Epigenomics, the Immune System and Neurodevelopmental and Psychiatric Disorders

Epigenomics, Immunity, and Brain Disorders: An Overview

Across neurodevelopmental and major psychiatric disorders, epigenetic mechanisms such as **DNA methylation**, histone modifications, and non-coding RNAs link immune activation and environmental exposures (infection, stress, microbiome, diet) to long-lasting changes in brain and immune function. These changes are often shared across diagnoses rather than disorder-specific.

Epigenetic Modulation of Immune Pathways Across Disorders

- Epigenome-wide association studies (EWAS) in schizophrenia, depression, PTSD, panic disorder and ASD repeatedly find differentially methylated genes enriched in **immune and inflammatory pathways**, including T-cell development, cytokine secretion, and broader immune response genes (Alameda et al., 2022; Bergdolt & Dunaevsky, 2019; Herrera-Rivero et al., 2025).
- Cross-diagnostic reviews report immune-related DNA methylation and histone changes as common epigenetic signatures in major mental disorders, alongside neurotransmission and neurogenesis pathways (Alameda et al., 2022; Han et al., 2025; Shirvani-Farsani et al., 2021; Delphin et al., 2024).
- In depression, discordant twin and post-mortem studies identify methylation changes in loci regulating inflammatory processes, and immune-gene methylation profiles cluster with distinct inflammatory biomarker patterns over time (Alameda et al., 2022; Herrera-Rivero et al., 2025).

Neurodevelopmental Disorders, Maternal Immune Activation, and Microglia

- Maternal immune activation (MIA) is linked to increased risk of ASD, ADHD, Tourette syndrome and schizophrenia; integrated brain transcriptome–epigenetic analyses in NDDs show **convergent dysregulated immune pathways** (Han et al., 2021; Conway & Brown, 2019; Weber-Stadlbauer, 2017).
- Infection-mediated MIA models indicate that prenatal immune challenges induce stable epigenetic modifications that alter brain development and can transmit across generations (Bergdolt & Dunaevsky, 2019; Weber-Stadlbauer, 2017).
- Whole-genome bisulfite sequencing of cortex in ASD, Rett and Dup15q identifies shared differentially methylated regions in neuronal and **microglial** regulatory elements; associated genes show developmental expression patterns pointing to altered microglial function (Ciernia et al., 2019).

Microbiome–Immune–Epigenetic Axis

- Gut microbes and their metabolites modulate immune cell activity and brain function through epigenetic mechanisms (DNA methylation, histone modifications, non-coding RNAs), contributing to neuroinflammation in neuropsychiatric disorders (Alam et al., 2017; Nohesara et al., 2025).
- Bioactive nutrients and gut microbiota can reshape methylation and histone marks, influence inflammatory cytokines, and thereby impact the “gut–brain axis” in depression and other disorders (Alam et al., 2017; Nohesara et al., 2025).

Clinical and Therapeutic Implications

Aspect	Epigenomic–immune insight	Citations
Biomarkers	Immune-gene methylation and neural–immune DMRs proposed as diagnostic/prognostic markers in NDDs and major psychiatric disorders	(Alameda et al., 2022; Han et al., 2025; Shirvani-Farsani et al., 2021; Herrera-Rivero et al., 2025; Ciernia et al., 2019)
Gene–environment interface	Early adversity, infections, microbiome, and stress imprint epigenetic marks that interact with genetic risk	(Han et al., 2021; Cattane et al., 2020; Conway & Brown, 2019; Hoffmann et al., 2017; Weber-Stadlbauer, 2017)
Intervention potential	Epigenetic processes are reversible; diet, microbiome-targeted strategies, and epigenetic/immune-modulating therapies are proposed	(Alam et al., 2017; Han et al., 2025; Conway & Brown, 2019; Hoffmann et al., 2017; Nohesara et al., 2025)

FIGURE 1 Roles of immune-related epigenetic changes across disorders

Conclusion

Immune dysregulation in neurodevelopmental and psychiatric disorders is tightly intertwined with epigenomic change. Prenatal and postnatal immune challenges, gut microbiome alterations, and psychosocial stress can leave lasting epigenetic “imprints” in neurons and immune cells—especially microglia—shaping brain development, inflammation, and disease risk. These findings support immune-related epigenetic marks as promising biomarkers and therapeutic targets, while highlighting the importance of early-life environments.

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