How is the DSM and Symptom-Based Traditional Mental Health Care failing to recognize the importance of In-Born Errors of Immunity and Neuro-Immune Mechanisms in Neurodevelopmental & Psychiatric Disorders?

Symptom-Based Psychiatry Overlooks Immune Mechanisms in Neurodevelopmental Disorders

The DSM's symptom-based classification system fragments disorders by surface presentation rather than underlying pathophysiology, leaving immune-mediated subtypes unrecognized and untreated (Pape et al., 2019; Gagliano et al., 2025; Bertollo et al., 2025). Psychiatric diseases lack reliable diagnostic biomarkers and molecularly targeted therapies, a gap that persists partly because the brain's immune dimensions are excluded from diagnostic frameworks (Bennett & Molofsky, 2019).

Structural Limitations of Symptom-Based Classification

The DSM defines neurodevelopmental disorders by behavioral deficits in social, academic, or occupational functioning without reference to etiology (Bertollo et al., 2025). This approach groups phenotypically distinct but pathogenically related disorders separately, impeding identification of immune-mediated subgroups that cross diagnostic boundaries (Pape et al., 2019). A transnosographic approach — grouping disorders by shared pathogenic pathways rather than symptom clusters — has been proposed to capture the immune and neuroinflammatory mechanisms that span ASD, schizophrenia, OCD, and PANS (Gagliano et al., 2025; Bertollo et al., 2025).

DSM Limitation	Immune Mechanism Missed	Consequence
Behavior-only diagnostic criteria	Microglial activation, cytokine dysregulation, anti-neuronal autoantibodies	Immune-mediated subtypes go undetected (Pape et al., 2019; Siniscalco et al., 2018)
No immunological biomarkers	Elevated CRP, IL-6, TNF-α across diagnoses	No patient stratification by inflammatory status (Ermakov et al., 2022; Van Den Noortgate et al., 2025)
Siloed diagnostic categories	Shared neuroinflammation across NDDs and mood disorders	Fragmented, discipline-separated care (Bertollo et al., 2025)
Infection-centered IEI warning signs	Autoimmunity, hyperinflammation as sole presentation	~25% of IEI patients missed at initial presentation (Cortesi et al., 2024)

FIGURE 1 DSM structural limitations and their immunological consequences

Inborn Errors of Immunity Presenting as Psychiatric Disorders

Inborn errors of immunity (IEIs) are increasingly recognized as causing neurodevelopmental and psychiatric phenotypes that are routinely misdiagnosed under DSM categories without immunological investigation (Xiao et al., 2025; Jyonouchi, 2023). A substantial subset of IEI patients present with autism spectrum disorder, intellectual disability, or ADHD as primary diagnoses, while the underlying immune defect goes unrecognized (Xiao et al., 2025; Jyonouchi, 2023).

- **DiGeorge syndrome** (22q11.2 deletion) causes thymic hypoplasia and immunodeficiency, yet is often initially diagnosed as autism; ~30% of these patients develop schizophrenia (Xiao et al., 2025; Ermakov et al., 2022).
- **Ataxia-telangiectasia**, a DNA repair defect, produces combined immunodeficiency and cerebellar degeneration, illustrating how single genes affect both immune and neural development (Xiao et al., 2025).
- IEIs need not be rare or exclusively immunological — increasing numbers present with severe CNS dysregulation, and segregated specialty medicine delays their diagnosis (Akalu & Bogunovic, 2023).

Genetic overlaps between immunity and brain development — including defects in DNA repair, chromatin remodeling, and cytokine signaling — generate combined immunological and neurological phenotypes that DSM categories cannot capture (Xiao et al., 2025). Some ASD patients show laboratory evidence of neuroinflammation resembling IEI patterns, suggesting that gene-specific treatments used for IEIs could benefit ASD patients if immune mechanisms were recognized (Jyonouchi, 2023).

Neuro-Immune Mechanisms Across Diagnostic Boundaries

Immune dysregulation is a transdiagnostic pathway spanning schizophrenia, bipolar disorder, depression, ASD, and ADHD, yet the DSM's categorical structure prevents recognition of these shared mechanisms (Pape et al., 2019; Clerc et al., 2026; Van Den Noortgate et al., 2025; Sreenivas et al., 2023). Schizophrenia involves abnormalities across all immune system components — innate, adaptive, humoral, and cellular — with peripheral immune changes contributing to neuroinflammation and cognitive alterations (Ermakov et al., 2022). However, severe inflammation appears in only about one-third of schizophrenia patients, underscoring the need for immunological stratification that the DSM does not support (Ermakov et al., 2022).

- Machine learning identifies **three immunologically distinct NDD clusters** — enhanced neurogenesis, Th-1 polarization, or IL-1 signaling — that could serve as novel drug targets if diagnostically recognized (Sreenivas et al., 2023).
- Childhood maltreatment produces transdiagnostic pro-inflammatory elevations in psychiatric patients, with IL-6 mediating between trauma exposure and psychiatric diagnosis — a mechanism invisible to symptom-based categories (Van Den Noortgate et al., 2025).
- Maternal immune activation during gestation is a well-established risk factor for ASD and schizophrenia in offspring, yet DSM criteria do not incorporate perinatal immune history (Gagliano et al., 2025; Zengeler & Lukens, 2021; Hughes et al., 2022).

A cultural delay persists in accepting the brain as an organ susceptible to immune-inflammatory injury, rooted in the historical view of brain immune privilege and Cartesian mind-body dualism (Gagliano et al., 2025; Bennett & Molofsky, 2019). This delay reinforces the DSM's symptom-based framework and blocks adoption of mechanism-based immune treatments that could address subgroups currently lumped under heterogeneous diagnostic labels (Pape et al., 2019; Xiao et al., 2025; Gagliano et al., 2025). Without integrating immunological and genetic perspectives into psychiatric diagnosis, patients with treatable immune-mediated neuropsychiatric conditions remain misclassified and receive therapies that target symptoms rather than underlying disease mechanisms (Clerc et al., 2026; Cortesi et al., 2024).

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