

Metabolomics, the Immune System and Neurodevelopmental and Psychiatric Disorders

Metabolomics, Immunity, and Brain Disorders: What the Data Show

Metabolomic and multi-omics studies link disturbed metabolism tightly to immune dysregulation in autism and broader neurodevelopmental and psychiatric conditions. Key themes are oxidative stress, altered amino-acid and lipid metabolism, and gut–brain–immune interactions.

Neurodevelopmental Disorders (Especially ASD)

Integrated metabolomics + immune changes

- Combined transcriptomics–metabolomics in ASD shows **upregulated IL-1 β /IFN- γ and immune genes**, downregulated synaptic genes, and increased phenylalanine, citrulline, and disturbed lipid metabolism, pointing to intertwined immune and metabolic disturbance (Meng et al., 2025).
- Urine proteomic–metabolomic profiling in ASD identifies 277 altered metabolites; ~40% of differentially expressed proteins are neuroinflammation-related (glutathione, leukocyte antigens, immunoglobulins). Dysregulated pathways include **glutathione metabolism, xenobiotic metabolism, leukocyte migration, antigen presentation, and tryptophan metabolism**, with PGE2 linked to inflammatory response (Liu et al., 2022).

Brain and gut metabolic signatures

- Genome-scale metabolic modeling of ASD prefrontal cortex predicts elevated oxidative stress, mitochondrial dysfunction markers (pyruvate, ALT/AST), and **abnormal sphingolipid metabolism** (S1P, ceramide, glucosylceramide) as candidate neuroinflammatory biomarkers (Esvap & Ulgen, 2023).
- Non-human primate maternal immune activation leads to offspring with atypical neurodevelopment, **elevated immune profiles**, and broad shifts in lipid, amino-acid, and nucleotide metabolism across plasma, CSF, gut, and feces; specific metabolites correlate with cytokines and behavior (Boktor et al., 2022).
- In children with NDDs (ASD, ADHD, etc.), combined metagenomics–metabolomics shows gut dysbiosis plus fecal and plasma metabolic disruption in amino acids, TCA cycle, neurotransmitter, and lipid pathways; shared alterations include **arginine/proline metabolism and HIF-1 signaling**, linking metabolism, hypoxia responses, and neuroimmune signaling (Wang et al., 2025).

Early-life metabolites and risk

- A 20-year birth cohort finds that **cord serum metabolome/lipidome, infant microbiota, and stool metabolome** associate with later NDD diagnoses, alongside infections and antibiotics, suggesting convergent metabolic–immune risk profiling in infancy (Ahrens et al., 2024).

Key Metabolite–Immune Links in ASD/NDDs

Feature	Immune link	Citations
Oxidative stress & low glutathione	Promotes pro-inflammatory cytokine activation	(Esvap & Ulgen, 2023; Liu et al., 2022; Mohammedsaeed & Alharbi, 2025)

Feature	Immune link	Citations
Altered tryptophan/phenylalanine pathways	Tied to neuroimmune and neurotransmitter changes	(Liu et al., 2022; Meng et al., 2025; Wang et al., 2025)
Sphingolipids (S1P, ceramide)	Involved in inflammatory/immune signaling	(Esvap & Ulgen, 2023)

FIGURE 1 Representative metabolite pathways connected to immune changes

Mood and Stress-Related Psychiatric Disorders

- Reviews in MDD and bipolar disorder emphasize **neuroimmune–metabolic–oxidative stress networks**, linking cytokine activation, lipid metabolism, mitochondrial dysfunction, and kynurenine pathway shifts to depressive symptoms and suicidality (Maes et al., 2025; Pinzi et al., 2025; De Melo et al., 2017).
- Shared immune-inflammatory and metabolic pathways (low-grade inflammation, oxidative/nitrosative stress, lipid peroxidation, reduced HDL, leaky gut) are described in metabolic syndrome and mood disorders, supporting a systemic “**neuro-IO&NS–metabolic**” view of depression/BD (Nishida et al., 2025).
- Clinical and preclinical work in stress-related disorders shows that vulnerability (e.g., anhedonia) associates with **pro-inflammatory cytokines and altered metabolic hormones** (insulin, leptin, adiponectin), and that treatment response tracks normalization of these immune-metabolic markers (Cattaneo et al., 2025).

Integrative Multi-Omics and Mechanistic Insights

- Methodological reviews highlight that combining transcriptomics, proteomics, metabolomics, and microbiome data in NDDs consistently uncovers convergent **synaptic, mitochondrial, and immune dysregulation**, with urine and feces offering non-invasive windows into neuroinflammation and metabolic stress (Airoldi et al., 2025; Liu et al., 2022; Meng et al., 2025).

Conclusion

Across autism, broader neurodevelopmental disorders, and mood/psychotic conditions, metabolomic profiles repeatedly intersect with immune and inflammatory pathways. Altered amino-acid, lipid, oxidative, and gut-derived metabolites correlate with cytokine activity, microglial/immune signaling, and behavioral symptoms, and in some cases emerge years before diagnosis. These findings support a metabolite–immune–brain axis as a core dimension of neurodevelopmental and psychiatric pathology and a promising source of early biomarkers and targeted interventions.

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