How does Maternal Immune Activation Prime Life-Long Immune-Brain Vulnerability?

Maternal immune activation **reprograms the fetal brain and immune system**, creating **long-term vulnerability** to neurodevelopmental and psychiatric disorders.

Maternal immune activation (MIA) during pregnancy or early postnatal life acts as an early-life “hit” that reshapes fetal brain development, neuroimmune circuits, and epigenetic regulation, with effects lasting into adolescence and adulthood.

Mechanisms: From Maternal Inflammation to Fetal Brain Reprogramming

- MIA (infection or inflammatory states) triggers maternal cytokines and placental inflammation, altering fetal cytokine milieu, neurotransmission, synaptic plasticity, and inducing neuroinflammation and epigenetic changes in the developing brain. (Suleri et al., 2024; Woods et al., 2022)- Specific maternal immune cell responses can directly perturb fetal neuroimmune cells: decidual NK cells release extracellular granzyme B that crosses the maternal–fetal barrier, driving fetal macrophage accumulation and microglial activation and “neuroimmune disorders” later in life. (Bian et al., 2025)## Lasting Brain and Circuit Changes
- In rats and mice, Poly I:C or LPS MIA rapidly induces antiviral/inflammatory gene programs and represses neurodevelopmental genes in the conceptus, thickens cortical zones, enhances neural precursor self-renewal, and alters Notch signaling, producing sustained dysregulation of cortical structure and NPC function. (Baines et al., 2020)- Nonhuman primate MIA causes persistent reductions in frontal gray/white matter volumes and subtle cognitive alterations from infancy to 45 months, (Vlasova et al., 2021)and, at 4 years, thousands of cell-type–specific gene changes in amygdala neurons and microglia, enriched for synaptic, neuroimmune, and ASD/psychosis-risk pathways. (Ander et al., 2025)- Human brain organoid MIA models show IL-6–driven STAT activation, MHCI upregulation, selective vulnerability and transcriptional reprogramming of radial glia, and long-term abnormal cortical layering. (Sarieva et al., 2023)## Epigenetic and Immune “Priming” Across Life
- Influenza-based MIA in mice induces enduring epigenetic reprogramming (histone marks, enhancers, promoters) in frontal cortical neurons, affecting genes for forebrain development, axonogenesis, and synapse organization; these MIA-responsive elements are enriched at neuropsychiatric GWAS loci, supporting long-term risk programming. (Zhu et al., 2026)- Systematic review of rodent MIA shows replicated long-term increases in inflammatory markers, and reductions in myelin and GABAergic proteins in key brain regions, consistent with durable neuroimmune and circuit vulnerability. (Woods et al., 2021)- MIA or lactational immune activation can “program” the offspring immune system: adult offspring show altered cytokine responses and leukocyte profiles after a second immune hit, implying persistent immune rewiring. (Merengueli & Kentner, 2025; You et al., 2024)### Examples of Life-Long Vulnerability Features

Level	Lasting change after MIA	Citation
Brain structure	Persistent frontal gray/white matter reductions in primates	(Vlasova et al., 2021)
Cell-type programs	Long-term amygdala neuron/microglia transcriptomic dysregulation	(Ander et al., 2025)
Epigenetics	Stable enhancer/promoter remodeling in adult cortex	(Zhu et al., 2026)

Level	Lasting change after MIA	Citation
Immune response	Altered adult cytokine/immune responses to later challenges	(Merengueli & Kentner, 2025)

FIGURE 1 Multi-level lasting effects of maternal immune activation

Behavioral and Clinical Endpoints

- Rodent and primate MIA models show behaviors relevant to autism, schizophrenia, anxiety, and cognitive deficits, with prolonged immune alterations in offspring brains proposed to underlie these phenotypes. (Bergdolt & Dunaevsky, 2018; Quagliato et al., 2021)- Human and animal data link elevated maternal IL-6 and other cytokines to altered newborn brain connectivity and delayed sensory/cognitive processing, supporting translation of these vulnerability mechanisms to humans. (Schepanski et al., 2018; Sarieva et al., 2023)## Summary

MIA primes lifelong immune–brain vulnerability by: (1) altering placental signaling and fetal cytokine balance; (2) reprogramming neural progenitors, microglia, and macrophages; (3) inducing durable epigenetic and transcriptomic changes in neural circuits; and (4) reshaping offspring immune responses to later challenges. Together, these processes create a long-lasting, system-wide susceptibility to neurodevelopmental and psychiatric disorders.

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