What are the Transdiagnostic Effects of Maternal Immune Activation?

Maternal Immune Activation as a Transdiagnostic Risk Factor: Cross-Disorder Effects on Offspring Brain and Behavior

Maternal immune activation (MIA) during pregnancy is linked to a broad spectrum of neurodevelopmental and psychiatric outcomes in offspring, not just a single diagnosis. Across human and animal work, MIA appears to "prime" fetal brain development toward atypical trajectories that can later manifest as different disorders depending on timing, intensity, genetics, sex, and postnatal environment.

Transdiagnostic Clinical and Behavioral Outcomes

Multiple diagnoses linked to MIA

- Human studies associate maternal infection/inflammation with increased risk of **autism spectrum disorder (ASD), schizophrenia, ADHD, Tourette syndrome, bipolar disorder, and other NDDs** (Estes & McAllister, 2016; Han et al., 2021; Knuesel et al., 2014; Hall et al., 2023; Brown & Meyer, 2018; Careaga et al., 2017; Guma et al., 2019; Solek et al., 2018; Han et al., 2021; Schaer et al., 2026; Xu et al., 2024).
- Systematic reviews show diverse maternal inflammatory states (infection, obesity, diabetes, pre-eclampsia, asthma, autoimmune disease, stress, pollution, depression) link to ASD, ADHD, and Tourette outcomes (Han et al., 2021).

Shared behavioral domains

- Animal MIA models show overlapping **social, communicative, cognitive, anxiety/depression-like, sensorimotor-gating, hyperactivity, and stereotypic behaviors** that map onto ASD, schizophrenia, ADHD, and mood disorders (Haddad et al., 2020; Gumusoglu & Stevens, 2019; Knuesel et al., 2014; Bergdolt & Dunaevsky, 2019; Careaga et al., 2017; Carbone et al., 2023; Mueller et al., 2020; Woods et al., 2021; Schaer et al., 2026; Bauman & Van De Water, 2020; Xu et al., 2024).

Common Neurobiological Mechanisms

Shared mechanism	Brief description	Citations
Fetal immune/microglial priming	Lasting immune and microglial changes, "primed" to over-respond later	(Estes & McAllister, 2016; Gumusoglu & Stevens, 2019; Knuesel et al., 2014; Bergdolt & Dunaevsky, 2019; Brown & Meyer, 2018; Careaga et al., 2017; Guma et al., 2019; Solek et al., 2018; Mueller et al., 2020)
Synaptic & circuit disruption	Altered synapses, brain growth, connectivity, myelination, GABA signaling	(Estes & McAllister, 2016; Gumusoglu & Stevens, 2019; Knuesel et al., 2014; Bergdolt & Dunaevsky, 2019; Careaga et al., 2017; Guma et al., 2019; Carbone et al., 2023; Woods et al., 2021)
Epigenetic changes	Lasting transcriptional/epigenetic reprogramming, possibly transgenerational	(Gumusoglu & Stevens, 2019; Han et al., 2021; Knuesel et al., 2014; Bergdolt & Dunaevsky, 2019; Brown & Meyer, 2018; Guma et al., 2019; Carbone

Shared mechanism	Brief description	Citations
		et al., 2023; Mueller et al., 2020; Woods et al., 2021; Bauman & Van De Water, 2020)

FIGURE 1 Key shared mechanisms linking MIA to many disorders

Moderators of Heterogeneous Outcomes

Why different diagnoses from the same insult?

- **Timing and severity** of immune challenge, type of immunogen (viral-like poly I:C vs LPS), and acute vs chronic inflammation shape which brain systems are affected (Haddad et al., 2020; Gumusoglu & Stevens, 2019; Knuesel et al., 2014; Bergdolt & Dunaevsky, 2019; Hall et al., 2023; Careaga et al., 2017; Han et al., 2021; Bauman & Van De Water, 2020; Xu et al., 2024).
- **Genetic susceptibility, sex, and postnatal "second hits"** (stress, caregiving, additional immune challenges) modulate risk, producing subgroups of resilient vs susceptible offspring with distinct brain, immune, and transcriptional profiles (Knuesel et al., 2014; Hall et al., 2023; Conway & Brown, 2019; Meyer, 2019; Carbone et al., 2023; Mueller et al., 2020; Schaer et al., 2026; Bauman & Van De Water, 2020; Xu et al., 2024).
- Some rodent work shows **transgenerational transmission** of MIA-induced abnormalities via epigenetic mechanisms (Brown & Meyer, 2018; Bauman & Van De Water, 2020).

Implications for Prevention and Treatment

- MIA is viewed as a **shared environmental risk factor across CNS disorders**, acting as a disease "primer" rather than a disease-specific cause (Estes & McAllister, 2016; Knuesel et al., 2014; Brown & Meyer, 2018; Careaga et al., 2017; Bauman & Van De Water, 2020).
- This supports strategies targeting **maternal inflammation, immune pathways, and epigenetic/immune signatures** for preventive and potentially disease-modifying interventions (Estes & McAllister, 2016; Gumusoglu & Stevens, 2019; Han et al., 2021; Knuesel et al., 2014; Bergdolt & Dunaevsky, 2019; Brown & Meyer, 2018; Careaga et al., 2017; Han et al., 2021; Bauman & Van De Water, 2020).

Summary

Across human and animal research, maternal immune activation is a transdiagnostic risk factor that increases vulnerability to multiple neurodevelopmental and psychiatric disorders. It acts through shared immune, microglial, synaptic, and epigenetic mechanisms, but the ultimate clinical outcome depends on timing, intensity, genetics, sex, and later-life environment. This framework shifts focus from single diagnoses to common pathways and suggests broad preventive targets in the maternal–fetal immune environment.

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