPS exposure at PND21 does not induce increased microglial activation (Christensen et al., 2014), suggesting that neonatal microglia are more sensitive to LPS stimulation than adult microglia (Wang et al., 2022b). These findings highlight the complexity of microglial responses to early-life immune challenges and the significance of timing in determining long-term effects.

ELS-induced changes in microglial morphology, density, and function are closely related to alterations in transcriptional profiles. Reemst et al. (2022) reported that the hippocampal microglial transcriptome remained unchanged immediately after the LBN period. However, in adulthood, genes related to microtubule polymerization were downregulated, indicating reduced phagocytic capability. Conversely, inflammation-related genes, including those involved in cytokine signaling, cell migration, the innate immune response, and protein ubiquitination, were upregulated (Reemst et al., 2022). This pattern differs from the findings of increased phagocytosis in hippocampal microglia of prepubertal mice exposed to MS (Delpech et al., 2016) and the blunted striatal microglial immunoreactivity resulting from MIA (Matcovitch-Natan et al., 2016; Mattei et al., 2017). These complex transcriptional changes may be influenced by the heterogeneity of stressors, including their specific characteristics, timing, and duration, along with the regional specificity of microglia.

A study on neonatal immune activation shows significant changes in the microglial transcriptome. Functional annotation of differentially expressed genes (DEGs) indicates upregulation in clusters related to histone modification, inflammation, and chromatin organization (Schwabenland et al., 2023). These findings suggest that epigenetic reprogramming, including histone modifications and chromatin remodeling, may mediate the long-term effects of postnatal stressors on microglial transcriptome and immunoreactivity. For instance, neonatal alcohol exposure increases H3K9ac enrichment in the promoter regions of the pro-inflammatory cytokines IL-6 and TNF-α in microglia, alongside a reduction in inhibitory transcriptional regulators such as HDAC and SIRT1, which maintains microglial sensitivity (Chastain et al., 2019). Furthermore, ELS reduces global DNA methylation in microglia within the NAc, striatum, hippocampus, and amygdala (Catale et al., 2020). Low methylation in inflammatory gene promoter regions is associated with microglial-trained immunity (Netea et al., 2020). Poly I:C-induced neonatal immune activation also increases H3K9ac enrichment in microglia promoters of Ccl12 and Sesn3, alongside elevated H3K4me3 binding at Enpp2 (Schwabenland et al., 2023). Epigenetically, histone acetylation enhances gene transcription (Han et al., 2021), while increased H3K4me3 in inflammatory genes is closely related to microglial-trained immunity (Zhang et al., 2022). Since microglial innate immune memory is governed by epigenetic reprogramming, investigating the mechanisms underlying ELS-induced epigenetic changes in microglia is essential. Additionally, exploring the heterogeneity and overlap of

epigenetic reprogramming in response to different ELS types is crucial to elucidate the observed transcriptomic and functional phenotypic differences.

In conclusion, ELS alters microglial phagocytosis, synaptic pruning, and inflammatory responses while inhibiting microglial neurotrophic effects. **Figure 4** illustrates the publication trends related to microglia in ELS animal models. Persistently altered transcriptomes and immunoreactivity may be linked to ELS-induced epigenetic modifications in microglia. Further research is necessary to elucidate how these microglial abnormalities contribute to subsequent pathological changes and behavioral manifestations.

Microglial Dysfunctions in the Dopaminergic System Perturbed by Early Life Stress

Disruption in microglial function during critical developmental periods delays neuronal circuit development (Bergamini et al., 2018), including DA circuits (Kopec et al., 2018). Pro-inflammatory mediators produced by M1-type microglia directly damage DA neurons (Ferrari et al., 2021). Furthermore, reactive oxygen species (ROS) and nitric oxide (NO) generated by microglia irreversibly oxidize tetrahydropterin (BH4), a crucial cofactor for phenylalanine hydroxylase (PAH) and tyrosine hydroxylase (TH) (Kalkman and Feuerbach, 2016). During embryonic and early postnatal development, microglia eliminate redundant synaptic connections to enhance neurotransmission efficiency, which depends on the interaction between chemokines fractalkine (CX3CL1) and C–X3–C Motif Chemokine Receptor 1 (CX3CR1) (Wolf et al., 2017). Microglia clusters at decision points along axonal tracts. At E14.5, microglial phagocytosis facilitates DA axon innervation in the basal ganglia and neocortex, with their extension ceasing upon entering the subpallium (Prestoz et al., 2012), while CX3CR1 knockout causes DA axon postnatal over-innervation in the striatum (Squarzoni et al., 2014). Another study reports that a premature increase in DA axon innervation in the PFC may cause cognitive deficits in adolescent mice (Lolier and Wagner, 2021; Reynolds and Flores, 2021). Therefore, abnormal microglial phagocytosis, synaptic pruning, and pro-inflammatory state are crucial regulatory factors of the DA system, inhibiting axonal development, synthesis, and transmission.

Abnormalities in primary microglia cultured *in vitro* disrupt DA neuron function, indicating that microglia affect the DA system under ELS conditions. For example, primary microglia derived from prenatally stressed offspring exhibit altered morphology increased pro-inflammatory cytokines, and reduced insulin-like growth factor 1 (IGF-1) levels (Ślusarczyk et al., 2015). IGF-1 inhibits microglial activation and ameliorates the reduced TH immunoreactivity caused by neonatal LPS exposure (Tien et al., 2017). Additionally, the addition of interferon-γ to microglia/DA neurons co-cultures *in vitro* activates microglia and damages DA neurons. However, DA neurons remain unaffected in the absence of microglia or when interferon-γ receptors on microglia are knocked out (Tsutsumi et al., 2019). These findings suggest that reduced neurotrophic effects and enhanced microglia immune response in offspring exposed to ELS may contribute to DA neuron damage.

Since Gao et al. first demonstrated in 2002 that microglial activation induces delayed nigrostriatal DA neuronal damage (Gao et al., 2002; Ling et al., 2004), 16 seminal literatures show that ELS—including MIA, fetal alcohol spectrum disorders, prenatal diesel exhaust particles exposure, neonatal infection, postpartum manganese exposure, and early social stress (ESS)—simultaneously disrupts microglial function and damages DA system (**Figure 1**). Scholars established a causal link between ESS-induced microglial activation and DA system dysfunction through minocycline intervention (Lo Iacono et al., 2018; Catale et al., 2022). Hayes et al. (2022) reported that replacing prenatal naive microglia alleviates MIA-induced reductions in microglial immunoreactivity and spontaneous excitatory postsynaptic current (sEPSC) in striatal D2R circuits (Hayes et al., 2022). While studies show that celecoxib, TLR4 inhibitors, and IL-1R antagonists inhibit neonatal infection-induced microglial activation and DA neuron damage (Kaizaki et al., 2013; Pang et al., 2015; He et al., 2020), their incomplete targeting limits a fully established microglial causality. These findings suggest the emerging role of microglia in mediating ELS-induced DA system disorders.

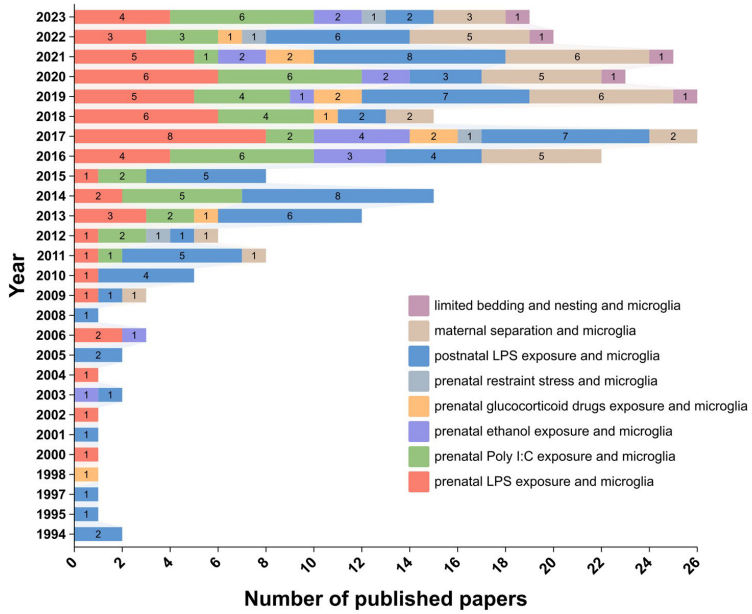

Figure 4 | **Annual trends in the publication count of research articles on animal models of ELS and microglia.** Created with Chiplot (https://www.chiplot.online/). LPS: Lipopolysaccharide; poly I:C: polyinosinic acid-polycytidylic acid.

Substantia nigra–striatum

Microglial dysfunction can impair DA neurons within the substantia nigra–striatum (SN-STR) pathway. Research shows that rat pups accumulate clusters of activated microglia around DA neurons in the SN 2 weeks after birth, suggesting a structural mechanism by which ELS affects the DA system by altering microglial function (Taguchi et al., 2020). For instance, prenatal glucocorticoid exposure reduces the TH-positive cell count in the SN of male offspring (McArthur et al., 2016), while prenatal restraint stress lowers DA levels (Katunar et al., 2009). However, research on the role of microglia in these processes is limited. Additionally, MIA or neonatal infections induce persistent microglial activation, leading to gradual DA neuron loss in the SN (Delattre et al., 2017; He et al., 2020). Prepubertal high manganese level exposure increases inflammatory responses and oxidative stress in basal ganglia microglia, correlating with abnormally elevated striatal DA levels (Moreno et al., 2011). These findings suggest that enhanced microglial activation contributes to DA neuron damage in the SN-STR pathway under ELS conditions. Future research should focus on elucidating the role of microglia in midbrain DA neuron dysfunction induced by prenatal stress in offspring.

Ventral tegmental area–nucleus accumbens

The ventral tegmental area–nucleus accumbens (VTA-NAc) pathway is a crucial component of the mesolimbic system, crucial for regulating motivation, reward processing, and pleasure (Ronström et al., 2023). Microglia density in the VTA is 4.5 times higher than that in other brain regions (Sugama and Kakinuma, 2016). Additionally, chemokine ligand 5 (CCL5), localized in glia within the VTA and co-expressed with DA neurons, indicates DA neuron susceptibility to microglia–neuron interactions (Lanfranco et al., 2017). In male rats, DA receptor (D1R) levels in the NAc decline between postnatal day 30 (PND30) and PND38 while still maintaining normal social play behavior. This decline correlates with microglial phagocytosis of D1R complexes (Kopec et al., 2018). However, prenatal oxycodone exposure reduces microglial phagocytosis of D1R in the NAc, impairing conditioned place preference for oxycodone (Smith et al., 2022). Additionally, repetitive stress affects the BBB in the NAc, exacerbating CNS inflammation by allowing

peripheral monocyte infiltration and reducing DA receptor (D1R) activity in neurons (Furuyashiki and Kitaoka, 2019). Impaired microglial phagocytosis and enhanced neuroinflammation disrupt DA-dependent reward and social behaviors regulated by the VTA-NAc circuit.

ELS affects microglial proliferation, morphology, and immune response in the VTA-NAc, potentially disrupting DA reward circuits. For instance, prenatal exposure to LPS or poly(I:C) infection increases TH-positive cell count, DA neuron firing rates, and D1R and D2R expression levels in the VTA and NAc (Weber-Stadlbauer et al., 2021; Perez-Palomar et al., 2023; Debs et al., 2024). These changes are linked to ASD and schizophrenia (Luchicchi et al., 2016). The increased DA activity is related to microglial pro-inflammatory activity (Santoni et al., 2023). Conversely, neonatal immune challenges can damage TH^+ neurons by persistently activating VTA microglia in adult offspring (Fan et al., 2011). MS and LBN inhibit the mesolimbic DA system, reducing TH mRNA expression, firing rates, and DA projections to the NAc (Jahng et al., 2010; Majcher-Maślanka et al., 2017; Masrouri et al., 2020). MS-induced inhibition of cleaved caspase-9 increases microglial density in the VTA (Chocyk et al., 2011). The variability in timing, duration, and intensity between prenatal infection and postnatal stress may account for the varying changes in the DA system. Additionally, prenatal ethanol exposure activates VTA microglia and damages DA neurons, potentially leading to ADHD (Aghaie et al., 2020). Therapeutically, minocycline mitigates decreases in DA synthesis, transmission, and reuptake in the VTA induced by early life stress (Lo Iacono et al., 2018). These findings highlight the relationship between ELS and immune, neurological, and behavioral manifestations, suggesting that an improved microglial immune response may mediate various DA-related abnormalities in the VTA-NAc circuits under ELS conditions.

Ventral tegmental area-prefrontal cortex

The mesocortical DA pathway, originating in the VTA and projecting to the PFC, is crucial for memory, learning, attention, and cognition. The PFC also coordinates stress responses and emotional-motivational assessments related to VTA activity (Douma and de Kloet, 2020). ELS can disrupt DA circuitry within the VTA-PFC pathway through microglial phagocytosis and immune dysfunction. For example, prenatal exposure to poly(I:C) activates microglia in the PFC, significantly reducing DA turnover in adolescent male rats (Edemann-Callesen et al., 2023). Similarly, prenatal ethanol exposure promotes pro-inflammatory microglial differentiation and inhibits DA axonal projections to the PFC (Komada et al., 2017). Conversely, MD increases excitatory currents in PFC-projecting DA neurons in the VTA and enhances the excitability of layer 2/3 PFC neurons through DA D2 receptor (D2R) activation (Oh et al., 2021). However, the effects of MS on microglial morphology and function in the PFC remain inconsistent, with some studies reporting reduced microglial intensity (Majcher-Maślanka et al., 2019), while others show increased microglial activation (Wang et al., 2020b; Mi et al., 2022). These discrepancies may stem from variations in MS procedures (e.g., 3 h/d *vs.* 4 h/d) and differences in animal models (mice *vs.* rats). In conclusion, prenatal and postnatal ELS exert opposing effects on the DA system and microglial responses within the PFC. The mechanisms underlying these contrasting outcomes require further investigation.

Other regions

Microglia can influence the DA system beyond primary microglia/DA neuron co-cultures and DA neural circuits. For example, ablation of norepinephrine (NE) in the locus coeruleus triggers microglial activation in the nigrostriatal pathway, characterized by increased neuroinflammation, decreased neurotrophic factor levels, and reduced antioxidant capacity, ultimately impairing DA neurons (Yao et al., 2015). Minocycline reduces microglial activation and upregulates DA levels in the hippocampus (Du et al., 2019). Similar effects are observed in olfactory bulbectomized depressed mice (Arakawa et al., 2012) and in minocycline-treated learned helplessness rats in the amygdala (Takahashi et al., 2018). Maternal stress (MS) reduces DA content in the amygdala and decreases DA release from the NAc during exposure to palatable food (Romano-López et al., 2016), along with an increased Iba-1 density (Garcia et al., 2023). Therefore, ELS-induced microglial activation may also affect the DA system in other brain regions. Exploring the causal links between microglia and the DA system in these regions under ELS conditions and how these links relate to ELS-induced behavioral abnormalities is crucial. **Table 1** and **Figure 5** summarize the effects of ELS on microglia and the DA system in the mesocorticolimbic and nigrostriatal pathways.

Role of Microglia in the Pathogenesis of Early Life Stress-Induced Neurodevelopmental and Neurodegenerative Disorders

The studies discussed above show that ELS activates microglial responses, resulting in aberrant alterations in microglial morphology, density, and function (Squarzoni et al., 2014; Ślusarczyk et al., 2015; Bordeleau et al., 2020). These microglial changes are linked to glial cells, the neuroendocrine system, the microbiota-gut-brain axis, and maternal immune signals, ultimately influencing the formation and refinement of neural circuits (Desplats et al., 2020). Microglia support the development and refinement of the DA system during critical periods (Catale et al., 2022), suggesting that microglia may mediate ELS-induced disorders in the DA system.

Microglia–neuron and microglia–glia crosstalk

Microglia continuously monitor and respond to various signals, regulating neuronal and glial activities. Under physiological and pathological conditions, the interaction between microglia and DA neurons involves local mediators, including purinergic signaling (Furuyashiki and Kitaoka, 2019), chemokine receptors (Tristao et al., 2016), and complement pathways (Kopec et al., 2018). Kv1.3, a member of the Shaker family of voltage-gated potassium channels, plays a crucial role in microglia-mediated neuroinflammation in the midbrain. Postnatal LPS exposure increases Kv1.3 expression in microglia, enhancing potassium efflux (Di Lucente et al., 2018). This efflux promotes DA release from adjacent DA neurons, counteracting NLRP3 inflammasome activation and mitigating microglia-mediated neurotoxicity (Pike et al., 2022). However, as microglia progressively deplete DA, NLRP3 inflammasome activation and Kv1.3 channel activity increase, ultimately impairing DA neurons.

Microglia-glia interactions transmit signals that regulate neuronal structure and function (Liddelow et al., 2020). Microglia-induced neuroinflammation can transform astrocytes into neurotoxic A1 phenotypes, exacerbating neurotoxicity in DA neurons (Liddelow et al., 2017). In tryptophan metabolism, ELS increases pro-inflammatory cytokine production and activates indoleamine 2,3-dioxygenase (IDO) in microglia, resulting in the conversion of tryptophan to kynurenine (Reus et al., 2019). Kynurenine is further converted into kynurenic acid (KA) by kynurenine aminotransferase II, an enzyme primarily expressed in astrocytes (Kindler et al., 2020). KA decreases glutamate release to DA neurons, thereby reducing their excitability (Felger and Miller, 2012). These microglia–neuron and microglia–glia interactions may contribute to DA neuron damage under ELS conditions.

Microglia-mediated neuronal extension and survival in the dopaminergic system under early life stress

Microglia-derived neurotrophic factors also play a role in the pathological processes associated with ELS. Studies on microglia-derived brain-derived neurotrophic factor (BDNF) have primarily focused on neurogenesis and medial prefrontal cortex (mPFC)-dependent social behavior (Harley et al., 2021; Komori et al., 2024). However, direct evidence linking microglia-derived BDNF to DA system abnormalities under ELS remains limited. Prenatal stress reduces microglia-derived IGF-1, a neuroprotective and anti-inflammatory factor (Ślusarczyk et al., 2015). IGF-1 can reverse microglial pro-inflammatory phenotypes and prevent DA neuron damage (Tien et al., 2017).

Beyond their immune functions, microglia modulate neural circuit maturation in perinatal pups through activity-dependent network remodeling (Hayes et al., 2022). Section 3 summarizes the distinctive features of DA axonal extension during mid-embryogenesis, a phase when microglia engulf DA axonal fragments as they enter the subpallium. $Cx3cr1^{gfp/+}$ depleted and Pu.1 mutant embryos exhibit excessive TH-positive axon extension into the subpallium and striatum, while MIA diminishes this extension by enhancing microglial phagocytosis (Squarzoni et al., 2014). Other research shows that MIA downregulates microglial phagocytosis-related genes, including CX3CR1, TREM2, and TMEM119 (Bordeleau et al., 2020; Chamera et al., 2020). Differences in immunogen types (e.g., LPS and Poly I:C), experimental protocols (infections *vs*. maternal high-fat diets), and testing period (neonatal *vs*. adult) may explain the discrepancies in microglial phagocytosis-associated receptor expression. Although the conflicting effects of MIA on microglial phagocytosis remain unresolved,

Table 1 | **Effects of ELS on microglia and the DA systems in key brain regions and mediated behavioral effects**

Modeling method	Species	Detection time	Microglia	Dopaminergic system	Behavioral effect	Disease	Reference
Prenatal poly I:C exposure; E15; 4 mg/kg/d	Sprague-Dawley rats; M	PND34-PND36	Total brain: Iba-1↑	VTA: dopamine neuron bursting activity↑	Locomotor activity↑; PPI deficiency	Schizophrenia	Santoni et al., 2023
Prenatal poly I:C exposure; E9.5; 10–20 mg/kg	C57BL/6J; M, F	8–10 wk	STR: $CD68^+$ microglia↓; microglial immunoreactivity↓	STR: frequency of sEPSC in D2R MSN↓	NA	NA	Hayes et al., 2022
Prenatal LPS exposure; E11; 1 mg/kg	Wistar rats	PN21; PN99	SNpc, STR: no change	SNpc: TH-ir↓ Striatum: DA↓, TH-ir↓	Object location memory deficit	Parkinson's disease	Delattre et al., 2017
Neonatal LPS exposure; PND1; 1 mg/kg	Sprague–Dawley rats; M, F	PND4, PND80–PND85	SN: Iba-1↑, TLR4↑, NF-κB↑	SN: TH-positive neuron↓	Active behaviors↓, learning and memory abilities↓	Parkinson's disease	He et al., 2020
Prenatal ethanol exposure; 3 g/kg/d; E8–E20	Sprague–Dawley rats; M	8–12 wk	VTA: microglial branching↓, activated microglia↑	VTA: DA neuron body size↓	NA	NA	Aghaie et al., 2020
Prenatal ethanol exposure; 1–2 g/kg/d (25% w/v); E6-E18	ICR mice	PND3	PFC: amoeboid microglia↑, ramified-type microglia↓, Iba-1↑, $CD11b^+$↑, $CD206^+$↓	PFC: TH^+ expression↓	NA	NA	Komada et al., 2017
Postnatal LPS exposure; 2 mg/kg/d; PND5	Sprague–Dawley rats	PND6	SN, striatum: Iba1↑; activated microglia↑; IL-1β↑	SN: DAT↑; TH-ir↓, α-synuclein↑	Sensorimotor behavioral deficits: righting reflex latency↑; negative geotaxis latency↑	NA	Kaizaki et al., 2013
Postnatal LPS exposure; 1 mg/kg; PND5	Sprague–Dawley rats; M	PND70	SN: microglia activation↑; IL-1β↑	SN: TH^+ NeuN↓; Dopaminergic dendrites↓	Motor behavioral deficits	Parkinson's disease	Pang et al., 2015
Early social stress exposure; PND14–22	DBA/2J@Ico mice M	PND22, PND100	VTA: Iba-1↑; microglial density↑, soma size↑	VTA: DA-induced currents↓; DAT↓; TH↓; DAT-mediated currents↓; VMAT2↓; D2R↓	CPP deficits	Substance use disorder	Lo Iacono et al., 2018; Catale et al., 2022
Early manganese exposure; 10 mg/kg, 30 mg/kg; PND20–34	C57Bl/6J mice; M, F	PND35	SNpr, STR: amoeboid microglia↑; Iba-1↑	SNpr, STR: no change of TH	NA	NA	Moreno et al., 2009
Early manganese exposure; 100 mg/kg; PND21–34	NF-κB-EGFP mice; M	PND35	SNpr, STR: Iba-1^+/NF-$κB^+$ co-expressing cell↑, Iba-1^+/$NOS2^+$ co-expressing cell↑	STR: DA↑, DOPAC/DA↓	NA	NA	Moreno et al., 2011
Postnatal LPS exposure; PND5; 1 mg/kg	Sprague-Dawley rats	PND6, PND70	SN, VTA: $OX42^+$ cells ↑, Amoeboid microglia↑, IL-1β↑, IL-6↑	SN, VTA: TH^+ positive neuron↓	Stereotyped tasks, hyperactive locomotion	Parkinson's disease	Fan et al., 2011
Prenatal dexamethasone exposure; 50 μg/kg; E16–E18	C57BL/6; M, F	10 wk	mPFC: microglial branch length↑, CX3CR1↑	mPFC: DAT, DRD2, and TH↓	Prepulse inhibition deficit, immobile time↑	Schizophrenia, depressive-like behavior	Rim et al., 2022
Prenatal DEP/MS; 50 μg/50 μL	C57BL/6J; M	PND28-PND40, PND45	NAc: microglial ramifications↑	NAc: D1R and D2R↓, dopamine axonal innervation↓	Social deficit	Autism disorder	Smith et al., 2023

Arg-1: Arginase-1; CD11b: cluster of differentiation 11b; CD206: cluster of differentiation 206; CD68: cluster of differentiation 68; CPP: conditioned place preference; D2R: dopamine 2 receptor; DA: dopamine; DAT: dopamine transporter; DEP: diesel exhaust particle; E: embryonic day; F: femaleIba1: Ionized calcium binding adaptor molecule-1; IL-1β: interleukin-1 beta; IL-6: interleukin-6; ir: immunoreactivity; LPS: lipopolysaccharide; M: male; mPFC: medial prefrontal cortex; MS: maternal stress; MSN: medium spiny neurons; NA: not applicable; NF-κB: nuclear factor kappa B; NOX2: NADPH oxidase 2; OX42: cluster of differentiation 204; PND: postnatal day; Poly I:C: polyinosinic-polycytidylic acid; PPI: prepulse inhibition; sEPSC: spontaneous excitatory postsynaptic potential; SN: substantia nigra; SNpc: substantia nigra pars compacta; SNr: substantia nigra reticulata; STR: striatum; TH: tyrosine hydroxylase; TLR4: toll-like receptor 4; VMAT2: vesicular monoamine transporter 2; VTA: ventral tegmental area.

these findings suggest that prenatal stress disrupts microglial phagocytosis, ultimately influencing the normal development and innervation of DA neurons.

Priming microglia of the innate immune system and memory challenged by early life stress

Neurodevelopmental and neurodegenerative disorders often correlate with elevated neuroinflammation (Han et al., 2021). Toll-like receptors (TLRs), which are abundantly expressed on microglia, are activated by damage-associated molecular patterns and pathogen-associated molecular patterns, regulating the innate immune response to neuronal injury. Recent studies report that early-life infections prime inflammatory transcription in microglia through TLRs. For example, LPS injection at E12 results in persistent TLR-2 and TLR-4 expression, leading to sustained microglial activation in the amygdala (O'Loughlin et al., 2017). Additionally, LPS administration at PD14 increases TLR-4 and CX3CR1 expression in microglia, enhancing dendritic spine engulfment and axon initial segments (Cao et al., 2021). Poly(I:C) injection at PND 7 induces long-term learning deficits by activating TLR3 expression in the PFC and hippocampus (Baghel et al., 2018). TLRs activate NLRP3 inflammasome through a two-step classical pathway: priming and inflammasome assembly. Initially, TLR signaling triggers the priming process, activating the MAPK and NF-κB pathways to promote pro-inflammatory cytokine expression. Subsequently, adenosine triphosphate (ATP), α-synuclein, and oxidative stress stimulate inflammasome assembly (Dimatelis et al., 2013; Maes et al., 2022), resulting in caspase-1 maturation and the cleavage of pro-IL-1β and pro-IL-18 into their mature forms. Notably, the ESS model of ELS induces microglial activation, reducing DA-induced outward current amplitude and inhibiting *Gch1* (a key gene for BH4), TH, and DAT expression in the VTA (Catale et al., 2022). This suggests that ELS-related DA deficits may arise from microglial activation and elevated neurotoxic cytokine levels, contributing to DA neuron damage.

Perinatal stressors trigger immediate inflammatory activation and establish long-term innate immune memory in microglia, influencing their responses to future challenges in adulthood (Cao et al., 2021; Bolton et al., 2022). This immune memory, reprogrammed by early infections and environmental stressors through epigenetic modifications, is not antigen-specific (Carloni et al., 2021). Lajqi et al. (2020) reported that neonatal microglia are more sensitive to LPS-induced priming and tolerance, with low-dose LPS exposure increasing their vulnerability to subsequent stress. Conversely, MIA suppresses microglial immunoreactivity throughout the lifespan, resulting in decreased presynaptic vesicle release onto postsynaptic D2R medium

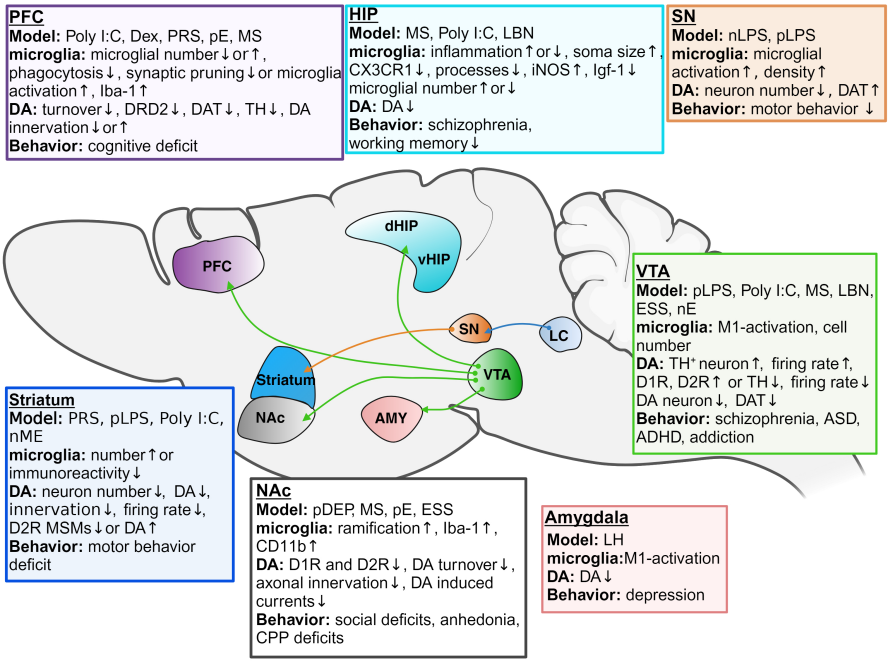

Figure 5 | **Abnormal functional patterns and behavioral manifestations of microglia and DA systems caused by ELS.** ELS induces disorders in the DA system, resulting in neuronal damage and impairments in synthesis, transport, reuptake, and receptor function within the mesocorticolimbic and nigrostriatal DA pathways. Furthermore, abnormalities in microglial density, morphology, and phenotypic function have been observed, collectively mediating disruptions in behavioral, emotional, and cognitive functions. Created with BioRender.com. Arrows indicate alterations in relevant molecular indicators: "↑" indicates an increase while "↓" indicates a decrease. ADHD: Attention deficit/hyperactivity disorder; ASD: autism spectrum disorder; CPP: conditioned place preference; CX3CR1: c-x3-c motif chemokine receptor 1; D1R: dopamine receptor D1; DA: dopamine; DAT: dopamine transporter; Dex: dexamethasone; DRD2: dopamine receptor D2; ELS: early life stress; ESS: early social stress; HIP: hippocampus; Iba1: ionized calcium binding adapter molecule 1; Igf-1: insulin-like growth factor 1; iNOS: inducible nitric oxide synthase; LBN: limited bedding and nesting; LH: learned helplessness; MS: maternal separation; MSN: medium spiny neurons; NAc: nucleus accumbens; nE: neonatal ethanol exposure; nLPS: neonatal lipopolysaccharides exposure; pDEP: prenatal diesel exhaust particle exposure; PE: prenatal ethanol exposure; PFC: prefrontal cortex; pLPS: prenatal lipopolysaccharides exposure; pME: postnatal manganese exposure; Poly I:C: polyinosinic-polycytidylic acid; PRS: prenatal restraint stress; SN: substantia nigra; TH: tyrosine hydroxylase; VTA: ventral tegmental area.

spiny neurons and a reduced sEPSCs frequency. This suppression relates to more open chromatin regions but reduced transcription factor binding. Prenatal replacement with naive microglia can ameliorate this suppressed immunoreactivity and restore striatal DA circuit development (Hayes et al., 2022). These findings suggest that early stress-mediated microglial epigenetic reprogramming plays a significant role in DA circuit formation.

Interaction between maternal immune signals and microglia

Pregnancy presents an immunologically complex condition requiring a delicate balance between maternal and fetal immune responses to combat pathogens effectively (Hussain et al., 2022). Inflammatory states during pregnancy can arise from infections, psychosocial stress, autoimmune diseases, and obesity (Kwon et al., 2022). In this context, MIA is characterized by elevated inflammatory markers transmitted to the fetal brain, contributing to neurodevelopmental disorders in offspring. Prenatal infection activates the maternal immune response, releasing pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (Theoharides et al., 2016; Bordeleau et al., 2020; Cieslik et al., 2020). IL-6 activates maternal TH17 cells, which release IL-17A (Reed et al., 2020). These cytokines, alongside activated maternal TH17 cells, reach the placenta, activating resident immune cells and transmitting inflammatory signals to the fetus (Zawadzka et al., 2021). Pro-inflammatory cytokines can cross the BBB, initiating an inflammatory cascade that activates microglia and disrupts neuronal development. MIA also disrupts BBB formation throughout the lifespan (Zhao et al., 2022), which is linked to increased proliferation of COX-2-positive microglia and impaired pericyte-endothelium coupling (Haruwaka et al., 2019). MIA further increases burst firing in DA neurons within the VTA, correlating with microglial activation and neuroinflammation (Santoni et al., 2023). These findings highlight the significant role of maternal immune signals and fetal microglial activation in the DA system under MIA conditions.

Microbiota–gut–brain axis and microglia

Emerging evidence highlights that microbiota significantly influences both gut and brain functions (Cryan et al., 2019; Morais et al., 2021). For instance, germ-free mice exhibit downregulated microglial genes, resulting in an immature and hyper-ramified microglial phenotype (Erny et al., 2015), indicating the role of gut microbiota in microglial maturation. In an MIA-induced ASD model, *Lactobacillus reuteri* supplementation restores DA neuron plasticity (Sgritta et al., 2019). Additionally, prenatal exposure to DEP/MS disrupts gut microbiome composition and compromises gut barrier integrity in adult male offspring. This disruption results in hyper-ramified microglial phenotypes and reduced D1 and D2 receptor expression in the NAc. Cross-fostering with a healthy gut microbiome at birth prevents microglial hyper-ramification (Smith et al., 2023). These findings suggest a potential role for the gut microbiome in mediating abnormal microglial phenotypes and related DA system dysfunction following perinatal stress.

Microglia and hypothalamic–pituitary–adrenal axis

The hypothalamic-pituitary-adrenal (HPA) axis, a crucial component of the neuroendocrine system, regulates stress responses by promoting glucocorticoid (GC) release. HPA axis dysfunction is closely linked to neuropsychiatric disorders (Mikulska et al., 2021). HPA axis activity correlates with microglia-mediated phagocytosis and synaptic pruning. For instance, maternal exposure to dexamethasone, a GC analog, increased HPA axis activity while inhibiting DA synthesis and transport. This resulted in decreased DRD2, DAT, and TH expression in the mPFC, with microglia adopting hyper-ramified phenotypes (Rim et al., 2022). Given that microglia can eliminate DA receptors through synaptic pruning (Kopec et al., 2018), these findings suggest a potential link between HPA axis activation, microglial phagocytosis, synaptic pruning, and DA circuit development under ELS.

Microglial oxidative stress in the dopaminergic system induced by early life stress

ELS-induced microglial activation triggers neuroinflammation alongside promoting oxidative stress through the catalytic subunit gp91 and regulatory subunit p47 of NOX2 (Jiang et al., 2016). Oxidative damage to DA axonal terminals can result in DA oxidizing to dopamine-sulfonic acid (DASQ) (Block and Hong, 2007; Nguyen et al., 2019). This oxidative stress disrupts the glutamatergic/GABAergic balance in the mesolimbic system, mediating MIA-induced schizophrenia-positive symptoms (Caruso et al., 2020).

In conclusion, perinatal stress alters microglial morphology, density, and function, affecting immune responses, phagocytosis, synaptic pruning, and neurotrophic support. These long-lasting dysfunctions can occur directly through ELS-induced microglial epigenetic modifications. Indirect influences such as astrocytic activation, HPA axis activation, maternal immune signals, and the gut-brain axis further modulate microglial activity, contributing to ELS-induced DA system disorders. These disorders encompass neuronal damage and impaired synthesis, transmission, reuptake, and receptor function. **Figure 6** illustrates these processes.

Therapeutics to Alleviate Microglial Dysfunction in the Dopaminergic System Under Early-Life Stress Challenge

Classical antidepressants and antipsychotics

Common antidepressants, such as selective serotonin reuptake inhibitors (paroxetine, sertraline, fluoxetine) and amitriptyline, primarily function by inhibiting the reuptake of serotonin (5-HT) or NE. These medications also exhibit anti-

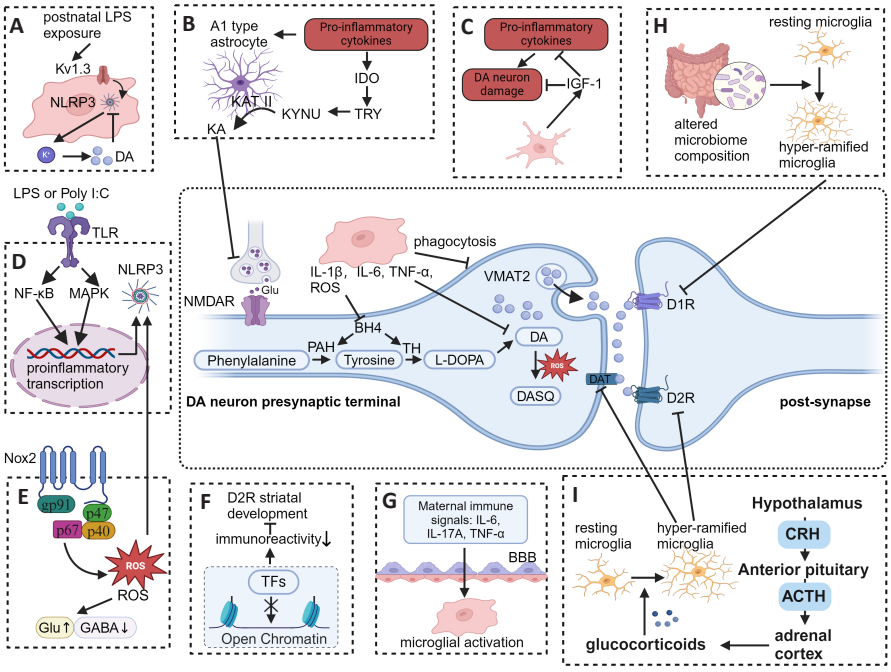

Figure 6 | **Potential pathogenesis of ELS-mediated microglia-associated abnormalities in the DA system.**
(A) Postnatal LPS exposure increases K^+ efflux and NLRP3 inflammasome activation in microglia, which progressively depletes DA from adjacent dopamine neurons. (B) Proinflammatory factors released upon microglial activation promote production of neurotoxic A1 astrocytes. Proinflammatory factor also activates IDO, which promotes the conversion of tryptophan to kynurenine. Kynurenine is catalyzed by KAT II in astrocytes to produce KA, which inhibits the release of glutamate to DA neurons. (C) Prenatal stress reduces microglial secretion of IGF-1, which can alleviate neuroinflammation and DA neuron damage. (D, E) Perinatal stress and infection initiate pro-inflammatory transcription via TLRs and increase NLRP3 expression, then NLRP3 inflammasome assembly is stimulated by elevated levels of ROS. (F) Maternal immune activation blunts microglial immunoreactivity and inhibits development of striatal D2R circuits. (G) Maternal immune signals stimulated by MIA, such as IL-6, IL-17A, and TNF-α, can cross the immature BBB of the fetal brain and promote microglial activation. (H) Prenatal stress and pollution lead to altered microbiome composition in offspring, resulting in hyper-ramified microglial phenotype and reduced D1R and D2R expression. (I) Maternal dexamethasone exposure increases HPA axis activation in offspring, with microglia switching to a hyper-ramified phenotype, which may contribute to reduced D2R and DAT expression. Created with BioRender.com. Arrows indicate alterations in pathological process: "→" indicates promotion while "┤" represents inhibition. ACTH: Adrenocorticotropic hormone; BBB: blood-brain barrier; BH4: tetrahydrobiopterin; CRH: corticotropin-releasing hormone; D1R: dopamine receptor D1; D2R: dopamine receptor D2; DASQ: dopamine o-semiquinone; GABA: γ-aminobutyric acid; Glu: glutamate; IDO: indoleamine 2,3-dioxygenase; IL-17A: interleukin-17A; IL-18: interleukin-18; IL-1β: interleukin-1beta; IL-6: interleukin-6; Kv1.3: voltage-gated potassium channel 1.3; KYNU: kynurenine; L-DOPA: L-3,4-dihydroxyphenylalanine; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor kappaB; NLRP3: NOD-like receptor family pyrin domain containing 3; NMDAR: N-methyl-D-aspartate receptor; NOX2: NADPH oxidase 2; PAH: phenylalanine hydroxylase; Poly I:C: polyinosinic-polycytidylic acid; ROS: reactive oxygen species; TFs: transcriptional factor; TH: tyrosine hydroxylase; TLR: toll-like receptor; TNF-α: tumor necrosis factor alpha; TRY: tyrosine; VMAT2: vesicular monoamine transporter 2.

neuroinflammatory properties, further enhancing their therapeutic efficacy. For instance, venlafaxine suppresses prenatal stress-induced microglial activation in the hippocampus and mitigates LPS-induced IL-1β production (Obuchowicz et al., 2019). Escitalopram alleviates MS-induced dysphoria by restoring DA release in the NAc (Minami et al., 2017) and lowering hippocampal IL-1β levels, improving depression-like behaviors (Wang et al., 2017b). Sertraline reduces MS-induced microglial activation in both the PFC and hippocampus (Ye et al., 2019), while fluoxetine protects midbrain DA neurons from LPS-induced damage by inhibiting microglial activation (Zhang et al., 2012).

Antipsychotic drugs, primarily D2R antagonists, exhibit anti-neuroinflammatory properties. For example, risperidone and its metabolite paliperidone can inhibit MIA-induced microglial activation through Nrf2 and PPARγ pathways (Zhu et al., 2014; MacDowell et al., 2017). Clozapine also reverses microglial activation and iNOS secretion, demonstrating significant anti-inflammatory effects (Ribeiro et al., 2013), though it poses serious side effects such as leukopenia and granulocyte deficiency, potentially leading to severe infections.

Antibiotics and anti-inflammatory agents

Recent studies show the potential of antibiotics and anti-inflammatory agents in mitigating ELS-induced microglial activation and associated DA system dysfunction. Minocycline, for instance, inhibits ELS-induced microglial neuroinflammation, protecting DA neurons and enhancing DA synthesis (Lo Iacono et al., 2018; Catale et al., 2022). Celecoxib significantly inhibits neonatal LPS exposure-induced microglial activation, thereby attenuating nigrostriatal DA neuron damage (Kaizaki et al., 2013). Sulfasalazine, an immunomodulatory agent, mitigates MS-induced microglial activation in the PFC, thereby improving synaptic plasticity (Wang et al., 2023a). Additionally, inhibition of microglia-derived inflammatory factors through IL-1R antagonist and TLR4 inhibitor prevents LPS-induced DA neuron damage and increases TH expression (Pang et al., 2015; He et al., 2020). Similarly, TNF-α inhibitors suppress prenatal poly I:C exposure-induced microglial activation in the hippocampus and PFC, thereby restoring prepulse inhibition (Shelton et al., 2021). These findings indicate that targeting microglia presents a promising strategy for alleviating ELS-induced DA system disorders.

Herbal-derived medicine

Herbal-derived medicines, comprising active ingredients or mixtures from natural plants, hold the potential for modulating microglia activity to address neuroinflammation and neuronal damage. For example, maternal supplementation with resveratrol increases DA content and its metabolites in the striatum (Rose et al., 2014), with microglia mediating its neuroprotective effects (Zhang et al., 2010). Herbal compounds, such as *Thymelaea lythroides* extract and *Ganoderma lucidum triterpenoids*, reverse M1-type microglial activation (Berkiks et al., 2018; Mi et al., 2022). Curcumin alleviates microglial activation in the dentate gyrus induced by prenatal alcohol exposure or MIA (Cantacorps et al., 2020), restoring neuronal morphology (Chen et al., 2018). Paeoniflorin inhibits LPS-induced hippocampal microglial activation via TLR4/NF-κB/NLRP3 signaling, reducing depressive behaviors (Cheng et al., 2021). Similar effects were observed in postnatal LPS-exposed mice treated with *Achyranthes bidentata polypeptide* and Gastrodin (Wang et al., 2021; Yao et al., 2022). Zhao et al. (2019) reported the role of PPARγ in reducing ELS-induced microglial activation. PPARγ-targeting compounds such as *asperosaponin* VI and ginsenoside Rb1 promote neuroprotective microglial phenotypes (Zhang et al., 2021; Jiang et al., 2022). Collectively, herbal-derived medicines may represent a potential therapeutic strategy to alleviate ELS-induced microglial activation and neuronal damage. **Table 2** summarizes the therapeutic interventions and molecular mechanisms.

Limitations

This review has some limitations. First, findings from systematic reviews and meta-analyses, which could offer a more comprehensive analysis of complex microglial changes, were not included. Second, postnatal microglia exhibit physiological differences in density, morphology, and transcriptomic characteristics across various brain regions (Li et al., 2019; Tan et al., 2020). Therefore, future studies should consider these variations when examining ELS-induced DA system disorders. Lastly, the review inadequately addresses sex factors despite evidence of a clear sex bias in ELS effects on microglial responsiveness in adulthood (Bordeleau et al., 2020).

Conclusion

Recent preclinical studies report that ELS disrupts microglial functions such as phagocytosis, synaptic pruning, and immune responses while

Table 2 | Potential therapeutics targeting microglia to recover the DA system in the context of ELS

Type	Drug	Cell line/animal model	Modeling method	Drug administration	Brain region	Mechanism	Reference
Anti-depressant drug	Venlafaxine	Primary microglia from Wistar rats of 1-day-old pups	Oral gavage stress from GD7–GD22	Oral venlafaxine (20 mg/kg) from GD7–GD22	NA	Venlafaxine reduces microglial activation and levels of IL-1β, TNF-α, iNOS, and Bcl-2.	Obuchowicz et al., 2019
	Escitalopram	C57BL/6, M	MS (PND2-PND9, 4 h/d; PND10-PND16, 6 h/d; PND17-PND20, 8 h/d)	i.p escitalopram (10 mg/kg) from PND33–PND54	Ventral hippocampus	Escitalopram reduces microglial activation and IL-1β levels and increases IL-10 expression.	Wang et al., 2017b
	Sertraline	Sprague–Dawley rats, F	MS (PND2-PND21, 3 h/d) combined with chronic mild stress	Oral sertraline from PND22–PND42 PND	Hippocampus, prefrontal cortex	Sertraline inhibits PI3K/Akt/NF-κB pathway and attenuates microglial activation.	Ye et al., 2019
	Fluoxetine	Primary rat midbrain neuron–glia from rats at E14–E15	Incubated with LPS (10 ng/mL) for 15 min	Pretreated with fluoxetine (3 μM) for 30 min	NA	Fluoxetine inhibits microglial activation and neurotoxic factor release, protecting midbrain DA neurons.	Zhang et al., 2012
Antipsychotic drugs	Clozapine	Primary neuron-glia culture	Incubated with LPS (15 ng/mL) for 1 wk	Pretreated with indicated concentrations of clozapine for 30 min	NA	Clozapine protects DA neurons by inactivating microglia through inhibition of NOX2.	Jiang et al., 2016
		Male Wistar rats	Injected with poly I:C (2 mg/kg) from PND5–PND7	i.p clozapine (25 mg/kg) from PND60–PND74	Striatum	Clozapine reduces microglial activation and iNOS levels.	Ribeiro et al., 2013
	Paliperidone	C57BL/6J	Injected with poly I:C (5 mg/kg) at E9.5	i.p paliperidone (0.05 mg/kg) from PND60–PND81	Prefrontal cortex	Paliperidone activates Nrf2 and PPARγ pathways to block microglial activation.	MacDowell et al., 2017
	Risperidone	Sprague–Dawley rats	Ventral hippocampal LPS injection (10 μg/μL, 0.3 μL) at PND7	Oral risperidone (0.5 mg/kg) for 2 wk from PND42–PND56	Hippocampus	Risperidone inhibits microglial activation.	Zhu et al., 2014
Anti-inflammatory candidate drug	Minocycline	C57BL/6J	MS (PND1–PND14, 3 h/d) combined with restraint stress	i.p minocycline (20 mg/kg) for 2 wk from PND22–PND35	Hippocampus	Minocycline reduces microglial activation and IL-1β, IL-6 levels.	Han et al., 2019
		DBA/2J@Ico mice, M	Early social stress (PND14–PND21, 30 min/d)	i.p. injection of minocycline (50 mg/kg) for 1 wk from PND14–PND21	VTA	Minocycline inhibits microglial activation, thereby increasing DA-induced outward currents and D2R, TH, DAT expression.	Lo Iacono et al., 2018; Catale et al., 2022
	Celecoxib	Sprague-Dawley rats, M, F	Injected with LPS (2 mg/kg) at PND5	i.p. injection of celecoxib (20 mg/kg) after LPS injection.	SN	Celecoxib reduces microglial activation and IL-1β levels, attenuating dopamine neuron damage.	Kaizaki et al., 2013
	Sulfasalazine	C57BL/6J mice	MS (PND1–PND21, 3 h/d)	i.p sulfasalazine (75 mg/kg) from PND61–PND74	Prefrontal cortex	Sulfasalazine inhibits SLC7A11 and reduces microglial activation-induced neuroinflammation.	Wang et al., 2023a
	IL-1 receptor antagonist	Sprague–Dawley rat, M	Intracerebral injection of LPS (1 mg/kg) at PND5	Intracerebral injection of IL-1 receptor antagonist (0.1 mg/kg) at PND5	SN	IL-1R antagonist reduces microglial activation and IL-1β, IL-6, TNF-α levels, attenuating dopamine neuron damage.	Pang et al., 2015
	TLR4 inhibitor	Sprague–Dawley rats	Injection with LPS (1 mg/kg) at PND1	i.p TLR inhibitor (3 mg/kg) before LPS injection from PND1–PND21	SN	Inhibition of TLR4/NF-κB pathway suppresses microglial activation and dopamine neuron damage.	He et al., 2020
	TNF-α inhibitor	Sprague–Dawley male rats	Injection with Poly I:C (2 mg/kg) from PND5–PND7	Oral TNF-α inhibitor (10 mg/kg) from PND30–PND67	Hippocampus	TNF-α inhibitor reduces microglial activation and TNF-α levels.	Shelton et al., 2021
Herb-derived natural products	Resveratrol	Primary rat midbrain neuron-glia at E14–E15	Incubation with LPS (10 ng/mL) for 15 min	Pretreated with Resveratrol (60 μM) for 30 min	NA	Resveratrol inhibits MAPK and NF-κB signaling, attenuating microglial activation and dopamine neurodegeneration	Zhang et al., 2010
	Thymelaea lythroides	Wistar rats, M	Injection of LPS (250 mg/kg) at PND14	i.p Thymelaea lythroides (200 mg/kg) once 6 h after LPS injection	Hippocampus	Thymelaea lythroides inhibit microglial activation and TNF-α levels	Berkiks et al., 2018
	Ganoderma lucidum triterpenoids	C57BL/6J	MS (PND1–PND21, 4 h/d)	i.p. injection of Ganoderma lucidum triterpenoids (40 mg/kg) from PND56–PND77	Hippocampus	Ganoderma lucidum triterpenoids inhibits microglial activation and decreases IL-1β, IL-6, and TNF-α levels.	Mi et al., 2022
	Curcumin	C57BL/6	Alcohol exposure (20% EtOH) from E1-PND21	i.p. injection of curcumin (100 mg/kg) from PND28–PND35	Hippocampus	Curcumin inhibits microglial activation and reduces IL-6, TNF-α, and NF-κB levels.	Cantacorps et al., 2020
	Achyranthes bidentata polypeptide fraction k (ABPPk)	Sprague–Dawley rats	Intracerebral injection of LPS (1 mg/kg, 2 μL) at PND5	Intracerebral injection of Achyranthes bidentata polypeptide fraction k (2.5 mg/kg, 2 μL) at PND5	NA	Achyranthes bidentata polypeptide fraction k activates PI3K/Akt pathway and inhibits microglial activation and NOX2, ROS expression.	Wang et al., 2021
	Paeoniflorin	ICR mice, M	Injection of LPS (0.83 mg/kg) once after the last paeoniflorin injection.	Oral gavage (20, 40, and 80 mg/kg) once daily for 1 wk.	Hippocampus	Paeoniflorin inhibits TLR4/NF-κB/NLRP3 signaling and reduces microglial activation	Cheng et al., 2021
	Gastrodin	Sprague–Dawley rats	Injection of LPS (1 mg/kg) at PND3	i.p. injection of gastrodin (200 mg/kg) at PND3	NA	Gastrodin inhibits Notch-1 signaling and reduces microglial migration	Yao et al., 2022

Akt: Protein kinase b; Bcl-2: b-cell lymphoma 2; DA: dopamine; DAT: dopamine transporter; D2R: dopamine d2 receptor; E: embryonic; F: female; i.p: intraperitoneal injection; IL-10: interleukin-10; IL-1β: interleukin-1 beta; iNOS: inducible nitric oxide synthase; LPS: lipopolysaccharide; M: male; MAPK: mitogen-activated protein kinase; mPFC: medial prefrontal cortex; MS: maternal separation; NA: not applicable; NF-κB: nuclear factor kappa-b; Notch-1: notch homolog 1, translocation-associated; NOX2: nadph oxidase 2; Nrf2: nuclear factor erythroid 2–related factor 2; PI3K: phosphatidylinositol 3-kinase; PND: postnatal day; poly (I:C): polyinosinic-polycytidylic acid; PPARγ: peroxisome proliferator-activated receptor gamma; ROS: reactive oxygen species; SLC7A11: solute carrier family 7 member 11; SN: substantia nigra; TH: tyrosine hydroxylase; TLR4: toll-like receptor 4; TNF-α: tumor necrosis factor alpha; VTA: ventral tegmental area.

reducing neurotrophic effects, thereby impairing CNS development (Squarzoni et al., 2014; Ślusarczyk et al., 2015; Chamera et al., 2020). ELS induces abnormalities in the DA system, leading to neuronal damage and synthesis impairment, transmission, reuptake, and receptor function. This increases susceptibility to neurodevelopmental and neurodegenerative disorders, such as autism, schizophrenia, ADHD, and PD (Fan et al., 2011; Perez-Palomar et al., 2023; Debs et al., 2024). While many studies suggest a link between microglial dysfunction and DA system disorders (Squarzoni et al., 2014; Kopec et al., 2018), research establishing a causal relationship between ELS, microglial dysfunction, and the DA system remains limited (Lo Iacono et al., 2018; Catale et al., 2022; Hayes et al., 2022). This review synthesizes evidence that ELS may induce DA system disorders through its influence on microglial function, with specific consequences depending on the degree of microglial dysfunction. Specifically, microglial damage can disrupt DA circuitry through reduced neurotrophic effects (e.g., IGF-1) (Tien et al., 2017) and impair DA axons extension owing to defective phagocytosis (Squarzoni et al., 2014). Blunted microglial immunoreactivity inhibits striatal DA circuit development and reduces sEPSCs frequency (Hayes et al., 2022). Conversely, inflammatory factors secreted by activated microglia— IL-1β, TNF-α, iNOS, and ROS—can damage DA neurons and inhibit DA synthesis, transmission, and reuptake (Kaizaki et al., 2013; Catale et al., 2022). Enhanced microglial phagocytosis may further inhibit DA axonal extension (Squarzoni et al., 2014). The long-term effects of microglial disruptions may result from ELS-induced epigenetic reprogramming of microglia. Additionally, ELS may exert indirect influence through multiple pathways, including astrocytic activation, the HPA axis, the gut–brain axis, and maternal immune signaling, further modulating microglial activity. Targeting microglia offers a promising strategy to mitigate ELS-induced DA system dysfunction. Future research should investigate how restoring microglial homeostasis after ELS—through cellular co-cultures, pharmacological interventions, or genetic strategies—affects DA circuits. Such studies could help elucidate causal links and underlying molecular mechanisms.

Deep single-cell RNA sequencing has revealed that microglia consist of subpopulations with distinct transcriptional and functional properties at each developmental stage (Vecchiarelli and Tremblay, 2023). This heterogeneity may complicate ELS outcomes, potentially explaining some contradictory findings. Additionally, inflammatory factors and pro-apoptotic molecules released by microglia can damage vascular endothelial cells (Haruwaka et al., 2019), with both cell types synergistically impairing CNS development (Wu et al., 2022a). However, the synergistic interactions between microglia and vascular endothelial cells in ELS-induced DA system disorders remain unclear. Furthermore, ELS reduces microglia-derived IGF-1 (Ślusarczyk et al., 2015), which is crucial for oligodendrocyte survival and myelination (Benmamar-Badel et al., 2020). Neonatal immune challenges that induce microglial inflammation can also target oligodendrocytes, impairing neuronal myelination (Yeh et al., 2021). White matter damage owing to neuronal demyelination can adversely affect DA neurons by releasing various neurotransmitters (Gregorio et al., 2024). These findings suggest that oligodendrocytes and vascular endothelial cells, in synergy with microglia, may contribute to ELS-induced DA system dysregulation.

The review highlights studies showing that MIA simultaneously activates the mesolimbic DA system while suppressing DA function in the frontal cortex. Research has shown blunted microglial immunoreactivity in the striatum (Hayes et al., 2022), contrasting with the microglial activation observed in the PFC (Edemann-Callesen et al., 2023). Microglia can act as a "brake" on neuronal activity. Striatal microglia sense signals from extracellular ATP and activate ATP/AMP/adenosine/A1 receptor (A1R)-dependent signaling, inhibiting D1 neuronal activation (Badimon et al., 2020). This raises the question of whether MIA-induced abnormal DA activation in the mesolimbic pathway is related to a diminished "brake" effect of microglia.

Current research on microglia and DA neurons under ELS conditions has not explored CX3CR1-mediated microglia-DA neuron crosstalk, leaving its role in DA system disorders unclear. ELS also inhibits TREM2 receptor expression in hippocampal microglia, reducing synaptic pruning and phagocytosis (Dayananda et al., 2023). TREM2 ligands are found on DA neurons (Hsieh et al., 2009). Additionally, CD200, a neuron-derived anti-inflammatory protein, interacts with microglial CD200R. In a mouse model overexpressing α-synuclein, $CD200^{-/-}$ mutant mice exhibit increased microglial activation and DA neuron damage (Wang et al., 2020a). Furthermore, prenatal LPS exposure inhibits CD200-CD200R signaling in the PFC (Chamera et al., 2020). Therefore, impaired TREM2 and CD200R expression may contribute to the ELS-induced abnormal pruning and phagocytosis of DA neurons. Nurr1 Knockdown results in severe DA neuron dysgenesis (Montarolo et al., 2022), and prenatal LPS exposure combined with neonatal hyperoxia decreases microglial Nurr1 expression through increased neuroinflammation (Lallier et al., 2016). Therefore, future studies should investigate whether microglial CX3CR1, TREM2, CD200R, and Nurr1 mediate ELS-induced DA system disorders.

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