# Relationships among Systems Biology and Neurodevelopmental and Psychiatric Disorders beyond the Brain and Central Nervous System

## Systems Biology, Neurodevelopment, and Psychiatry Beyond the Brain

Neurodevelopmental and psychiatric disorders arise from brain-based changes but are increasingly understood as **whole-body, systems-level conditions** involving immune, metabolic, gut, and other peripheral systems. Systems biology connects genetics, networks, and multi-organ interactions to explain these disorders more comprehensively.

### Peripheral Systems and Brain–Body Crosstalk

- **Gut microbiome–brain axis:** Gut bacteria influence blood–brain barrier formation, myelination, neurogenesis, microglial maturation, and behaviors relevant to anxiety, depression, cognition, and autism spectrum disorder (ASD) (Sharon et al., 2016).
- **Immune and metabolic systems:** Nervous system development and function are tightly coupled with immune function, bioenergetics, and the gut microbiome; many neurological and psychiatric disorders show systemic comorbidities in these domains (Qureshi & Mehler, 2013).
- **Stress and immunity:** Stress-related psychiatric disorders involve central regulation of peripheral immune responses, linking specific brain circuits to bone marrow, spleen, gut, adipose tissue, and liver via autonomic and hormonal pathways (Chan et al., 2023).
- **Shared medical comorbidities:** Many psychiatric risk genes are expressed in non-brain tissues and overlap with cardiovascular, renal, respiratory, and metabolic phenotypes, supporting linked brain–peripheral pathology (Plummer et al., 2016).

**Examples of Peripheral Links**

| Peripheral system / tissue | Key role in neurodevelopment/psychiatry | Citations |
|---|---|---|
| Gut microbiome | Shapes neurodevelopment, ASD, mood, behavior | (Sharon et al., 2016; Qureshi & Mehler, 2013; Chen et al., 2022; Plummer et al., 2016) |
| Immune system | Stress-induced inflammation, comorbid metabolic issues | (Qureshi & Mehler, 2013; Chan et al., 2023; Plummer et al., 2016) |
| Heart & musculoskeletal | Affected by psychiatric risk gene expression | (Torres, 2020; Plummer et al., 2016) |

FIGURE 1 Peripheral systems implicated in brain–body psychiatric links.

### Genetic and Network-Level Systems Biology

- Gene networks across ASD, ADHD, schizophrenia, and intellectual disability show **shared and distinct pathways**, including synaptic transmission and regulatory variants in intergenic regions (TF and miRNA sites) (Cristino et al., 2014).
- Systems and network analyses integrate gene expression, GWAS, and protein–protein interactions to reveal convergent modules across ASD, schizophrenia, and Alzheimer's disease (Parikshak et al., 2015; Willsey et al., 2018).
- Many neurodevelopmental/psychiatric risk genes are mutation-intolerant and act during prenatal brain development, especially for childhood-onset conditions (Shohat et al., 2020).
- Long-range regulatory SNPs in both brain and **non-brain tissues** affect synaptic and neuroinflammatory processes, creating cross-disorder clusters that include gut/small bowel modules with therapeutic potential (Chen et al., 2022).

### Reframing Diagnosis and Research

- Psychiatric conditions share genetic architecture with neurological diseases and strongly involve central and **peripheral** tissues (heart, muscle-skeletal), underscoring the brain–body connection (Torres, 2020).
- Genetic overlap between neurodevelopmental disorders and medical comorbidities argues against siloed brain-only views and supports integrated models and preclinical systems that include peripheral organs (Owen, 2021; Plummer et al., 2016).
- Systems biology and network medicine approaches that combine multi-omics across organs are highlighted as the necessary "future of systems physiology" for nervous system disorders (Qureshi & Mehler, 2013; Dougherty et al., 2017).

### Conclusion

Neurodevelopmental and psychiatric disorders emerge from interacting networks that span brain, immune system, metabolism, gut microbiome, and other organs. Systems biology shows that shared genetic and regulatory architectures operate in both CNS and peripheral tissues, helping explain comorbid medical conditions and suggesting new diagnostic and therapeutic strategies that treat mental illness as a truly systemic brain–body disorder.



### References

Chan, K., Poller, W., Swirski, F., & Russo, S. (2023). Central regulation of stress-evoked peripheral immune responses. *Nature Reviews Neuroscience, 24*, 591 - 604. https://doi.org/10.1038/s41583-023-00729-2

Chen, J., Song, L., Yang, A., Dong, G., & Zhao, X. (2022). Disrupted long-range gene regulations elucidate shared tissue-specific mechanisms of neuropsychiatric disorders. *Molecular Psychiatry, 27*, 2720 - 2730. https://doi.org/10.1038/s41380-022-01529-3

Cristino, A., Williams, S., Hawi, Z., Hawi, Z., An, J., Bellgrove, M., Bellgrove, M., Schwartz, C., Costa, L., & Claudianos, C. (2014). Neurodevelopmental and neuropsychiatric disorders represent an interconnected molecular system. *Molecular Psychiatry, 19*, 294-301. https://doi.org/10.1038/mp.2013.16

Dougherty, J., Yang, C., & Lake, A. (2017). Systems biology in the central nervous system: a brief perspective on essential recent advancements.. *Current opinion in systems biology, 3*, 67-76. https://doi.org/10.1016/j.coisb.2017.04.011

Owen, M. (2021). Psychotic Disorders and the Neurodevelopmental Continuum. **. https://doi.org/10.7551/mitpress/9780262029865.003.0003

Parikshak, N., Gandal, M., & Geschwind, D. (2015). Systems biology and gene networks in neurodevelopmental and neurodegenerative disorders. *Nature Reviews Genetics, 16*, 441-458. https://doi.org/10.1038/nrg3934

Plummer, J., Gordon, A., & Levitt, P. (2016). The Genetic Intersection of Neurodevelopmental Disorders and Shared Medical Comorbidities – Relations that Translate from Bench to Bedside. *Frontiers in Psychiatry, 7*. https://doi.org/10.3389/fpsyt.2016.00142

Qureshi, I., & Mehler, M. (2013). Towards a 'systems'-level understanding of the nervous system and its disorders.. *Trends in neurosciences, 36 11*, 674-84. https://doi.org/10.1016/j.tins.2013.07.003

Sharon, G., Sampson, T., Geschwind, D., & Mazmanian, S. (2016). The Central Nervous System and the Gut Microbiome.. *Cell, 167 4*, 915-932. https://doi.org/10.1016/j.cell.2016.10.027

Shohat, S., Amelan, A., & Shifman, S. (2020). Convergence and Divergence in the Genetics of Psychiatric Disorders From Pathways to Developmental Stages.. *Biological psychiatry*. https://doi.org/10.1016/j.biopsych.2020.05.019

Torres, E. (2020). Reframing Psychiatry for Precision Medicine. *Journal of Personalized Medicine, 10*. https://doi.org/10.3390/jpm10040144

Willsey, A., Morris, M., Wang, S., Willsey, H., & Krogan, N. (2018). The Psychiatric Cell Map Initiative: A Convergent Systems Biological Approach to Illuminating Key Molecular Pathways in Neuropsychiatric Disorders.. *Cell, 174 3*, 505-520. https://doi.org/10.1016/j.cell.2018.06.016