H-ow has research evolved in seeing Neurodevelopmental and Psychiatric Disorders as isolated brain disorders to Developmental, Heterogeneous, Multi-System Neuro-Immune Disorders?

From **Isolated Brain Disorders** to **Multi-System Neuro-Immune** Conditions

Research has shifted from viewing neurodevelopmental and psychiatric disorders as brain-centric conditions toward understanding them as developmental, heterogeneous, multi-system disorders involving bidirectional communication between the immune system and the brain (Pape et al., 2019; Zengeler & Lukens, 2021; Volpedo et al., 2025). This evolution spans three conceptual phases: the brain-privilege paradigm, the discovery of homeostatic neuroimmune functions, and the current multi-system, transdiagnostic framework.

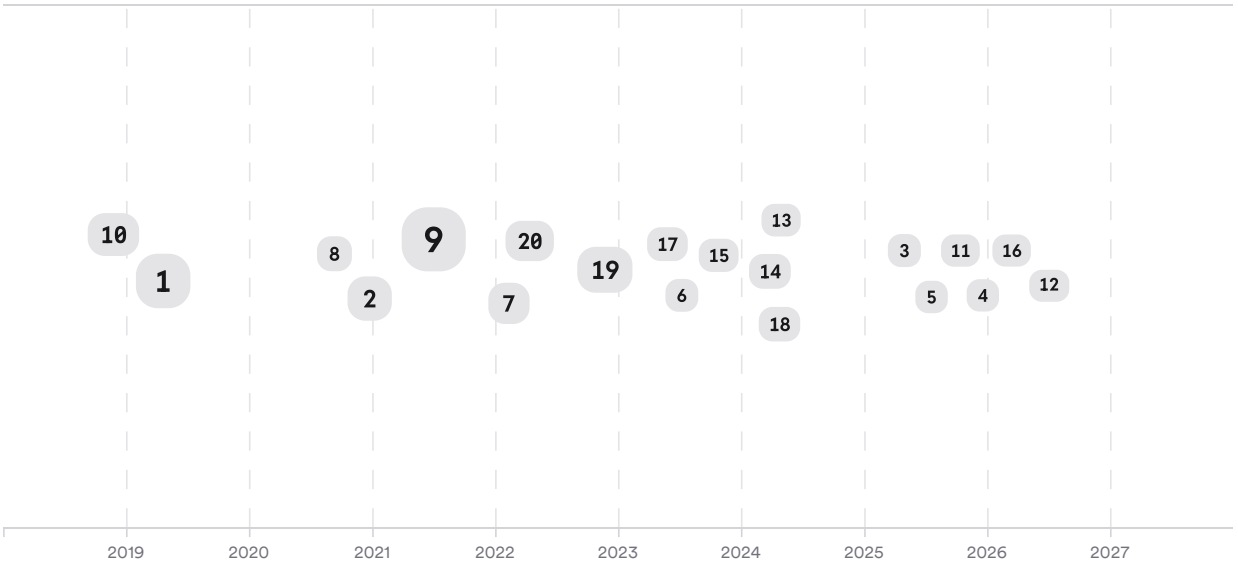

FIGURE 1 Evolution of neuroimmune conceptual frameworks across three research phases

The Brain-Centric Paradigm and Its Erosion

Historically, the brain was considered an immune-privileged site, and neurodevelopmental disorders were attributed primarily to genetic and structural brain abnormalities (Zengeler & Lukens, 2021; Yong et al., 2025). Neuropsychiatric conditions were classified categorically — as distinct disorders of brain function — with little consideration of peripheral immune contributions (Pape et al., 2019; Gagliano et al., 2025).

Early clues came from historical observations that neuropsychiatric symptoms followed infectious epidemics, from the 1385 German Flu through the 1918 Spanish Flu and modern COVID-19 (Monet & Quan, 2023). Large-scale epidemiological studies subsequently established that maternal infection during pregnancy significantly increased offspring risk for disorders including ASD, schizophrenia, and ADHD (Kwon et al., 2022; Han et al., 2021; Gumusoglu & Stevens, 2019). These findings were initially framed as evidence that inflammatory "intrusions" damaged an otherwise self-contained brain (Monet & Quan, 2023).

Discovery of Homeostatic Neuroimmune Functions

A major conceptual shift occurred when researchers discovered that immune cells and molecules — microglia, astrocytes, T cells, cytokines, complement, and MHC molecules — perform essential homeostatic roles in normal brain development, including synaptic pruning, circuit formation, and neural refinement (Monet & Quan, 2023; Zengeler & Lukens, 2021; Anderson et al., 2025; Martino et al., 2020). The term "neuroimmune" replaced "neuroinflammatory" to encompass these non-inflammatory, physiological functions (Monet & Quan, 2023).

This reframing meant that pathology could arise not only from inflammatory insults but also from inappropriate deviation — up or down — of normal neuroimmune activity during critical developmental windows (Monet & Quan, 2023). The long-held belief in brain immune privilege underwent a paradigm shift as extensive work showed that immune and nervous systems are critically intertwined from the earliest developmental stages (Zengeler & Lukens, 2021).

Conceptual Shift	Old Paradigm	New Paradigm
Brain-immune relationship	Immune-privileged, isolated organ	Intertwined systems from early development
Pathogenic mechanism	Inflammatory intrusion damages brain	Deviation of homeostatic neuroimmune activity
Classification	Categorical disease entities	Dimensional, transdiagnostic frameworks
System scope	Brain-only	Gut-immune-brain axis, peripheral crosstalk

FIGURE 2 Paradigm shifts in neurodevelopmental disorder conceptualization

Multi-System and Transdiagnostic Frameworks

The current paradigm integrates multiple organ systems and developmental timing into a unified framework. The gut-immune-brain axis is now recognized as a key pathway, with microbial dysbiosis modulating immune maturation, cytokine production, and blood-brain barrier dynamics (Leisman et al., 2026; Volpedo et al., 2025; Kwon et al., 2022; Martino et al., 2020). Maternal immune activation is understood as a "primer" that interacts with genetic susceptibility and later environmental hits — a multiple-hit model — rather than a singular cause (Zengeler & Lukens, 2021; Monet & Quan, 2023; Martino et al., 2020).

Genomic evidence further supports shared substrate: 50–90% of immune disorder genetic variants overlap with neurodevelopmental disorders, and pleiotropic loci map to common pathways including neural signaling, inflammatory response, and PI3K-Akt signaling (Xiu et al., 2024; Gagliano et al., 2025). Nationwide studies confirm familial co-clustering of NDDs with autoimmune diseases, and umbrella reviews of ~12.5 million participants link broad mental disorders to activated immune systems (Gagliano et al., 2025).

- **Dimensional classification**: The RDoC and HiTOP frameworks replaced categorical diagnoses with dimensional, transdiagnostic approaches examining mechanisms agnostic to diagnosis (Gagliano et al., 2025; Nusslock et al., 2024).
- **Immune heterogeneity**: Machine learning identifies three immunologically distinct NDD subgroups — enhanced neurogenesis, Th-1 polarization, or IL-1 signaling — rather than a shared mechanism (Sreenivas et al., 2023).
- **Transdiagnostic inflammation**: Inflammation is heightened across depression, bipolar disorder, schizophrenia, anxiety, and PTSD, pushing the field beyond single-disorder models (Nusslock et al., 2024; Pape et al., 2019).
- **Developmental cascade**: ASD models now conceptualize immune processes as modulators of developmental trajectories across distributed brain networks, not as a singular cause (Leisman et al., 2026).

Clinical and Therapeutic Implications

The shift to multi-system neuroimmune frameworks carries direct clinical consequences. Children with juvenile systemic autoimmune and autoinflammatory diseases are now recognized as at elevated risk for neurodevelopmental disorders, prompting calls for early screening and multidisciplinary management (Ellul & Melki, 2026). PANS (Pediatric Acute-Onset Neuropsychiatric Syndrome) exemplifies a transnosographic construct bridging neurodevelopmental, autoimmune, and psychiatric categories, with pre-existing neurodevelopmental abnormalities in 52–71% of cases (Gagliano et al., 2023).

Mechanism-based immune treatments are emerging, including IL-1β receptor blockade (anakinra) guided by inflammasome genotyping, and microglial modulation strategies (Gagliano et al., 2023; Yong et al., 2025; Pape et al., 2019). The emerging field of immunoneuropsychiatry calls for combined neurologist–psychiatrist expertise to identify phenotypically distinct but pathogenically related subgroups and deliver mechanism-based therapies (Pape et al., 2019). Future progress requires longitudinal, stratified research linking immune profiles to developmental timing, neural circuitry, and treatment responsiveness (Leisman et al., 2026; Yong et al., 2025).

The trajectory implies that neurodevelopmental and psychiatric disorders are neither isolated brain conditions nor purely immune diseases, but developmental multi-system disorders whose heterogeneity demands precision frameworks integrating genetics, immunity, microbiota, and environment across the lifespan.

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