How have advances in Immunology spurred advances in understanding Neurodevelopmental and Psychiatric Disorders and their relationships to Immune Dysregulations across the Lifespan and other complicated diseases and disorders, including Auto-Immunity, Cancer and Neuro-Degenerations?

Immunoneuropsychiatry Links Brain Disorders to Immune Dysregulation Across the Lifespan

Advances in immunology have dismantled the doctrine of CNS immune privilege, revealing that immune processes are integral to brain homeostasis, resilience, and higher-order network function (Pape et al., 2019; Guo et al., 2026; Toader et al., 2024). This paradigm shift has reframed neurodevelopmental and psychiatric disorders as conditions with substantial immune-mediated pathophysiology, sharing mechanistic pathways with autoimmunity, cancer, and neurodegeneration (Pape et al., 2019; Nussinov et al., 2022; De Haan et al., 2017).

Shared Immune Mechanisms Across Disease Categories

Disease Category	Key Immune Mechanisms	Representative Conditions
Neurodevelopmental	Maternal immune activation, microglial pruning, innate immune signaling	ASD, ADHD, schizophrenia (Gagliano et al., 2025; Nussinov et al., 2022)
Psychiatric	Cytokine dysregulation, anti-neuronal autoantibodies, BBB disruption	Depression, bipolar disorder, PTSD (Pape et al., 2019; Gibney & Drexhage, 2013)
Neurodegenerative	Microglial priming, immunosenescence, chronic neuroinflammation	Alzheimer's, Parkinson's, ALS (Novellino et al., 2020; Chen et al., 2025)
Autoimmune	Molecular mimicry, self-reactive T cells, immune tolerance breakdown	Multiple sclerosis, autoimmune encephalitis (Pape et al., 2019; Segal et al., 2025)
Cancer	Paraneoplastic autoantibodies, IL-6–mediated inflammation	Lung cancer–associated limbic encephalitis (Novellino et al., 2020)

Pathways common to these disease categories include microglial activation, pro-inflammatory cytokines, molecular mimicry, anti-neuronal autoantibodies, self-reactive T cells, and blood-brain barrier disturbance (Pape et al., 2019). Genome-wide association studies have highlighted associations with immune system genes, including HLA and KIR regions, across Parkinson's, Alzheimer's, schizophrenia, and psychosis (Altmann, 2018). More than 60% of curated immune-related genes show significantly altered expression in at least one of six major brain disorders—schizophrenia, bipolar disorder, ASD, depression, Alzheimer's, and Parkinson's—with shared differentially expressed genes mainly related to innate immunity (Chen et al., 2022).

Lifespan Trajectory: From Fetal Development to Aging

- **Prenatal vulnerability**: Maternal immune activation during pregnancy is a well-recognized risk factor for neurodevelopmental disorders and schizophrenia in offspring, with the first 1000 days from conception being critical for neural, cognitive, and social-emotional development (Gagliano et al., 2025).
- **Familial clustering**: Co-occurrence of neurodevelopmental and autoimmune disorders within families indicates a shared genetic substrate, with increased ASD, ADHD, bipolar disorder, and depression risk in children of mothers with rheumatoid arthritis (Gagliano et al., 2025).
- **Inborn errors of immunity**: Monogenic immune disorders frequently present with neurodevelopmental or neurodegenerative manifestations through genetic overlaps in DNA repair, chromatin remodeling, and cytokine signaling (Xiao et al., 2025).
- **Immunosenescence**: Age-related immune dysregulation drives neurodegenerative progression in Alzheimer's and Parkinson's, with 11 proposed hallmarks including chronic inflammation, mitochondrial dysfunction, and cellular senescence (Chen et al., 2025).

Translational Frontiers and Therapeutic Targets

Mendelian randomization analyses have identified 29 immune-response biomarkers with potential causal roles across seven neuropsychiatric conditions, with 20 being therapeutically tractable—including ACE, TNFRSF17, and CD40, which have drugs in advanced clinical trials (Dardani et al., 2024). Neurodevelopmental disorders and cancer share signaling pathway involvement of small GTPases (Ras, RhoA, Rac) as well as TLR, IL-1, and FGFR pathways, with the decisive differentiating factors being timing windows and cell-type-specific perturbation levels (Nussinov et al., 2022). Paraneoplastic syndromes illustrate the cancer–immune–brain axis directly, as pulmonary and other neoplasms trigger autoimmune mechanisms producing autoantibodies that sustain limbic encephalitis with prominent psychiatric symptoms (Novellino et al., 2020).

Neuromodulation strategies—including vagus nerve stimulation and optogenetics—are being evaluated for their immune-modifying effects on neuronal function across neurodegenerative and psychiatric conditions (Hours et al., 2025; Guo et al., 2026). Nanotheranostic approaches aim to deliver immunomodulatory drugs precisely to affected CNS tissues, reducing systemic side effects (Rai et al., 2025; Toader et al., 2024). The emerging field of immunoneuropsychiatry calls for identifying phenotypically distinct but pathogenically related subgroups of neuropsychiatric disorders to enable mechanism-based immune treatments (Pape et al., 2019; Gagliano et al., 2025).

These advances converge on a transnosogenic framework in which immune dysregulation serves as a common denominator across neurodevelopmental, psychiatric, neurodegenerative, autoimmune, and neoplastic diseases, with shared pathways offering cross-disciplinary therapeutic targets (Novellino et al., 2020; Guo et al., 2026; De Haan et al., 2017).

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