Proteomics, the Immune System and Neurodevelopmental and Psychiatric Disorders

Proteomics, Immune Dysregulation, and Brain Disorders: An Integrative Overview

Research across proteomics, transcriptomics, and genomics shows that immune and inflammatory pathways are deeply intertwined with neurodevelopmental and major psychiatric disorders, from autism spectrum disorder (ASD) to schizophrenia, bipolar disorder (BD), and major depression (MDD). Many findings converge on chronic low-grade inflammation, altered cytokine signaling, and neuroimmune cross-talk.

Shared Immune and Proteomic Signatures Across Disorders

- Peripheral blood proteomics in SZ, BD, and MDD identifies **486 altered proteins** with strong enrichment of immune pathways: interleukin signaling, Toll-like receptor, complement, JAK–STAT, PI3K–Akt, and IL-17 pathways (Fernandes et al., 2022).
- Transcriptomic analyses of postmortem brains across SZ, BD, ASD, MDD, Alzheimer's and Parkinson's diseases show >60% of curated immune-related genes altered in at least one disorder, mainly in **innate immunity** (Chen et al., 2022).
- Plasma and genetic proteome-wide MR studies repeatedly highlight immune-related plasma proteins (e.g., BTN3A3, IRF3, ACE, CSK) as putatively causal across multiple psychiatric disorders (Dardani et al., 2024; Liu et al., 2022; Gong et al., 2024).

Immune-Related Proteins and Psychiatric Risk

Finding	Disorder(s) linked	Citations
IL-6 causally ↑ risk	SZ, MDD	(Yotova et al., 2023; Williams et al., 2022)
Immune plasma proteins (BTN3A3, AIF1, IRF3, CFHR4, etc.) associated	SZ, BD, depression	(Liu et al., 2022; Gong et al., 2024)
Pro-inflammatory serum profile tracks **severity** across diagnoses	SZ, BD, MDD (severe mental disorders)	(Solomon et al., 2025)

FIGURE 1 Key immune proteins linked to psychiatric risk and severity

Neurodevelopmental Disorders and Prenatal Immune Activation

- Maternal immune activation (MIA) in mice induces **persistent synaptic proteome changes** in hippocampus from embryo to adulthood, affecting lipid/glycosphingolipid metabolism, neuronal guidance, and kinase signaling (AKT3, PAK1/3, PPP3CA) relevant to SZ, ASD, ADHD and comorbid disorders (Poletti et al., 2024; Pinzi et al., 2025).
- Nearly all overlapping MIA-altered proteins are associated with psychiatric and cognitive phenotypes in human genetic–phenome datasets (Poletti et al., 2024; Pinzi et al., 2025).
- Reviews of ASD emphasize **maternal immune activation, brain-reactive antibodies, autoimmunity, cytokine imbalance, oxidative stress, and gut inflammation** as key immune mechanisms (Perry et al., 2021).
- Urine proteome/metabolome in children with ASD shows that about **40% of differentially expressed proteins** relate to neuroinflammation, with dysregulated leukocyte migration, antigen presentation, and tryptophan/neuroimmune metabolism (Erbescu et al., 2022).

Brain–Immune Cross-talk and Structural/Functional Consequences

- Elevated IL-6, CRP, and TNF-α mark an **"inflammatory biotype"** of mood disorders with greater severity, cognitive impairment, and poorer treatment response (Dardani et al., 2024; Yotova et al., 2023; Ebstein et al., 2021).
- Genetically predicted IL-6 levels associate with **regional gray matter and cortical thickness changes** in temporal and frontal cortex, regions implicated in SZ and ASD (Williams et al., 2022).
- Postmortem profiling shows widespread **brain inflammation specific to schizophrenia** (IL-6, IL-2, IL-12p70 and other markers increased in hippocampus, prefrontal cortex, striatum) (Lanz et al., 2019).
- Multi-omics in atypical, psychotic depression links upregulated synaptic and immune proteins (e.g., complement C5), altered neutrophil/monocyte transcriptomes, and stressed brain organoids, supporting a neuroimmune stress-vulnerability model (Ahn et al., 2025).

Therapeutic and Biomarker Implications

- Multiple reviews argue that immune dysregulation is not only correlated but may be **causal** in subsets of patients, with 20+ immune proteins being druggable (e.g., ACE, TNFRSF17, SERPING1, CD40) (Dardani et al., 2024; Yotova et al., 2023; Gong et al., 2024).
- Anti-inflammatory strategies (COX-2 inhibitors, TNF-α blockers, minocycline, N-acetylcysteine, omega-3s) show promise as augmentation treatments in mood disorders and schizophrenia, particularly in inflamed subgroups (Almulla & Maes, 2025; Dang et al., 2023; Ebstein et al., 2021; Mehterov et al., 2022).
- Peripheral proteomic signatures and cytokine panels (e.g., IL-6-centered profiles) are emerging as candidate **biomarkers for diagnosis, severity, and treatment stratification** across disorders (Fernandes et al., 2022; Solomon et al., 2025; Dardani et al., 2024; Yotova et al., 2023; Dang et al., 2023; Ebstein et al., 2021; Ahn et al., 2025).

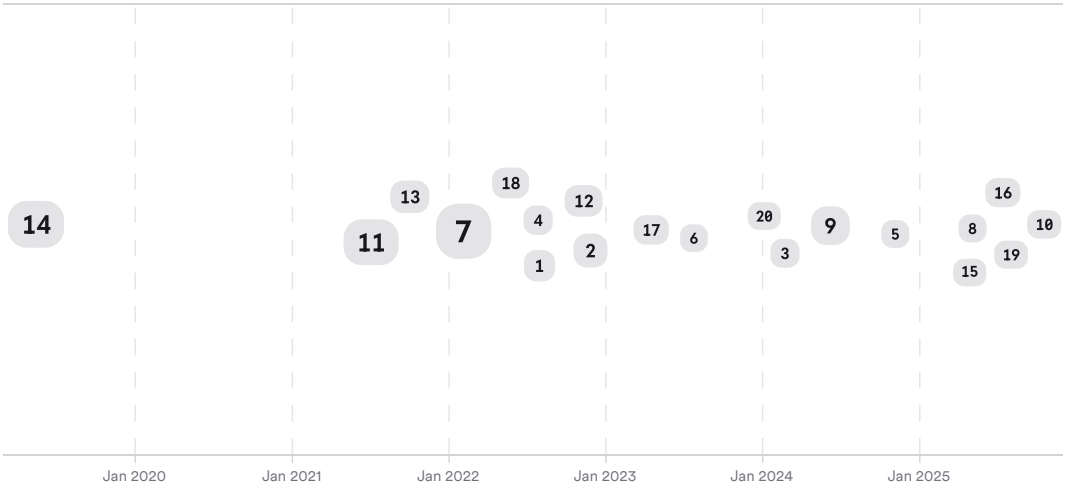

FIGURE 2 Recent progression of neuroimmune and proteomic psychiatry research. Larger markers indicate more citations.

Summary

Across ASD, SZ, BD, and MDD, converging proteomic and genomic data indicate that chronic immune activation, especially IL-6–centered and innate immune pathways, is tightly linked to disease risk, brain structure, symptom severity, and treatment response. Prenatal immune insults can imprint long-lasting, synapse-level proteomic changes that map onto human psychiatric genetics. These findings support neuroimmune cross-talk as a core dimension of neurodevelopmental and psychiatric pathology and motivate immune-targeted biomarkers and therapies within a precision medicine framework.

References

Ahn, I., Chang, S., Choi, S., Han, J., & Kim, Y. (2025). Exploration of Novel Biomarkers through a Precision Medicine Approach Using Multi-omics and Brain Organoids in Patients with Atypical Depression and Psychotic Symptoms. *bioRxiv*. https://doi.org/10.1002/advs.202508383

Almulla, A., & Maes, M. (2025). Peripheral Immune-Inflammatory Pathways in Major Depressive Disorder, Bipolar Disorder, and Schizophrenia: Exploring Their Potential as Treatment Targets. *CNS Drugs, 39*, 739 - 762. https://doi.org/10.1007/s40263-025-01195-3

Chen, Y., Dai, J., Tang, L., Mikhailova, T., Liang, Q., Li, M., Zhou, J., Kopp, R., Weickert, C., Chen, C., & Liu, C. (2022). Neuroimmune transcriptome changes in patient brains of psychiatric and neurological disorders. *Molecular Psychiatry, 28*, 710-721. https://doi.org/10.1038/s41380-022-01854-7

Dang, X., Song, M., Lv, L., Yang, Y., & Luo, X. (2023). Proteome-wide Mendelian randomization reveals the causal effects of immune-related plasma proteins on psychiatric disorders. *Human Genetics, 142*, 809-818. https://doi.org/10.1007/s00439-023-02562-0

Dardani, C., Robinson, J., Jones, H., Rai, D., Stergiakouli, E., Grove, J., Gardner, R., McIntosh, A., Havdahl, A., Hemani, G., Smith, D., Richardson, T., Gaunt, T., & Khandaker, G. (2024). Immunological drivers and potential novel drug targets for major psychiatric, neurodevelopmental, and neurodegenerative conditions. *Molecular Psychiatry, 30*, 4487 - 4496. https://doi.org/10.1038/s41380-025-03032-x

Ebstein, F., Küry, S., Papendorf, J., & Krüger, E. (2021). Neurodevelopmental Disorders (NDD) Caused by Genomic Alterations of the Ubiquitin-Proteasome System (UPS): the Possible Contribution of Immune Dysregulation to Disease Pathogenesis. *Frontiers in Molecular Neuroscience, 14*. https://doi.org/10.3389/fnmol.2021.733012

Erbescu, A., Papuc, S., Budisteanu, M., Arghir, A., & Neagu, M. (2022). Re-emerging concepts of immune dysregulation in autism spectrum disorders. *Frontiers in Psychiatry, 13*. https://doi.org/10.3389/fpsyt.2022.1006612

Fernandes, B., Dai, Y., Jia, P., & Zhao, Z. (2022). Charting the proteome landscape in major psychiatric disorders: From biomarkers to biological pathways towards drug discovery.. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology, 61*, 43-59. https://doi.org/10.1016/j.euroneuro.2022.06.001

Gong, W., Guo, P., Liu, L., Yan, R., Liu, S., Wang, S., Xue, F., Zhou, X., Sun, X., & Yuan, Z. (2024). Genomics-driven integrative analysis highlights immune-related plasma proteins for psychiatric disorders.. *Journal of affective disorders*. https://doi.org/10.1016/j.jad.2024.10.126

Lanz, T., Reinhart, V., Sheehan, M., Rizzo, S., Bove, S., James, L., Volfson, D., Lewis, D., & Kleiman, R. (2019). Postmortem transcriptional profiling reveals widespread increase in inflammation in schizophrenia: a comparison of prefrontal cortex, striatum, and hippocampus among matched tetrads of controls with subjects diagnosed with schizophrenia, bipolar or major depressive disorder. *Translational Psychiatry, 9*. https://doi.org/10.1038/s41398-019-0492-8

Liu, W., Li, L., Xia, X., Zhou, X., Du, Y., Yin, Z., & Wang, J. (2022). Integration of Urine Proteomic and Metabolomic Profiling Reveals Novel Insights Into Neuroinflammation in Autism Spectrum Disorder. *Frontiers in Psychiatry, 13*. https://doi.org/10.3389/fpsyt.2022.780747

Mehterov, N., Minchev, D., Gevezova, M., Sarafian, V., & Maes, M. (2022). Interactions Among Brain-Derived Neurotrophic Factor and Neuroimmune Pathways Are Key Components of the Major Psychiatric Disorders. *Molecular Neurobiology, 59*, 4926 - 4952. https://doi.org/10.1007/s12035-022-02889-1

Perry, B., Upthegrove, R., Kappelmann, N., Jones, P., Burgess, S., & Khandaker, G. (2021). Associations of Immunological Proteins/Traits with Schizophrenia, Major Depression and Bipolar Disorder: A Bi-Directional Two-Sample Mendelian Randomization Study. *Brain, behavior, and immunity, 97*, 176 - 185. https://doi.org/10.1016/j.bbi.2021.07.009

Pinzi, M., Fagiolini, A., Koukouna, D., Gualtieri, G., Rescalli, M., Pierini, C., Pardossi, S., Patrizio, B., & Cuomo, A. (2025). Inflammatory and Immune Biomarkers in Mood Disorders: From Mechanistic Pathways to Clinical Translation. *Cells, 14*. https://doi.org/10.3390/cells14191558

Poletti, S., Mazza, M., & Benedetti, F. (2024). Inflammatory mediators in major depression and bipolar disorder. *Translational Psychiatry, 14*. https://doi.org/10.1038/s41398-024-02921-z

Solomon, P., Budde, M., Kohshour, M., Adorjan, K., Heilbronner, M., Navarro-Flores, A., Papiol, S., Reich-Erkelenz, D., Schulte, E., Senner, F., Vogl, T., Kaurani, L., Krüger, D., Sananbenesi, F., Pena, T., Burkhardt, S., Schütz, A., Anghelescu, I., Arolt, V., Baune, B., Dannlowski, U., Dietrich, D., Fallgatter, A., Figge, C., Juckel, G., Konrad, C., Lang, F., Reimer, J., Reininghaus, E., Schmauß, M., Spitzer, C., Wiltfang, J., Zimmermann, J., Fischer, A., Falkai, P., Schulze, T., Heilbronner, U., & Poschmann, J. (2025). Disease Severity Across Psychiatric Disorders Is Linked to Pro-Inflammatory Cytokines. *bioRxiv*. https://doi.org/10.1101/2025.03.28.645923

Williams, J., Burgess, S., Suckling, J., Lalousis, P., Batool, F., Griffiths, S., Palmer, E., Karwath, A., Barsky, A., Gkoutos, G., Wood, S., Barnes, N., David, A., Donohoe, G., Neill, J., Deakin, B., Khandaker, G., & Upthegrove, R. (2022). Inflammation and Brain Structure in Schizophrenia and Other Neuropsychiatric Disorders. *JAMA Psychiatry, 79*, 498 - 507. https://doi.org/10.1001/jamapsychiatry.2022.0407

Yotova, A., Li, L., O'Leary, A., Tegeder, I., Reif, A., Courtney, M., Slattery, D., & Freudenberg, F. (2023). Embryonic and adult synaptic proteome perturbations after maternal immune activation: Identification of persistent changes relevant for early intervention. *Research Square*. https://doi.org/10.21203/rs.3.rs-3100753/v1