



Research Article

Maternal Immune Activation as a Critical Environmental Risk Factor in Neurodevelopmental Disorders: Mechanisms and Therapeutic Implications

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Abstract

Neurodevelopmental Disorders (NDDs) represent chronic cerebral dysfunctions arising from gene-environment interactions, encompassing conditions such as Autism Spectrum Disorders (ASD) and attention-deficit/hyperactivity disorders (ADHD). Emerging evidence identifies Maternal immune activation (MIA) as a critical environmental risk factor for NDDs. Gestational infections, inflammatory responses, or immune dysregulation elevate maternal-fetal inflammatory mediators, which disrupt neurodevelopmental trajectories via placental-fetal signaling cascades. Preclinical models (rodents, non-human primates) demonstrate that MIA induces characteristic NDD phenotypes-including social deficits and cognitive impairments-through microglial hyperactivation, aberrant synaptic pruning, oxidative stress, and mitochondrial dysfunction. Concurrently, gut microbiota dysbiosis and Th17/Treg immune imbalance exacerbate neuroinflammatory processes. Novel therapeutic strategies targeting inflammatory pathways, microglial modulation, or microbial homeostasis restoration show translational promise. Future investigations must unravel MIA's molecular underpinnings and multifactorial interactions to enable early-risk stratification and precision interventions for NDDs.

Introduction

NDDs are chronic brain dysfunction syndromes arising from multifactorial genetic or acquired etiologies that impair pluripotent cerebral domains, including cognition, motor function, social adaptability, and behavioral regulation. Representative NDD subtypes encompass ASD, ADHD, intellectual disability (ID), and schizophrenia (SCZ). Large-scale twin studies estimate heritability at 0.6–0.9 for ASD and 0.76 for ADHD [1-3], with significant genetic overlap observed between ADHD and ASD. Genetic

contributions account for approximately 50% of idiopathic ID cases, escalating to ≥66% in moderate-to-severe presentations. However, NDD pathogenesis reflects dynamic interplay between polygenic susceptibility and environmental exposures, with non-genetic factors demonstrating substantial etiological weight. This is evidenced by the discordance rates in ASD and SCZ twin cohorts, underscoring environmental triggers' critical role in neurodevelopmental trajectory disruption [4].

MIA has been increasingly recognized as a critical risk factor for ASD and other neurodevelopmental disorders. MIA arises from gestational immune hyperactivation triggered by maternal infections, autoinflammatory conditions, or autoimmune diseases, encompassing but not limited to infection-induced inflammatory dysregulation [5]. Notably, MIA can be initiated by both infectious stimuli (e.g., viral/bacterial pathogens) and sterile triggers, including maternal asthma, obesity, and autoimmune disorders. Gestational immune perturbations exert enduring consequences, with MIA inducing persistent remodeling of developing neural circuits and altering fetal brain developmental trajectories [6]. When superimposed on genetic and environmental vulnerabilities, this immune dysregulation amplifies offspring risks for NDDs [7,8], including schizophrenia, bipolar disorder, ADHD, cerebral palsy, developmental delay, cognitive dysfunction, anxiety/depression, and ASD [9]. High-resolution *ex vivo* MRI and electron microscopy analyses in murine models reveal that late-gestation MIA exposure induces volumetric expansion in embryonic brain regions—specifically the striatum/caudoputamen, hippocampus, lateral septum, cingulate cortex, and cerebellum [10]. These neuroanatomical anomalies mirror structural abnormalities identified in neuroimaging studies of ASD and schizophrenia patient [11]. Furthermore, third-trimester MIA exacerbates neuroinflammation and compromises placental efficiency in prenatal rat models, as evidenced by elevated proinflammatory cytokines and impaired nutrient transport mechanisms [12].

Mechanistic and Translational Perspectives: This review systematically delineates the multi-tiered mechanisms underlying MIA-induced NDDs, encompassing: Maternal-fetal interface cytokine cascades (IL-17A/IL-6/TNF- α axis) disrupting neural progenitor cell differentiation; Microglia-driven synaptic pathology via aberrant pruning and oxidative stress-mediated damage; Gut-brain axis dysregulation coupled with Th17/Treg immune polarization amplifying neuroinflammatory cascades; Translational immunomodulatory strategies targeting IL-17A blockade, microbiota transplantation, and neuroprotective interventions.

We further evaluate the therapeutic potential of these mechanisms in reshaping developmental trajectories, establishing a conceptual framework for preemptive NDD interception during critical neurodevelopmental windows.

MIA and Neurodevelopmental Disorders

Epidemiological Evidence Linking MIA to Neurodevelopmental Disorders

The association between environmental factors, MIA, and NDDs is well-established. Epidemiological studies demonstrate significant correlations between gestational infections and elevated risks of SCZ, ASD, and epilepsy in offspring. Historical cohort analyses reveal marked increases in schizophrenia and ASD incidence

following the 1918–1919 influenza pandemic and 1964 rubella epidemic [13,14]. Second-trimester influenza infection confers a 2- to 8-fold increased schizophrenia risk [15], while prenatal exposure to *Toxoplasma gondii* [16], herpes simplex virus type 217, and urinary/respiratory infections [18–21] similarly elevates neuropsychiatric vulnerability.

Notably, the California Department of Developmental Services documented a “winter birth phenomenon,” wherein infants conceived during winter months exhibit heightened ASD susceptibility [22]. A 1990–2002 pediatric cohort study suggests this seasonal risk may correlate with increased respiratory infections in colder months [22]. A Danish nationwide study of 1.6 million children further confirmed that hospitalization-requiring maternal infections or inflammation significantly elevates offspring psychiatric risks, underscoring MIA’s pathogen-agnostic immunopathic effects.

Beyond infections, maternal autoimmune conditions (e.g., asthma, allergies), acute stress, environmental pollutants, and nutritional imbalances amplify ASD risk through immune hyperactivation [23–25]. The COVID-19 pandemic has intensified concerns regarding prenatal viral impacts, with SARS-CoV-2 infection linked to fetal growth restriction and neurodevelopmental sequelae [26]. Globalization-driven resurgent infections and autoimmune disease proliferation may synergistically fuel the NDD pandemic, necessitating urgent dissection of MIA-specific immune pathways and gene-environment interplay to inform early intervention strategies.

Experimental Animal Evidence of MIA

Mounting evidence from animal models has robustly validated neurodevelopmental abnormalities induced by MIA [27]. Experimental paradigms typically involve artificial immune system activation during gestation to assess offspring neurodevelopmental outcomes. Widely used MIA induction methods include exposure to human influenza virus, viral mimetic polyinosinic:polycytidylic acid (Poly(I:C)), bacterial endotoxin lipopolysaccharide (LPS), localized inflammatory agents (e.g., turpentine), or specific proinflammatory cytokines [7, 28]. Amodeo et al. demonstrated that gestational Poly(I:C) exposure impairs offspring learning and social interaction capabilities, inducing autism- and schizophrenia-like behavioral phenotypes. These effects correlate with persistent disruptions in glutamatergic neurotransmission, mTOR signaling, and potassium channel activity [29]. In murine models, O’Loughlin et al. observed upregulated amygdalar proinflammatory cytokine expression alongside chronic microglial activation and astrogliosis following intraperitoneal LPS administration during pregnancy [30]. Rat studies by Fortunato et al. revealed that LPS-induced MIA elevates stereotyped repetitive behaviors and reduces social engagement in offspring-phenotypes reversible through ω -3 polyunsaturated fatty acid intervention [31].

Complementing rodent studies, non-human primate (NHP) models-with closer physiological parallels to human pregnancy-are increasingly employed in MIA research [32]. Seminal work by Bauman et al. in rhesus macaques demonstrated that mid-gestation Poly(I:C) exposure exacerbates abnormal behaviors (e.g., tremors, tail claspings, self-claspings) during weaning, with adults exhibiting heightened stereotypies and impaired social reciprocity [33].

Inflammatory Mediators in MIA-Induced Neurodevelopmental Abnormalities

The developing brain exhibits heightened sensitivity to environmental signals, with MIA -driven cytokine cascades and inflammatory responses serving as pivotal disruptors of fetal neurodevelopment. Gilmore and Jarskog first proposed in 1997 that inflammatory mediators might underlie infection-associated fetal brain developmental disruptions [34], a hypothesis now substantiated by extensive epidemiological studies and experimental MIA models delineating cytokine network dysregulation as central to MIA pathophysiology.

Prenatal inflammatory exposure triggers maternal-fetal upregulation of cytokines and chemokines-including interferon-gamma (IFN- γ), IFN- β , tumor necrosis factor-alpha (TNF- α), interleukins (IL-4, IL-5, IL-6, IL-8, IL-1 α , IL-1 β , IL-17), granulocyte-macrophage colony-stimulating factor (GM-CSF), and C-reactive protein (CRP)-that induce fetal endogenous cytokine production, thereby altering cerebral ontogeny [35-37]. Maternal-fetal cytokine profiling demonstrates MIA-induced dysregulation critically contributes to ASD pathogenesis. Analysis of 60 inflammatory mediators and growth factors in mid-pregnancy maternal serum and umbilical cord blood from the Norwegian Mother, Father and Child Cohort Study (MoBa) identified TNF- α , Serpin E1, VCAM1, and IL-1 β as key predictors of neurodevelopmental trajectories and ASD diagnosis [37].

A longitudinal birth cohort study on ADHD revealed that elevated umbilical cord blood IL-6 and TNF- α levels-when integrated with polygenic risk scores-predicted increased ADHD symptom severity in 8- to 9-year-olds via structural equation modeling, implicating perinatal inflammation in ADHD pathogenesis through early neural circuit modulation [38]. Similarly, fetal exposure to IL-8 shows significant schizophrenia risk association [39]. Herein, we comprehensively review the mechanistic roles of key inflammatory mediators in MIA-induced neurodevelopmental perturbations.

Interleukin-6 (IL-6)

Dysregulated IL-6 levels critically disrupt fetal brain development, driving neurobehavioral abnormalities in MIA-exposed offspring [40] (Figure 1).

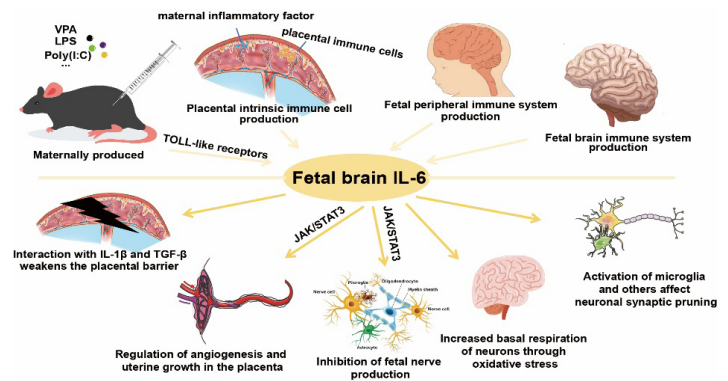


Figure 1: IL-6 in MIA.

Under physiological conditions, IL-6 remains minimally detectable in the brain, but its production escalates during pathological states. Severe peripheral or central inflammatory challenges-such as bacterial meningitis-trigger IL-6 accumulation in serum and cerebrospinal fluid (CSF) [41]. Elevated IL-6 levels are observed in the prefrontal cortex, CSF, and cerebellum of autistic children. In MIA models, maternal serum IL-6 peaks 3 hours post-challenge before returning to baseline within 24 hours [42]. Strikingly, recombinant IL-6 administration alone induces prepulse inhibition (PPI) deficits and ASD/schizophrenia-like behaviors in adult offspring [43,44]. Conversely, IL-6 antibody-treated or IL-6 knockout dams fail to transmit behavioral or transcriptional anomalies to progeny following immune challenge [40]. IL-6 has further emerged as a prognostic biomarker for neuropsychiatric disorders including depression, schizophrenia, bipolar disorder, and ASD [45]. In rodent MIA models, maternal IL-6 activates placental decidual immune cells, stimulating localized IL-6 production [46]. This placental IL-6 signaling initiates pathogenic cascades by: Downregulating placental growth hormone (GH) and insulin-like growth factor 1 (IGF-1)-critical neurodevelopmental regulators linked to ASD; Inducing cerebellum-specific Purkinje cell deficits in lobule VII; Driving neuronal loss and behavioral impairments reversible via IL-6 receptor α (IL-6R α) blockade [40]. Mechanistically, maternal IL-6 traverses the placental barrier during mid-late gestation, directly stimulating fetal IL-6 synthesis and establishing feedforward inflammatory loops [47,48]. It synergizes with IL-1 β and TGF- β to disrupt chorionic tight junctions (TJ), compromising placental integrity [49]. Placental JAK/STAT3 pathway activation-particularly in spongiotrophoblasts-upregulates proinflammatory genes while altering neurodevelopmental factor secretion [50]. IL-6/JAK2/STAT3 signaling further suppresses neurogenesis via DNMT1/TET3-mediated epigenetic remodeling, with JAK2 inhibition rescuing hippocampal neurogenesis and cognitive deficits in APP/PS mice [51]. In cortical neurons differentiated from induced

pluripotent stem cells (iPSCs), exposure to interleukin-6 (IL-6) resulted in upregulated gene expression within the chemokine signaling pathway and Toll-like receptor (TLR) signaling pathway categories. Concurrently, IL-6-induced oxidative stress elevated basal respiration, ATP production, and non-mitochondrial respiration in differentiated neurons, suggesting a marked increase in metabolic activity and energy demand [52]. Notably, Hyper-IL-6 treatment of dorsal forebrain organoids (DFOs) recapitulates MIA's early corticogenic effects [53], activating JAK/STAT cascades and inducing transcriptional shifts mirroring human neurodevelopmental perturbations [54].

Interleukin-17A

Interleukin-17A (IL-17A), a proinflammatory cytokine predominantly expressed by TH17 cells [55], plays pivotal roles in autoimmune disorders, inflammatory responses, tumorigenesis, and host defense against bacterial and fungal infections. Notably, IL-17A critically regulates neural function during cortical development and modulates neuroinflammatory processes. Genome-wide copy number variation (CNV) analysis in ASD patients identified IL-17A as one of the enriched genes [56]. Elevated IL-17A levels were observed in the serum of children with ASD and in neutrophils isolated from ASD patients [57,58], with its concentration positively correlating with autism severity [57]. These alterations were accompanied by upregulated phosphorylated nuclear factor- κ B (p-NF- κ B), IL-6, and NADPH oxidase 2 (NOX2)/reactive oxygen species (ROS) signaling. Murine studies confirmed that increased maternal IL-17A levels in MIA models induce elevated IL-17 receptor A (IL-17RA) expression in fetal brains, establishing IL-17A as a key pathogenic factor in ASD. IL-17A is primarily secreted by TH17 cells, and IL-6 serves as a critical factor for TH17 cell differentiation. Elevated IL-6 levels in the placenta or fetal brain following MIA may drive IL-17A upregulation. This upregulation further stimulates the production of multiple cytokines, including IL-6, IL-1 β , tumor necrosis factor- α (TNF- α), granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF). MIA induces aberrant expression of cortical layer-specific marker genes, including SATB2, TBR1, and CTIP2, in the cortical cells of offspring mice. However, offspring from MIA dams pretreated with IL-17A-blocking antibodies exhibit normal expression of these markers [59]. In miR-301a knockdown mice, suppression of the SOCS3/STAT3 pathway and subsequent reduction in downstream cytokines IL-6 and IL-17A significantly ameliorate poly(I:C)-induced ASD-like behaviors, including deficits in social interaction and anxiety-related behaviors [60].

IL-17A signaling influences fetal brain development through multiple mechanisms (Figure 2).

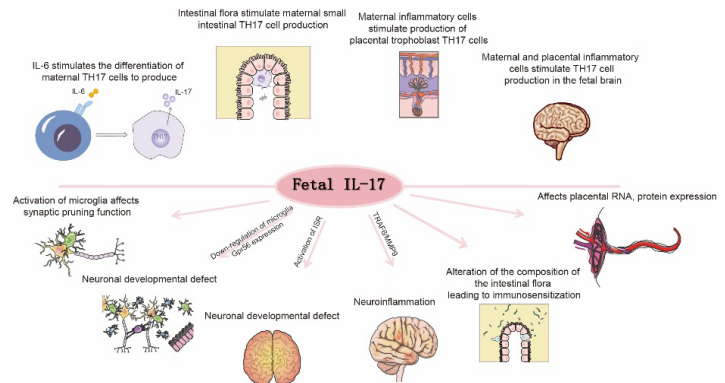


Figure 2: IL-17A in MIA.

Maternal IL-17A accumulates in the placenta and directly crosses the placental barrier to impact fetal development [61]. Concurrently, maternal IL-17A enhances IL-17 receptor (IL-17R) expression at both mRNA and protein levels in placental trophoblasts, amplifying signal transduction [62]. Elevated IL-17A does not alter placental permeability but binds to placental IL-17RA receptors and traverses the placenta [61]. Evidence indicates that MIA downregulates microglial Gpr56 expression in fetal brains in an IL-17A-dependent manner, leading to parvalbumin-positive (PV+) interneuron deficits and autism-like behavioral phenotypes in offspring [63]. Placental IL-17A signaling modulates fetal brain microglia; IL-17A administration activates microglia, enhancing their phagocytic activity without increasing cellular density [64]. Moreover, integrated stress response (ISR) activation in MIA offspring is IL-17A-dependent and necessary for the emergence of core behavioral phenotypes. Genetic knockdown of ISR components alleviates ASD-like phenotypes in male MIA offspring, revealing a novel mechanism by which IL-17A mediates MIA effects [65]. Additionally, the TRAF6/MMP9 pathway under IL-17A signaling is implicated in ASD pathophysiology. Modulation of the IL-17A/TRAF6/MMP9 axis ameliorates MIA-induced ASD-like behaviors in adulthood [66]. As a gut barrier cytokine, IL-17A is critical for maintaining intestinal microbiota homeostasis. MIA exacerbates IL-17A-driven immune responses, altering gut microbial composition and inducing immune sensitization in offspring, thereby increasing susceptibility to bacterial infection-triggered intestinal inflammation [67].

Interleukin-1 β (IL-1 β)

Interleukin-1 β (IL-1 β) is one of the key cytokines elevated in ASD [68]. In MIA models mimicking viral infection, fetal brain IL-1 β levels peaked 24 hours post-injection and continued to rise, exhibiting the highest concentration among cytokines analyzed [69]. Offspring of LPS-exposed MIA dams also showed increased

IL-1 β mRNA levels in fetal brains [70]. Multiple studies confirm that viral mimetics significantly elevate fetal brain IL-1 β expression for at least 24 hours post-MIA induction [69]. The association between ASD pathogenesis and IL-1 signaling, including its receptor family, has been experimentally validated [71], with IL-1 β gene polymorphisms being more prevalent in children with ASD [72,73]. Disrupted IL-1 β signaling during early development leads to synaptic homeostasis dysregulation and ASD-like behavioral deficits [73], as neuronal function critically depends on tightly regulated IL-1 β levels [74]. IL-1 β likely mediates MIA effects through microglial modulation: IL-1 receptor type 1 (IL-1R1) deficiency reduces microglial synaptic phagocytosis, while IL-1R1 antagonism in wild-type microglia similarly impairs synaptic engulfment capacity [73]. Furthermore, IL-1 β selectively enhances downstream mTOR pathway activity, influencing synaptic pruning and phagocytosis. Dysregulated IL-1 β expression is implicated in the etiology of multiple neurodevelopmental and neuropsychiatric disorders [73]. Maternal inflammation during pregnancy can indirectly damage placental integrity via IL-1 signaling, resulting in fetal mortality, abnormal brain development, or offspring neuropathology. Notably, IL-1 receptor antagonist administration effectively rescues maternal inflammation-induced placental and neurodevelopmental defects [12].

TNF- α and IFNs

In MIA models, male offspring of dams exhibit anxiety-like and obsessive-compulsive behavioral deficits, which correlate with reduced hypothalamic concentrations of granulocyte colony-stimulating factor (G-CSF), interleukin-4 (IL-4), interleukin-7 (IL-7), interferon-gamma (IFN- γ), and tumor necrosis factor-alpha (TNF α) [75]. Among these cytokines, TNF- α —primarily released by macrophages and microglia—modulates brain development and function [76,77]. Late-gestation immune challenges specifically activate IL-10 and TNF- α responses in fetal brains, which are linked to increased postnatal apoptosis [78]. Furthermore, offspring-derived TNF- α may impair fetal development by suppressing MAP2⁺ dendritic growth. In a human induced pluripotent stem cell (hiPSC)-derived neuron-macrophage co-culture system, MAP2⁺ dendritic growth was inhibited by TNF- α and IL-1 α secreted by GM-CSF-primed macrophages (GM-CSFM Φ), with this suppression being more pronounced in GM-CSFM Φ from ASD individuals compared to typically developing (TD) controls [79]. Inflammation also induces microglial activation in the medial prefrontal cortex (mPFC) of offspring mice, triggering proinflammatory cytokines such as IL-1 α and TNF- α . This leads to dendritic shortening, reduced branching, and subsequent social avoidance behaviors [80,81].

In murine and zebrafish models, type I interferons (IFN-I) promote microglial phagocytosis of neurons during cortical developmental remodeling, thereby limiting the accumulation of

DNA-damaged neurons [82]. Within MIA mechanisms affecting fetal brain development, IFN- γ may regulate synaptic refinement. This immunomodulatory cytokine induces prolonged synaptic modifications to modulate synaptic activity while disrupting glutamate receptor clustering on dendrites [83]. Cortical neurons differentiated from iPSCs and exposed to IFN- γ during differentiation exhibit aberrant neurite outgrowth and altered dendritic spine density [52].

Given the association between MIA and diverse neurodevelopmental disorders, developing interventions targeting inflammatory mediators is critical. For instance, blocking specific cytokines (e.g., IL-17A) or their signaling pathways may effectively mitigate MIA-induced adverse effects on fetal neurodevelopment.

MIA-Associated Cellular Mechanisms in Neurodevelopmental Abnormalities

Peripheral Immune Cells

Aberrant T cell activation is closely linked to neurodevelopmental disorders. CD4⁺ T cell dysregulation has been observed in children with ASD, characterized by an elevated proportion of Th17 cells and reduced regulatory T cells (Tregs) [84,85]. The Th17/Treg ratio exhibits a significant positive correlation with ASD severity, while Treg abundance inversely correlates with symptom severity [86].

Using MIA animal models, Choi et al. demonstrated that maternal CD4⁺ T cells expressing ROR γ t are essential for the emergence of ASD-like phenotypes in offspring. In poly(I:C)-induced MIA offspring, CD4⁺ T cells exhibit enhanced differentiation into Th17 cells upon stimulation [87–89], constitutive upregulation of Toll-like receptor (TLR) expression [89], and systemic Treg deficiencies. Elevated CD4⁺ T cell reactivity in the spleen and mesenteric lymph nodes further reflects compromised immune homeostasis in MIA offspring [90]. Bioinformatic and experimental analyses revealed that activation of the PI3K/Akt/NF- κ B pathway in offspring upregulates STAT3 signaling, driving Treg/Th17 imbalance [91]. Similarly, in MIA models induced by *Toxoplasma gondii* infection, no significant differences in T or B cell percentages were observed in offspring at 2 or 4 weeks of age. However, granulocyte counts nearly doubled by 4 weeks, and TH1/TH17 subsets expanded dramatically in T cells by 10–12 weeks, accompanied by declining Treg and TH2 populations. This T cell dysregulation exhibited time-dependent exacerbation [92], representing a major contributor to neurodevelopmental impairments. Intravenous administration of purified Tregs to MIA offspring ameliorates Th1/Th17 skewing [93] and reverses behavioral deficits. Notably, Tregs isolated from MIA dams can remodel inflammatory microenvironments in offspring brains [92]. Parasite-specific T lymphocytes release high interferon-gamma (IFN- γ) levels, promoting Th1 effector differentiation and

macrophage activation-critical for antimicrobial functions such as nitric oxide release [94].

Lipopolysaccharide (LPS), a widely used MIA inducer, paradoxically increases natural regulatory CD4⁺Foxp3⁺ T cell numbers and proportions in offspring by weeks 8–10. Gene Ontology (GO) analysis identified upregulation of 18 proteins in LPS-treated CD4⁺ T cells, 13 of which are metabolism-associated [95]. LPS-induced MIA also shifts offspring immune development toward Th1-biased responses, disrupting Th1/Th2 balance. Additionally, offspring T cells display impaired IL-10 secretion in vitro, indicating MIA-induced dysregulation of immunomodulatory cytokine production [96]. In SARS-CoV-2-associated MIA offspring, CD14⁺ monocytes exhibit upregulated interferon-stimulated gene (ISG) expression, downregulated IFNAR2, and elevated TLR transcripts (TLR2, TLR4, TLR5) alongside increased FOS and reduced NF-κB inhibitor levels. These changes likely reflect prenatal IFN exposure. Fetal bone marrow CD14⁺ monocytes also show reduced antigen-presenting capacity and transcriptional signatures of B cell dysfunction [97].

Beyond offspring alterations, maternal T cells critically mediate intergenerational effects. Maternal antibodies and immune cells can cross the placenta to influence fetal brain development. Post-poly(I:C) administration, MIA dams exhibit pronounced M1 macrophage polarization (placenta, spleen, peritoneum) with concomitant M2 reduction. Macrophages are essential for MIA-induced placental maldevelopment and inflammation. Depleting maternal macrophages via chlorophosphate liposomes (CL) rescues anxiety-like phenotypes and autism-associated behaviors in adult offspring [98]. Helminth-derived Sjp90α protein induces Treg production of IL-10, modulating macrophage activity [99]. MIA rapidly elevates maternal plasma IL-17A levels within 12–24 hours post-poly(I:C) injection at E12.5. Pre-existing Th17 cells-not de novo differentiated populations-constitute the primary IL-17A source in inflamed pregnant mice [100].

Microglia

Microglia, a critical component of the central nervous system (CNS) glial population, play pivotal roles in CNS development and homeostasis maintenance [101]. These cells sense neuronal activity and regulate neurodevelopment through the release of immunomodulatory factors, including phagocytosis of neural progenitor cells, guidance of dopaminergic axon extension, neuronal positioning [102], structural integrity maintenance, and selective synaptic pruning [103–105]. Microglia can polarize into M1 or M2 phenotypes [106]. The M1 phenotype produces pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-1β) and chemokines, exerting pathogen clearance and tissue repair functions, yet excessive inflammatory mediator release may impair neuronal function. Conversely, the M2 phenotype secretes anti-inflammatory factors (e.g., IL-10, TGF-β) to promote tissue repair and neuroprotection.

Microglial priming-a major consequence of MIA-serves as a key mechanism underlying age-dependent neuronal dysfunction and behavioral phenotypes in offspring (Figure 3).

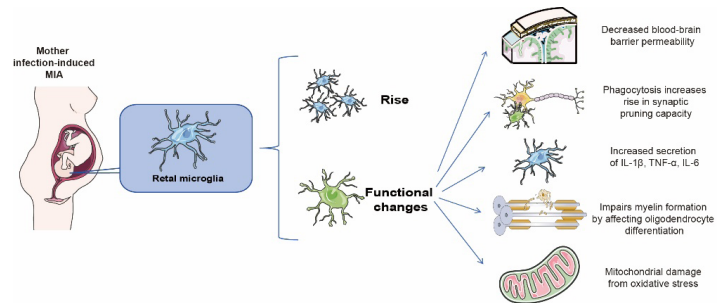


Figure 3: Microglia in MIA.

Distinct MIA induction methods differentially alter microglial phenotypes in postnatal and adult offspring brains [107]. For instance, prenatal valproic acid (VPA) exposure increases microglial soma size, while prenatal LPS exposure enhances hippocampal microglial activation in MIA offspring [108]. MIA also induces microglial hyperplasia in brain regions like the hippocampus (HPC). Although MIA does not alter microglial morphology, its timing may subtly influence postnatal microglial differentiation [109]. Activated microglia in MIA exhibit functional alterations, including upregulated inflammatory mediator gene expression, enhanced proliferation, phagocytic activity, and release of cytotoxic cytokines, chemokines, and reactive oxygen species (ROS) [110,111], collectively disrupting fetal brain development [10].

During development, microglia regulate neural progenitor cell (NPC) pool size by stimulating NPC proliferation [112] and subsequently phagocytosing excess NPCs [113]. MIA disrupts these microglia-mediated neurodevelopmental processes [102,114,115]. CX3CR1 deficiency impairs microglial signaling and function by altering developmental trajectories [116]. LPS- or poly(I:C)-induced MIA perturbs microglia-neuron communication in young male offspring via CX3CL1-CX3CR1 and/or CD200-CD200R signaling dysregulation, contributing to neurodevelopmental deficits [117]. LPS-MIA offspring show reduced CX3CR1 mRNA expression at postnatal day 15 [118]. Beyond providing neurotrophic support (e.g., insulin-like growth factor-1) [119,120], microglia dynamically remodel synapses through phagocytosis and trophocytosis [103], modulating synaptic plasticity and strength via activity-dependent interactions [121]. MIA exacerbates microglial synaptic pruning and phagocytosis [10], with dysfunctional phagocytosis implicated in ASD and schizophrenia (SCZ). Excessive NPC phagocytosis and defective synaptic pruning disrupt neuronal connectivity and brain circuitry [122]. Altered microglial homeostasis impedes NPC self-renewal/differentiation, predisposing to autism-like behaviors [123]. Microglia may

regulate MIA-induced interneuron deficits via G protein-coupled receptor 56 (GPR56) [63]. Aberrant microglial synaptic elimination and autophagy underlie MIA-associated circuit phenotypes [124]; mTOR inhibitor rapamycin rescues dendritic pruning defects and ASD-like behaviors in *Tsc2*^{+/-} mice [125], while activating microglial autophagy ameliorates SCZ-related abnormalities in MIA offspring [126]. Activated microglia release excess ROS [111], damaging mitochondria. Microglia immune receptors can specifically recognize mitochondrial components—such as mitochondrial DNA, transcription factor A (TFAM), and cardiolipin—released during mitochondrial dysfunction. This recognition activates pro-inflammatory processes and triggers mitochondrion-dependent inflammation [127], subsequently inducing intracellular cascades that regulate mitochondrial metabolism and function [128]. Microglia can help restore blood-brain barrier (BBB) permeability by limiting the penetration of peripheral factors into the CNS parenchyma. On the other hand, activated microglia increase BBB permeability and vascular leakage through the release of cytokines or reactive oxygen species, adversely affecting BBB integrity [129,130]. Chronic MIA-induced inflammation promotes microglial phagocytosis of astrocytic end-feet, further compromising the BBB [131].

Contrary to the prevailing view of microglial hyperactivation post-MIA, Akira Sawa et al propose that prenatal stress induces long-term microglial hyporesponsiveness. In MIA offspring, microglia exhibit sustained immune hypoactivation across development, accompanied by chromatin remodeling, altered transcription factor occupancy, and dysregulated gene expression—factors increasing schizophrenia risk. These “primed” microglia underlie ventral striatal circuit dysfunction, which prenatal microglial replacement can rescue alongside IL-1 β , TNF α , and IL-6 normalization [132]. MIA-induced microglial alterations represent a pathophysiological bridge linking maternal inflammation to neurodevelopmental disorder (NDD) risk, positioning microglia as novel therapeutic targets. Future research should dissect interactions among diverse cell types (T cells, microglia, astrocytes, neural stem cells) in MIA mechanisms and their collective impact on neurodevelopment.

Potential Mechanism of MIA-Induced Neurodevelopmental Disorders

Gut Microbiota Dysbiosis

The gut microbiota serves as a critical modulator of core symptoms in various neurological disorders [133], exerting profound effects on the central nervous system (CNS). The gut-brain axis—a bidirectional communication network involving neurons, hormones, immune cells, and microbial metabolites—mediates intimate crosstalk between the gut and brain [134,135]. Through this axis, gut microbes regulate host behaviors associated with neurodevelopmental dysfunction [136]. MIA compromises intestinal integrity. Offspring from poly(I:C)-induced MIA dams

exhibit reduced expression of zonula occludens-1 (ZO-1), a scaffold protein critical for tight junction (TJ) stabilization, in adult small and large intestines. *Bacteroides fragilis* supplementation restores intestinal permeability and upregulates genes governing gut barrier integrity in MIA offspring [137], while also promoting stem cell regeneration and enhancing mucus secretion [138]. MIA alters maternal gut microbiota composition and function, inducing dysbiosis that may impact maternal-fetal health through multiple pathways. Prenatal valproic acid (VPA) exposure induces ASD-like behaviors in offspring [139], accompanied by gut microbial compositional shifts. *Lactobacillus reuteri* treatment rescues social deficits in ASD mice via vagus nerve-dependent mechanisms, restoring social interaction-induced synaptic plasticity in the ventral tegmental area [135].

Elevated IL-17A levels during MIA are influenced by maternal gut microbiota. The presence of segmented filamentous bacteria (SFB) in the maternal microbiome drives increased maternal serum IL-17A. In SFB-deficient dams, even under immune challenge, IL-17A remains unchanged, and offspring behavioral abnormalities are absent [140]. Preemptive eradication of vancomycin-sensitive SFB prior to MIA induction prevents offspring behavioral deficits [140]. Accumulating evidence highlights the maternal and offspring microbiomes as key regulators of microglial development, homeostasis, and MIA-associated behavioral outcomes. Adult germ-free mice or those with microbiota complexity limitations exhibit global microglial defects and impaired innate immune responses [141]. Prenatally, maternal *Lactobacillus murinus* deficiency disrupts embryonic microglial transcriptomes, alters brain microglial colonization (e.g., increased density and hyper-ramification), and elevates chromatin accessibility [142,143]. Microbiota-targeted interventions in MIA offspring partially ameliorate gut alterations, stereotyped behaviors, anxiety-like phenotypes, and sensorimotor gating deficits [144].

While the gut microbiome modulates neurological outcomes via the microbiota-gut-brain axis, mechanisms underlying microbial rescue of neuronal dysfunction remain incompletely understood. Clinical interventions targeting gut microbiota to ameliorate neurobehavioral disorders represent a promising frontier.

Alterations in Synaptogenesis and Pruning

Synaptogenesis and synaptic pruning are critical processes during brain development, governing the formation of new synaptic connections and the refinement of neuronal networks. Impairments in synaptic structure and function are central to neurodevelopmental disorders such as ASD and attention-deficit/hyperactivity disorder (ADHD).

MIA disrupts synaptic development, maturation, and pruning through multiple pathways, including inflammatory cytokine-mediated interference with signaling cascades and microglial

activation. Maternal inflammatory signals traverse the placental barrier, perturbing neurodevelopmental pathways in offspring. For instance, IL-6 inhibits neurogenesis via JAK2/STAT3 signaling⁵¹, while offspring-derived TNF- α suppresses MAP2+ dendritic growth, impairing synaptic development⁷⁹. Poly(I:C)-induced MIA significantly reduces expression of presynaptic (e.g., synaptophysin) and postsynaptic (e.g., PSD95) proteins in offspring hippocampi, compromising basal synaptic transmission (field potential [FV] and excitatory postsynaptic potential [EPSP]) and plasticity (paired-pulse facilitation [PPF] and long-term potentiation [LTP]) [145]. Additionally, MIA downregulates Shank3 expression, disrupting neuronal connectivity, synaptogenesis, and dendritic spine maturation.

Beyond synaptogenesis, aberrant synaptic pruning profoundly impacts neurodevelopment¹⁴⁶. In male offspring of LPS-induced MIA dams, dendritic density in dentate gyrus granule cells remains elevated during peak pruning stages (postnatal day 15) [118], a phenotype linked to persistent network hyperconnectivity and ASD-like behaviors¹⁴⁷. IL-17A signaling enhances microglial phagocytic activity in fetal brains⁶⁴, while poly(I:C)-exposed MIA offspring exhibit upregulated hippocampal IL-1 β expression in adulthood [118]. IL-1 β selectively amplifies mTOR pathway activity, further dysregulating synaptic pruning and phagocytosis [73].

MIA disrupts fetal synaptogenesis and pruning primarily via microglial activation. Targeted interventions to modulate these pathways may mitigate long-term neurodevelopmental risks in offspring.

Other Mechanisms

MIA induces neurodevelopmental disorders through multiple mechanisms, including interference with critical signaling pathways, disruption of the blood-brain barrier (BBB), placental dysfunction, and activation of the hypothalamic-pituitary-adrenal (HPA) axis. The crosstalk between inflammatory and neurodevelopmental signaling pathways constitutes a complex regulatory network. MIA disrupts fetal neurodevelopmental processes by impairing key pathways such as Notch [148], NF- κ B⁹¹, and JAK/STAT [149], which modulate the expression of neurodevelopmental genes (e.g., BDNF, GSK-3 β , and components of Notch/Wnt pathways). These perturbations inhibit neural stem cell proliferation/differentiation and neuronal migration/synaptogenesis, ultimately altering cortical circuit architecture and function [150].

Notably, MIA increases BBB permeability, compromising its structural integrity and allowing immune cells, cytokines, and neurotoxic molecules to infiltrate the brain parenchyma, thereby amplifying neuroinflammation. The placenta serves as a physical and immunological interface during MIA. Animal studies

demonstrate that maternal inflammation transmits to the fetus via both direct (e.g., altered mRNA expression of placental amino acid transporters like leucine transporters) and indirect mechanisms, disrupting fetal brain growth trajectories [151].

Mechanistically, MIA dysregulates the neuroendocrine system through HPA axis hyperactivation—a hallmark of ADHD pathophysiology. Chronic stress-induced HPA dysfunction elevates corticotropin and cortisol levels, which promote catabolic states via lipolysis/gluconeogenesis. Inhibit neuronal growth and dendritic arborization; Impair synaptic plasticity and neurocognitive functions. This endocrine-metabolic cascade exacerbates both ADHD symptoms and metabolic disturbances³⁸.

Summary and Perspectives

Accumulating evidence underscores the pivotal role of MIA in neurodevelopmental disorders (NDDs). However, MIA lacks standardized diagnostic criteria and is broadly defined as prenatal exposure to infection, aberrant inflammation, or immune dysregulation. The interplay of environmental, genetic, and immunological factors complicates precise mechanistic delineation. While animal models and epidemiological studies have established cytokine-driven immune responses as central to MIA-induced neuropathology, the developmental mechanisms underlying human MIA-associated NDD phenotypes remain incompletely resolved.

Successful MIA modeling holds translational potential for developing therapeutic or preventive strategies against NDDs. Leveraging diverse MIA models enables dynamic tracking of disease progression and symptom-specific biomarker quantification, facilitating early identification of high-risk populations. A deeper understanding of MIA mechanisms—particularly immune-neuroinflammatory crosstalk—will inform targeted interventions. Strategies modulating immune pathways (e.g., cytokine blockade, microglial reprogramming) represent promising therapeutic avenues, warranting validation in preclinical models. Future research should prioritize: **Mechanistic Precision:** Deciphering synergistic interactions between genetic susceptibility, environmental triggers, and immune dysregulation. **Biomarker Discovery:** Identifying quantifiable immune or neurodevelopmental signatures for early diagnosis. **Therapeutic Innovation:** Developing immunomodulatory agents with blood-brain barrier permeability and temporal specificity.

Translational Integration: Bridging preclinical findings to human cohorts through longitudinal multi-omics approaches.

By addressing these challenges, MIA research may catalyze paradigm shifts in NDD prevention and treatment, ultimately mitigating the global burden of neurodevelopmental impairments.

Conflict of interest

The authors declare no competing interests.

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