

Maternal Immune Activation and Neurodevelopmental Disorders: Integrating Molecular, Cellular and Systems Mechanisms

Qi Yong^{1,*}, Chao Zhao^{1,*}, Lu Xia², Tengfei Zhu^{3,4}, Kun Xia³

¹The Seventh Affiliated Hospital Hengyang Medical School, University of South China (Hunan Provincial Veterans Administration Hospital), Changsha, Hunan, 410000, People's Republic of China; ²Hunan Key Laboratory of Medical Genetics, MOE Key Laboratory of Pediatric Rare Diseases, School of Life Sciences, Central South University, Changsha, Hunan, 410083, People's Republic of China; ³MOE Key Laboratory of Pediatric Rare Diseases, University of South China, Hengyang, Hunan, 421001, People's Republic of China; ⁴Department of Critical Care Medicine, Shenzhen Third People's Hospital, Shenzhen, Guangdong, 518112, People's Republic of China

*These authors contributed equally to this work

Correspondence: Kun Xia; Tengfei Zhu, MOE Key Laboratory of Pediatric Rare Diseases, University of South China, Hengyang, Hunan, 421001, People's Republic of China, Email xiakun@sklmg.edu.cn; zhutengfei0793@hotmail.com

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.

Keywords: MIA, NDD, Microglia

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

Neurodevelopmental disorders have diverse etiology and complex pathogenesis. Genetic and environmental factors are involved in the occurrence of neurodevelopmental disorders, and individual genetic susceptibility can be caused by gene mutation, chromosome abnormality and copy number variation. Hundreds of genes have been identified to be associated with neurodevelopmental disorders, including *FMRI*,⁵ *UBE3A*,⁶ *CACNA1C*,⁷ *SHANK3*,⁸ etc. Abnormal brain structure and development in NDDs patients are also considered to be one of the causes, such as abnormal development

of frontal lobe and cingulate cortex in ASD patients.⁹ The abnormal development of the frontal lobe^{10,11} and the asymmetry of the head end of the bilateral caudate nucleus¹² in ADHD patients are also important mechanisms for the pathogenesis of NDDs. The increased levels of inflammatory factors in the body can affect the normal growth and function of brain nerve cells and cause neurodevelopmental abnormalities. Studies have shown that there is neuroinflammation in the brain tissue of ASD patients, and the excessive activation of microglia plays a role in releasing pro-inflammatory factors, leading to nerve cell damage.¹³

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.¹⁴ Notably, MIA can be initiated by both infectious stimuli (eg, 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.¹⁵ When superimposed on genetic and environmental vulnerabilities, this immune dysregulation amplifies offspring risks for NDDs,^{16,17} including schizophrenia, bipolar disorder, ADHD, cerebral palsy, developmental delay, cognitive dysfunction, anxiety/depression, and ASD.¹⁸ 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.¹⁹ These neuroanatomical anomalies mirror structural abnormalities identified in neuroimaging studies of ASD and schizophrenia patient.²⁰ 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.²¹

Although existing research has confirmed that MIA is a key environmental risk factor for NDDs, several limitations remain. Firstly, the diverse triggers of MIA and the lack of a standardized definition make it difficult to directly compare and integrate results across studies. Secondly, the specific molecular and cellular mechanisms through which MIA affects neurodevelopment—particularly the causal relationships and synergistic effects between inflammatory cytokine transmission across the placenta, microglial dysfunction, and gut microbiota dysbiosis—have not been fully elucidated. Additionally, how interactions between genetic background and MIA exposure contribute to the phenotypic heterogeneity of NDDs requires further in-depth investigation.

This review aims to systematically analyze the multi-level mechanisms by which MIA contributes to NDDs, with a focus on key aspects such as the disruption of neural progenitor cell differentiation by inflammatory cytokine cascades at the maternal-fetal interface (eg, the IL-17A/IL-6/TNF- α axis), microglia-mediated synaptic pruning deficits and oxidative stress damage, as well as the amplification of neuroinflammation through gut-brain axis imbalances and Th17/Treg immune deviations. Furthermore, the translational prospects of targeting immune regulation (eg, IL-17A antagonists, microbiota transplantation) and neuroprotective strategies are discussed.

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.^{22,23} Second-trimester influenza infection confers a 2- to 8-fold increased schizophrenia risk,²⁴ while prenatal exposure to *Toxoplasma gondii*,²⁵ herpes simplex virus type 2,²⁶ and urinary/respiratory infections^{27–30} 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.³¹ A 1990–2002 pediatric cohort study suggests this seasonal risk may correlate with increased respiratory infections in colder months.³¹ 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. The

Kaiser Permanente Northern California Birth Cohort study also found that fever or infections (including viral and bacterial) during the second trimester (4–6 months of gestation) were no significantly increased risk of ASD, especially fever lasting ≥ 1 week.³² Influenza vaccination during pregnancy can reduce the risk of ASD associated with MIA.³³ Male offspring with high levels of HSV-2 IgG antibodies in maternal plasma during the second trimester have also been found to have an increased risk of autism spectrum disorders.^{34–37} The COVID-19 pandemic has intensified concerns regarding prenatal viral impacts, with SARS-CoV-2 infection linked to fetal growth restriction and neurodevelopmental sequelae.³⁸ Maternal COVID-19 infection may be associated with fetal neurodysplasia.³⁹ Analysis of 460 infants whose mothers were infected with COVID 19 (COVID+) from January 2020 to September 2021 found that reduced levels of certain immune molecules in newborns born to COVID+ mothers may increase the risk of NDDs.⁴⁰ 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. Beyond infections, maternal autoimmune conditions (eg, asthma, allergies), acute stress, environmental pollutants, and nutritional imbalances amplify ASD risk through immune hyperactivation.^{35–37} For example, a meta-analysis of the effects of maternal diabetes on neurodevelopmental disorders in offspring showed that maternal diabetes increased the risk of neurodevelopmental disorders in offspring by 28%, especially maternal pregestational diabetes was more strongly associated and may lead to impaired neurodevelopmental capacity.⁴¹ Antibiotic use during pregnancy may alter the maternal microbiome, affecting the colonization of microbes in the fetal gastrointestinal system, and maternal and early antibiotic use has been confirmed to be associated with a higher risk of ASD and ADHD.⁴²

In conclusion, the epidemiological evidence consistently demonstrates that the risk for ASD is substantially heightened specifically when maternal immune activation results from severe infectious or inflammatory insults. It is not just any case of infection, but rather the intensity and duration of the immune response that determines neurodevelopmental outcomes. This crucial distinction underscores the need for particular clinical attention to pregnancies experiencing significant inflammatory events, while reassuring that routine infections do not appear to carry the same level of risk.

Experimental Animal Evidence of MIA

Mounting evidence from animal models has robustly validated neurodevelopmental abnormalities induced by MIA.⁴³ 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 (eg, turpentine), or specific proinflammatory cytokines.^{16,44} 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.⁴⁵ 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.⁴⁶ 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.⁴⁷

Complementing rodent studies, non-human primate (NHP) models—with closer physiological parallels to human pregnancy—are increasingly employed in MIA research.⁴⁸ Seminal work by Bauman et al in rhesus macaques demonstrated that mid-gestation Poly(I:C) exposure exacerbates abnormal behaviors (eg, tremors, tail claspings, self-claspings) during weaning, with adults exhibiting heightened stereotypies and impaired social reciprocity.⁴⁹

Abnormal Levels of Cytokines in Neurodevelopmental Disorders 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,⁵⁰

a hypothesis now substantiated by extensive epidemiological studies and experimental MIA models delineating cytokine network dysregulation as central to MIA pathophysiology. Herein, we comprehensively review the mechanistic roles of key inflammatory mediators in MIA-induced neurodevelopmental perturbations.

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.^{51–53} Maternal-fetal cytokine profiling demonstrates MIA-induced dysregulation critically contributes to ASD pathogenesis. Clinical detection of interleukin-6 (IL-6), interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ) in blood, cerebrospinal fluid or brain tissue of patients with autism spectrum disorder and other diseases. Increased levels of Interleukin-17 (IL-17),^{54,55} Interleukin-10 (IL-10) and transforming growth factor- β (TGF- β) may be reduced or relatively insufficient.^{56,57}

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.⁵³ 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.⁵⁸ Similarly, fetal exposure to IL-8 shows significant schizophrenia risk association.⁵⁹

IL-6 has been shown that its level is increased in ASD subjects and autistic mice and its concentration may be positively correlated with the severity of symptoms in ASD patients.⁶⁰ IL-6 not only inhibits neurogenesis in neural stem cells (NSCs) via the JAK2/STAT3 pathway but also promotes Th17 cell differentiation, leading to IL-17 production.⁶¹ The concentration of IL-17 can be detected in the serum, cerebrospinal fluid or cerebral cortex of D children, which is significantly higher than that of the healthy control group.^{61,62} The increase of IL-17A in ASD patients with gastrointestinal symptoms is more significant.⁶² Studies have found that the expression of TNF- α in the amygdala and dorsolateral prefrontal cortex of ASD children is increased. Serum levels of proinflammatory factors such as TNF- α are also significantly elevated in individuals with ASD compared to healthy controls,⁶³ The risk of ADHD is increased in children of mothers with inflammation and immune system disorders.⁶⁴ Gustafsson's team was the first to link inflammation to defects in brain development/behavior. It is suggested that the imbalance of maternal serum IL-6, TNF- α and MCP-1 levels may be closely related to the risk of ADHD.⁶⁵

Interleukin-6 (IL-6)

Dysregulated IL-6 levels critically disrupt fetal brain development, driving neurobehavioral abnormalities in MIA-exposed offspring⁶⁶ (Figure 1). 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).⁶⁷ 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.⁶⁸ Strikingly, recombinant IL-6 administration alone induces prepulse inhibition (PPI) deficits and ASD/schizophrenia-like behaviors in adult offspring.^{69,70} Conversely, IL-6 antibody-treated or IL-6 knockout dams fail to transmit behavioral or transcriptional anomalies to progeny following immune challenge.⁶⁶ IL-6 has further emerged as a prognostic biomarker for neuropsychiatric disorders including depression, schizophrenia, bipolar disorder, and ASD.⁷¹ In rodent MIA models, maternal IL-6 activates placental decidual immune cells, stimulating localized IL-6 production.⁷² 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.⁶⁶ Mechanistically, maternal IL-6 traverses the placental barrier during mid-late gestation, directly stimulating fetal IL-6 synthesis and establishing feedforward inflammatory loops.^{73,74} It synergizes with IL-1 β and TGF- β to disrupt chorionic tight junctions (TJ), compromising placental integrity.⁷⁵ Placental JAK/STAT3 pathway activation—particularly in spongiotrophoblasts—upregulates

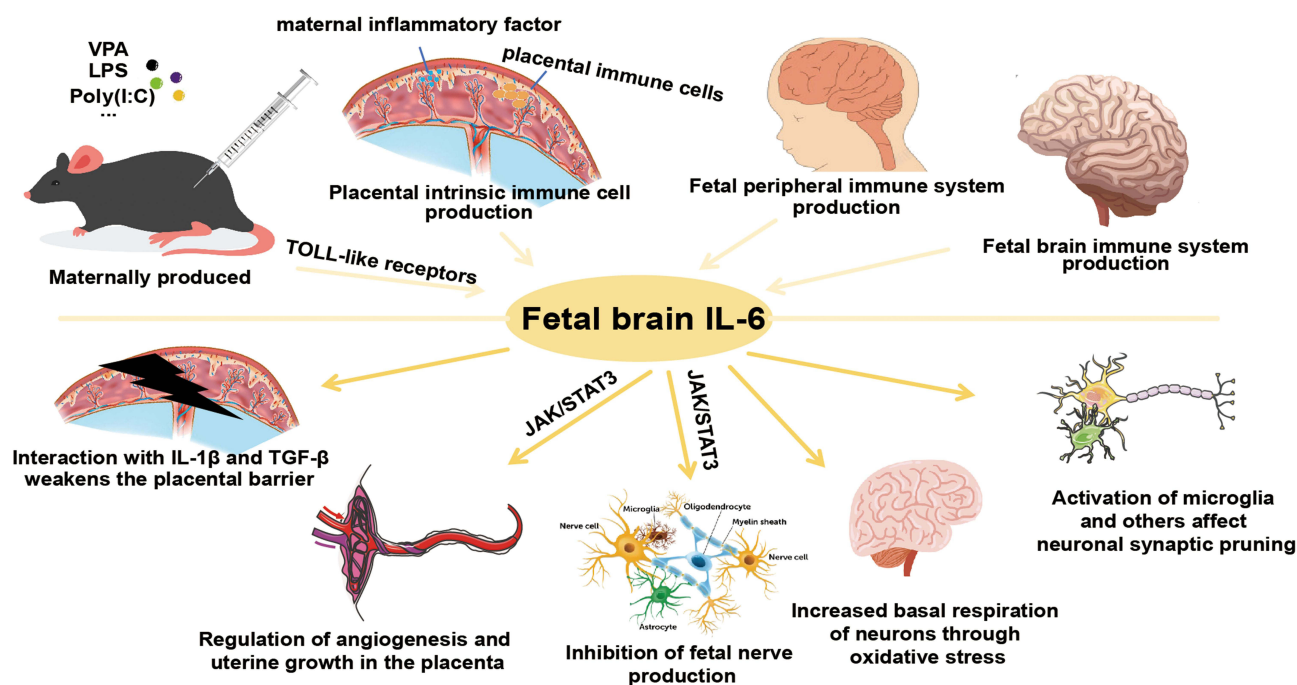


Figure 1 Mechanisms of IL-6-Mediated Disruption of Fetal Neurodevelopment through Placental and Neural Pathways. The schematic illustrates the cascade by which maternally derived IL-6 impairs fetal brain development via placental and direct neural mechanisms. Upper panel: Production and placental transfer of maternal IL-6. Maternal immune activation triggers release of inflammatory factors, which activate placental immune cells leading to IL-6 production. This maternal IL-6 either crosses the placental barrier directly or stimulates placental intrinsic immune cells to generate additional IL-6, which then enters fetal circulation. Lower panel: Multilevel impacts on fetal neurodevelopment. In the fetal brain, IL-6 synergizes with IL-1 β and TGF- β to disrupt placental barrier integrity; activates JAK/STAT3 signaling to regulate angiogenesis and uterine growth; directly inhibits fetal neuronal production; increases neuronal basal respiration via oxidative stress; and activates microglia and other immune cells, ultimately affecting neuronal synaptic pruning. These coordinated pathways collectively contribute to neurodevelopmental abnormalities associated with maternal immune activation.

proinflammatory genes while altering neurodevelopmental factor secretion.⁷⁶ 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.⁷⁷ 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.⁷⁸ Notably, Hyper-IL-6 treatment of dorsal forebrain organoids (DFOs) recapitulates MIA's early corticogenic effects,⁷⁹ activating JAK/STAT cascades and inducing transcriptional shifts mirroring human neurodevelopmental perturbations.⁸⁰

Interleukin-17A

Interleukin-17A (IL-17A), a proinflammatory cytokine predominantly expressed by TH17 cells,⁸¹ 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.⁸² Elevated IL-17A levels were observed in the serum of children with ASD and in neutrophils isolated from ASD patients,^{83,84} with its concentration positively correlating with autism severity.⁸³ 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.⁸⁵ 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.⁸⁶

IL-17A signaling influences fetal brain development through multiple mechanisms (Figure 2). Maternal IL-17A accumulates in the placenta and directly crosses the placental barrier to impact fetal development.⁸⁷ Concurrently, maternal IL-17A enhances IL-17 receptor (IL-17R) expression at both mRNA and protein levels in placental trophoblasts, amplifying signal transduction.⁸⁸ Elevated IL-17A does not alter placental permeability but binds to placental IL-17RA receptors and traverses the placenta.⁸⁷ 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.⁸⁹ Placental IL-17A signaling modulates fetal brain microglia; IL-17A administration activates microglia, enhancing their phagocytic activity without increasing cellular density.⁹⁰ 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.⁹¹ 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.⁹² 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.⁹³

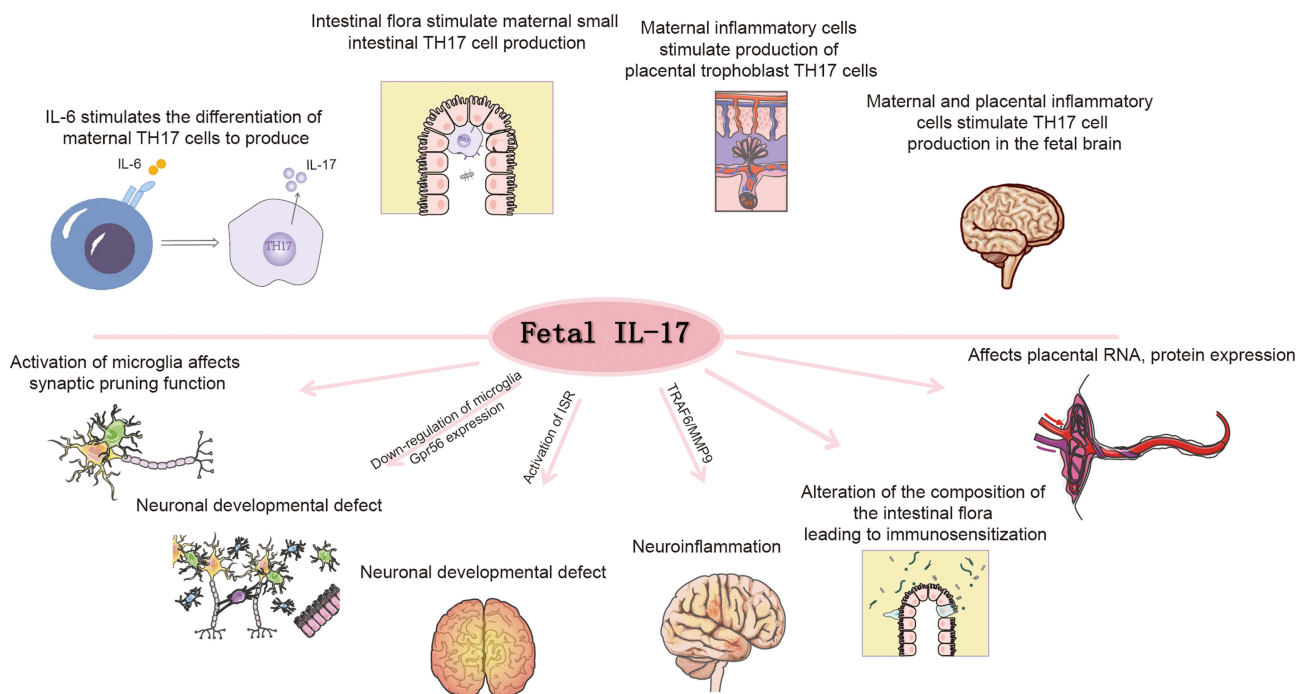


Figure 2 Mechanisms of IL-17A-Mediated Neurodevelopmental Impairment through Maternal-Fetal Immune Activation. This schematic illustrates the pathways through which IL-17A contributes to fetal neurodevelopmental abnormalities. Upper panel: Sources and production of IL-17A. Multiple pathways contribute to IL-17A production: IL-6 stimulates the differentiation of maternal TH17 cells; intestinal flora activate maternal small intestinal TH17 cells; maternal inflammatory cells trigger placental trophoblast TH17 cell production; and maternal-placental inflammatory cells induce TH17 cell production in the fetal brain. Lower panel: Neurodevelopmental consequences of IL-17A signaling. IL-17A exerts multiple detrimental effects including: activation of microglia leading to impaired synaptic pruning function; down-regulation of microglial Gpr56 expression causing neuronal developmental defects; induction of neuroinflammation; alteration of intestinal flora composition resulting in immune sensitization; and modulation of placental RNA and protein expression. These interconnected mechanisms collectively disrupt normal neurodevelopment and contribute to the pathogenesis of neurodevelopmental disorders.

Interleukin-1 β (IL-1 β)

Interleukin-1 β (IL-1 β) is one of the key cytokines elevated in ASD.⁹⁴ 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.⁹⁵ Offspring of LPS-exposed MIA dams also showed increased IL-1 β mRNA levels in fetal brains.⁹⁶ Multiple studies confirm that viral mimetics significantly elevate fetal brain IL-1 β expression for at least 24 hours post-MIA induction.⁹⁵ The association between ASD pathogenesis and IL-1 signaling, including its receptor family, has been experimentally validated,⁹⁷ with IL-1 β gene polymorphisms being more prevalent in children with ASD.^{98,99} Disrupted IL-1 β signaling during early development leads to synaptic homeostasis dysregulation and ASD-like behavioral deficits,⁹⁹ as neuronal function critically depends on tightly regulated IL-1 β levels.¹⁰⁰ 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.⁹⁹ 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.⁹⁹ 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.²¹

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).¹⁰¹ Among these cytokines, TNF- α —primarily released by macrophages and microglia—modulates brain development and function.^{102,103} Late-gestation immune challenges specifically activate IL-10 and TNF- α responses in fetal brains, which are linked to increased postnatal apoptosis.¹⁰⁴ 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.¹⁰⁵ 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.^{106,107}

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.¹⁰⁸ 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.¹⁰⁹ Cortical neurons differentiated from iPSCs and exposed to IFN γ during differentiation exhibit aberrant neurite outgrowth and altered dendritic spine density.⁷⁸

Given the association between MIA and diverse neurodevelopmental disorders, developing interventions targeting inflammatory mediators is critical. For instance, blocking specific cytokines (eg, 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).^{110,111} The Th17/Treg ratio exhibits a significant positive correlation with ASD severity, while Treg abundance inversely correlates with symptom severity.¹¹²

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,^{113–115} constitutive upregulation of Toll-like receptor (TLR) expression,¹¹⁵ and systemic Treg deficiencies. Elevated CD4⁺ T cell reactivity in the spleen and mesenteric lymph nodes further reflects compromised immune homeostasis in MIA offspring.¹¹⁶ Bioinformatic and experimental analyses revealed that activation of the PI3K/Akt/NF- κ B pathway in offspring upregulates STAT3 signaling, driving Treg/Th17 imbalance.¹¹⁷ 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,¹¹⁸ representing a major contributor to neurodevelopmental impairments. Intravenous administration of purified Tregs to MIA offspring ameliorates Th1/Th17 skewing¹¹⁹ and reverses behavioral deficits. Notably, Tregs isolated from MIA dams can remodel inflammatory microenvironments in offspring brains.¹¹⁸ 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.¹²⁰

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.¹²¹ 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.¹²² 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- κ B 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.¹²³

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.¹²⁴ Helminth-derived Sjp90 α protein induces Treg production of IL-10, modulating macrophage activity.¹²⁵ 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.¹²⁶

Microglia

Microglia, a critical component of the central nervous system (CNS) glial population, play pivotal roles in CNS development and homeostasis maintenance.¹²⁷ 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,¹²⁸ structural integrity maintenance, and selective synaptic pruning.^{129–131} Microglia can polarize into M1 or M2 phenotypes.¹³² The M1 phenotype produces pro-inflammatory cytokines (eg, IL-6, TNF- α , IL-1 β) 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 (eg, 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). Distinct MIA induction methods differentially alter microglial phenotypes in postnatal and adult offspring brains.¹³³ For instance, prenatal valproic acid (VPA) exposure increases microglial soma size, while prenatal LPS exposure enhances hippocampal microglial activation in MIA offspring.¹³⁴ 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.¹³⁵ Activated microglia in MIA exhibit functional alterations, including upregulated inflammatory mediator gene expression,

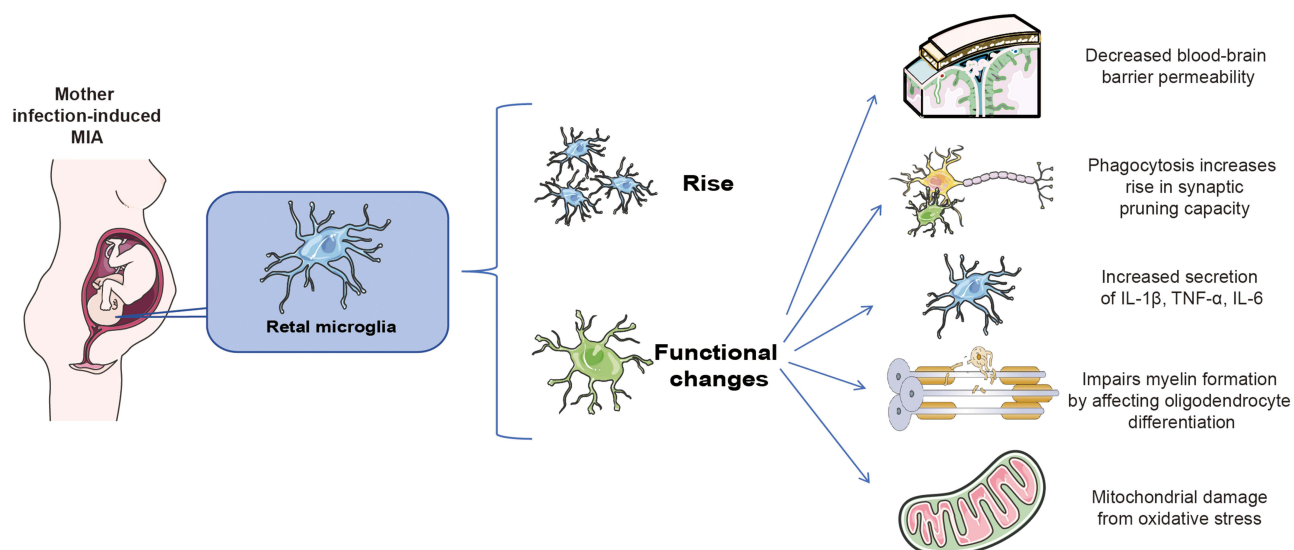


Figure 3 Central Role of Microglial Dysregulation in Maternal Immune Activation-Induced Neurodevelopmental Impairments. Maternal infection-induced immune activation triggers a cascade of microglial-mediated pathological events in the fetal brain. Microglia undergo significant activation characterized by population expansion and functional transformation, serving as the central effector in neurodevelopmental disruption. The activated microglia exhibit multiple pathological manifestations: compromised blood-brain barrier integrity; enhanced phagocytic activity with aberrant synaptic pruning; increased secretion of pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6); impaired myelin formation through disrupted oligodendrocyte differentiation; and mitochondrial damage via oxidative stress pathways. These microglial dysfunctions collectively drive neurodevelopmental impairments through disrupted neural circuitry, compromised white matter integrity, and sustained neuroinflammatory responses, establishing microglia as the pivotal cellular mediator linking maternal immune activation to fetal brain abnormalities.

enhanced proliferation, phagocytic activity, and release of cytotoxic cytokines, chemokines, and reactive oxygen species (ROS),^{136,137} collectively disrupting fetal brain development.¹⁹

During development, microglia regulate neural progenitor cell (NPC) pool size by stimulating NPC proliferation¹³⁸ and subsequently phagocytosing excess NPCs.¹³⁹ MIA disrupts these microglia-mediated neurodevelopmental processes.^{128,140,141} CX3CR1 deficiency impairs microglial signaling and function by altering developmental trajectories.¹⁴² 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.¹⁴³ LPS-MIA offspring show reduced CX3CR1 mRNA expression at postnatal day 15.¹⁴⁴ Beyond providing neurotrophic support (eg, insulin-like growth factor-1),^{145,146} microglia dynamically remodel synapses through phagocytosis and trogocytosis,¹²⁹ modulating synaptic plasticity and strength via activity-dependent interactions.¹⁴⁷ MIA exacerbates microglial synaptic pruning and phagocytosis,¹⁹ with dysfunctional phagocytosis implicated in ASD and schizophrenia (SCZ). Excessive NPC phagocytosis and defective synaptic pruning disrupt neuronal connectivity and brain circuitry.¹⁴⁸ Altered microglial homeostasis impedes NPC self-renewal/differentiation, predisposing to autism-like behaviors.¹⁴⁹ Microglia may regulate MIA-induced interneuron deficits via G protein-coupled receptor 56 (GPR56).⁸⁹ Aberrant microglial synaptic elimination and autophagy underlie MIA-associated circuit phenotypes;¹⁵⁰ mTOR inhibitor rapamycin rescues dendritic pruning defects and ASD-like behaviors in *Tsc2 \pm* mice,¹⁵¹ while activating microglial autophagy ameliorates SCZ-related abnormalities in MIA offspring.¹⁵² Activated microglia release excess ROS,¹³⁷ damaging mitochondria. Microglial 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,¹⁵³ subsequently inducing intracellular cascades that regulate mitochondrial metabolism and function.¹⁵⁴ 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.^{155,156} Chronic MIA-induced inflammation promotes microglial phagocytosis of astrocytic end-feet, further compromising the BBB.¹⁵⁷

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.¹⁵⁸ 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.

Astrocyte, Neuron and NSC

The density of microglia in the brain (especially in the prefrontal cortex) of ASD patients is increased,¹⁵⁹ and microglia are activated.¹⁶⁰ The secretion of proinflammatory cytokines such as IL-1 β and TNF- α is increased, while synaptic pruning is enhanced, the complement C3-CR3 pathway is activated, and the phagocytosis of dendritic spines is abnormal. In addition to microglia, multiple brain regions such as the cortex also show activation of astrocytes.¹⁶⁰ The expression of glutamate transporter GLT-1 in astrocytes is reduced, resulting in glutamate accumulation in synaptic cleft and subsequent excitotoxicity. May be closely related to the occurrence of ASD,¹⁶¹ ASD patients can show brain endothelial cell damage and dysfunction,¹⁶² increased permeability of the blood-brain barrier, and inflammatory cytokines can also cross the barrier to activate microglia. There are abnormalities in the number and function of neuronal synapses in the brain of patients with ASD, and the connection mode and strength between neurons may also change.^{163,164} At the same time, the number of microglia in the brain increases, and the activation of microglia triggers a variety of inflammatory cytokines and chemokines, and the generation of a large number of reactive oxygen species, which affects neurogenesis and synapse formation. ADHD patients have decreased expression of histamine H2 receptors on PV neurons in the substantia nigra pars reticulata (SNr), resulting in hyperactivity of dopaminergic neurons.,¹⁶⁵ ADHD patients show higher temporal variability and lower spatial stability in neural responses in the salience and frontoparietal network regions.¹⁶⁶ Mental retardation (ID) and fragile X syndrome (FXS) also show abnormalities in neuronal number and dendritic morphology, and synaptic development. Maternal immune activation (MIA) can alter the regulation of protein translation and phosphorylation of microtubule-associated protein 2 (MAP2) in neural stem cells, leading to defects in synaptic connectivity during neuronal maturation. It can also affect the neuromaturation and function of offspring¹⁶⁶ and induce abnormal synaptic development and pruning during neurodevelopment, destroying the excitation-inhibition balance of neurons (such as hippocampal neurons).¹⁶⁷ Maternal immune activation (MIA) has also been shown to interfere with the development and behavior of offspring microglia, thereby disrupting the coordinated neurodevelopment process of microglia,¹⁶⁸ MIA can also damage the integrity of the blood-cerebrospinal fluid barrier,¹⁶⁹ change the composition of cerebrospinal fluid, inhibit the concentration of neurotrophins such as insulin-like growth factor-I (IGF-I),¹⁶⁹ and destroy the brain microenvironment for neurodevelopment. It is noteworthy that maternal immune stimulation of the fetal immune system leads to increased levels of inflammatory cytokines in the offspring brain.¹⁷⁰ Cytokines such as IL-6 and IL-17A can interfere with the neural development program in the embryonic period and early postnatal period, and have a significant impact on the proliferation, differentiation, migration and survival of neural stem cells. It has been shown that H-IL-6 promotes the differentiation of neural stem cells (NSCs) into glutamate-responsive neurons, oligodendrocytes, and distinct glial subtypes, an effect that is highly dependent on the presence of the soluble IL-6 receptor (sIL-6R).¹⁷¹ Using a brain organoid model, Hyper-IL-6 treatment slightly increases the proportion of radial glial cells, which exhibit the most pronounced transcriptional alterations, including downregulation of protein translation-related genes.⁸⁰ Notably, even transient increases in systemic IL-6 can trigger short-term proliferation followed by lasting reductions in adult NSC pools, suggesting that IL-6 signaling is essential for NSC maintenance but that its dysregulation may contribute to neurodevelopmental and psychiatric disorders.¹⁷² IL-17 activation in neural stem cells (NSCs) leads to a notable reduction in cell numbers and impaired neurosphere formation, without causing cytotoxicity or apoptosis. While IL-17 inhibits NSC proliferation, it also disrupts their differentiation into astrocytes and oligodendrocyte precursor cells (OPCs). These effects are partially mitigated by blocking the p38 MAPK pathway.¹⁷³ A recent study examined the

impact of MIA using neural stem cells (NSCs), which demonstrated significant changes in protein expression and phosphorylation, particularly in proteins involved in neuronal function. Transcriptomic, proteomic, and phosphoproteomic analyses revealed alterations in proteins related to cytoskeletal dynamics and synaptic activity. Of particular note, changes in the phosphorylation of MAP family proteins, especially MAP2, were found to influence neuronal plasticity and synapse formation. These findings underscore the critical role of NSCs in studying the molecular mechanisms of MIA and highlight the importance of MAP2 phosphorylation in regulating neuronal structure and function.¹⁷⁴

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,¹⁷⁵ 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.^{176,177} Through this axis, gut microbes regulate host behaviors associated with neurodevelopmental dysfunction.¹⁷⁸ 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,¹⁷⁹ while also promoting stem cell regeneration and enhancing mucus secretion.¹⁸⁰ 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,¹⁸¹ 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.¹⁷⁷

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.¹⁸² Preemptive eradication of vancomycin-sensitive SFB prior to MIA induction prevents offspring behavioral deficits.¹⁸² 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.¹⁸³ Prenatally, maternal *Lactobacillus murinus* deficiency disrupts embryonic microglial transcriptomes, alters brain microglial colonization (eg, increased density and hyper-ramification), and elevates chromatin accessibility.^{184,185} Microbiota-targeted interventions in MIA offspring partially ameliorate gut alterations, stereotyped behaviors, anxiety-like phenotypes, and sensorimotor gating deficits.¹⁸⁶

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 signaling,⁷⁷ while offspring-derived TNF- α suppresses MAP2+ dendritic growth, impairing synaptic development.¹⁰⁵ Poly(I:C)-induced MIA significantly reduces expression of presynaptic (eg, synaptophysin) and postsynaptic (eg, PSD95) proteins in offspring hippocampi, compromising basal synaptic transmission (field potential [FV] and excitatory postsynaptic potential [fEPSP]) and plasticity (paired-pulse facilitation [PPF] and long-term potentiation [LTP]).¹⁸⁷ Additionally, MIA downregulates Shank3 expression, disrupting neuronal connectivity, synaptogenesis, and dendritic spine maturation.

Beyond synaptogenesis, aberrant synaptic pruning profoundly impacts neurodevelopment.¹⁸⁸ In male offspring of LPS-induced MIA dams, dendritic density in dentate gyrus granule cells remains elevated during peak pruning stages (postnatal day 15),¹⁴⁴ a phenotype linked to persistent network hyperconnectivity and ASD-like behaviors.¹⁸⁹ IL-17A signaling enhances microglial phagocytic activity in fetal brains,⁹⁰ while poly(I:C)-exposed MIA offspring exhibit upregulated hippocampal IL-1 β expression in adulthood.¹⁴⁴ IL-1 β selectively amplifies mTOR pathway activity, further dysregulating synaptic pruning and phagocytosis.⁹⁹

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,¹⁹⁰ NF- κ B,¹¹⁷ and JAK/STAT,¹⁹¹ which modulate the expression of neurodevelopmental genes (eg, 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.¹⁹²

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 (eg, altered mRNA expression of placental amino acid transporters like leucine transporters) and indirect mechanisms, disrupting fetal brain growth trajectories.¹⁹³

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, 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 disturbances.⁵⁸

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.

Accumulating evidence underscores the pivotal role of Maternal Immune Activation (MIA) as a key environmental risk factor for neurodevelopmental disorders (NDDs). The core pathogenesis hinges on a maternal immune response triggered by infection or inflammation during pregnancy, leading to a surge in pro-inflammatory cytokines such as IL-6, IL-17A, IL-1 β , and TNF- α . These cytokines disrupt fetal brain developmental programs directly or indirectly via the placental interface. IL-6 has been identified as a critical initiator, propagating downstream pathology by impairing placental function, altering epigenetic regulation via the JAK/STAT pathway, and directly suppressing neurogenesis. IL-17A, primarily derived from maternal Th17 cells, can not only cross the placenta but also bind to IL-17RA receptors in the fetal brain, provoking microglial dysregulation and the Integrated Stress Response (ISR), which ultimately disrupts cortical neuron differentiation and interneuron function. In tandem, cytokines like IL-1 β and TNF- α act synergistically to compromise neural circuit formation and plasticity by modulating microglial phagocytosis and synaptic pruning, as well as directly impairing neuronal dendrite development. This collaborative interplay among cytokines forms the immunopathological foundation of MIA-induced neurodevelopmental damage, culminating in the core behavioral phenotypes of NDDs such as ASD and ADHD.

Substantial research gaps remain in this field. Current mechanistic studies have primarily concentrated on a limited repertoire of cytokines and microglial responses, while paying inadequate attention to other significant pathogens like *Toxoplasma gondii* and crucial cellular components such as vascular endothelial cells. Moreover, the long-term pathophysiological processes through which maternal immune activation persistently disrupts neuronal circuitry—particularly the specific interactions between primed microglia and interneurons—are not yet fully elucidated. A more comprehensive investigation into the complex interplay between environmental triggers like MIA and individual genetic susceptibilities is essential to unravel the determinants of phenotypic heterogeneity in NDDs.

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 (eg, cytokine blockade, microglial replacement) represent promising therapeutic avenues, warranting validation in preclinical models. Given the central role of maternal immune activation (MIA) in neurodevelopmental disorders (NDDs), intervention strategies targeting its associated immune signaling pathways have become a major research focus. At the pharmacological level, studies indicate that bumetanide can ameliorate autism-like behaviors through immuno-behavioral covariation mechanisms by modulating the expression of inflammatory factors such as IFN- γ .¹⁹⁴ In more targeted receptor blockade strategies, animal studies have demonstrated that specifically blocking the signaling transduction of key cytokines like IL-17A^{85,195} or IFN- γ ¹⁶⁹ with antibodies significantly alleviates abnormal behavioral phenotypes in MIA offspring models.

Microglia play a central role in MIA-induced neurodevelopmental disorders, and microglia replacement therapy has emerged as a promising strategy with significant advances in treating neurological diseases. Compelling evidence from multiple disease models demonstrates the therapeutic potential of this approach. In CSF1R-related leukoencephalopathy (ALSP), researchers successfully replaced pathogenic microglia in the central nervous system, effectively blocking disease progression in animal models.¹⁹⁶ This strategy also showed promising results in a small-scale clinical trial involving eight patients, where it stabilized both motor and cognitive functions over a two-year follow-up period.¹⁹⁶ In Sandhoff disease models, two independent studies utilizing bone marrow transplantation and direct intracerebral injection of *in vitro*-cultured cells respectively confirmed the efficacy of microglia replacement. These interventions not only significantly improved neurological function but also remarkably extended the lifespan of treated mice from 135 to 250 days.^{197,198} Furthermore, in Krabbe disease models, perinatal microglia replacement completely normalized transcriptional signatures, rescued histopathological abnormalities, and achieved a two-fold extension in average survival.¹⁹⁹ These collective findings strongly support the broad applicability of microglia replacement strategies across various neurological disease models.

However, the field still faces important challenges. Studies have found that early microglia depletion may exacerbate seizure severity in adulthood, and transplanted cells from different sources (such as monocyte-derived versus authentic microglia) exhibit distinct functional characteristics in neural circuits. RNA sequencing revealed that the developmental origin of cells and the transplantation process significantly influence their response to excitotoxic brain environments.²⁰⁰ Additionally, traditional bone marrow transplantation methods suffer from low efficiency and require radiation preconditioning, while the novel “tricyclic microglial depletion for transplantation (TCMDT)” strategy enables efficient transplantation without preconditioning through CSF1R inhibitors,²⁰¹ demonstrating therapeutic potential in multiple disease models.

In conclusion, interventional strategies for neurodevelopmental disorders are continuously evolving, ranging from pharmacological modulation and antibody blockade to innovative cell replacement therapies. Future research should focus on optimizing cell source selection, improving replacement safety and efficiency, and deeply exploring the interaction mechanisms between transplanted cells and neural circuits, thereby advancing the clinical management of neurodevelopmental disorders into a new era of precision medicine.

This review has systematically elucidated the multi-level mechanisms through which MIA contributes to NDDs, encompassing inflammatory cytokine cascades at the maternal-fetal interface, microglia-mediated synaptic pruning deficits, gut-brain axis dysregulation, and Th17/Treg immune deviations. Evidence strongly supports the crucial role of specific cytokines including IL-6, IL-17A, and IL-1 β in disrupting neural circuit formation through various signaling

pathways. Current intervention strategies have evolved from pharmacological modulation to more targeted approaches, with antibody blockade of specific cytokine pathways and emerging microglia replacement therapy showing particular promise for resetting the neuroimmune environment.

Looking forward, several research priorities demand urgent attention. The intricate interactions between genetic susceptibility and environmental factors in determining NDD phenotypes require deeper investigation through integrated multi-omics approaches. Standardized protocols for cell replacement therapies need development to address critical challenges in transplantation safety and efficiency. Furthermore, the translation of immune-based interventions necessitates careful consideration of temporal windows, target specificity, and individual patient characteristics. The evolving landscape of NDD interventions—spanning immunomodulation, targeted blockade, and cellular replacement—heralds a new era in precision medicine for neurodevelopmental disorders. Future research integrating fundamental mechanistic insights with innovative therapeutic approaches will ultimately enable more effective prevention and treatment strategies for these complex conditions.

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Disclosure

The authors declare no competing interests in this work.

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