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Neuroimmune crosstalk in psychiatric disorders: Emerging evidence and implications.

Prianka Puri*

Department of Immunology & Microbiology, Kings College, London, United Kingdom

Correspondence to: Prianka Puri, Department of Immunology & Microbiology, Kings College, London, United Kingdom, E-mail: pp473@uowmail.edu.au

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Introduction

Psychiatric disorders have long been viewed through the lens of neurotransmitter imbalances, genetic predispositions, and psychosocial stressors. However, a growing body of research is reshaping this paradigm by highlighting the role of the immune system in brain function and mental health. Neuroimmune crosstalk—the bidirectional communication between the nervous and immune systems—is now recognized as a key player in the pathophysiology of conditions such as depression, schizophrenia, bipolar disorder, and autism spectrum disorder (ASD). This emerging evidence opens new avenues for understanding, diagnosing, and treating psychiatric illnesses [1].

The central nervous system (CNS) was once considered immune-privileged, shielded from peripheral immune activity by the blood-brain barrier (BBB). Today, we know that immune cells, cytokines, and signaling molecules regularly interact with neural circuits. Microglia, the brain's resident immune cells, play a central role in this dialogue. They monitor synaptic activity, prune neural connections, and respond to injury or infection. Peripheral immune signals can also influence brain function. Cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) can cross the BBB or signal through neural pathways like the vagus nerve, impacting mood, cognition, and behaviour [2].

Major depressive disorder (MDD) is one of the most studied psychiatric conditions in the context of neuroimmune crosstalk. Elevated levels of pro-inflammatory cytokines have been consistently observed in patients with depression. Meta-analyses show increased IL-6, TNF-α, and C-reactive protein (CRP) in depressed individuals compared to healthy controls. Inflammation affects neurotransmitter metabolism, neuroplasticity, and the hypothalamic-pituitary-adrenal (HPA) axis. For example, cytokines can reduce serotonin availability by activating indoleamine 2,3-dioxygenase (IDO), which diverts tryptophan metabolism toward kynurenine—a pathway linked to neurotoxicity and mood disturbances [3].

Schizophrenia has traditionally been viewed as a neurodevelopmental disorder, but immune dysfunction is increasingly implicated. Genome-wide association studies (GWAS) have identified risk loci in the major histocompatibility complex (MHC) region, suggesting a genetic link to immune regulation. Patients with schizophrenia often exhibit elevated inflammatory markers and altered microglial activity. PET imaging studies reveal increased translocator protein (TSPO) binding—a marker of microglial activation—in the brains of individuals with schizophrenia. Stress-induced immune changes may contribute to psychiatric vulnerability. For example, elevated IL-6 and CRP levels have been linked to increased risk of depression following stressful life events. Understanding this interplay may help identify individuals at risk and guide preventive interventions. The recognition of neuroimmune crosstalk has spurred interest in immunomodulatory treatments for psychiatric disorders. Anti-inflammatory agents such as NSAIDs, minocycline, and cytokine inhibitors are being explored as adjuncts to standard therapies. Minocycline, a tetracycline antibiotic with anti-inflammatory properties, has shown promise in schizophrenia and depression. Tocilizumab, an IL-6 receptor antagonist, is under investigation for treatment-resistant depression. These findings

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support the hypothesis that neuroinflammation contributes to psychosis and cognitive deficits [4].

Bipolar disorder (BD) is characterized by mood swings that may reflect underlying immune shifts. Studies show that pro-inflammatory cytokines are elevated during manic and depressive episodes but tend to normalize during euthymic states. This cyclical pattern suggests that immune dysregulation may drive mood instability. Moreover, BD patients have higher rates of autoimmune diseases and inflammatory conditions, reinforcing the link between systemic immune activity and psychiatric symptoms. ASD is increasingly viewed as a disorder of neuroimmune development. Maternal immune activation (MIA) during pregnancy—triggered by infection or inflammation—has been associated with increased risk of ASD in offspring. Animal models show that MIA leads to altered microglial function, synaptic pruning, and behavioral abnormalities. Postmortem studies of ASD brains reveal increased microglial density and activation, suggesting persistent neuroimmune alterations. These findings highlight the importance of early-life immune events in shaping neurodevelopmental trajectories. Psychological stress is a potent modulator of immune function. Chronic stress activates the HPA axis and sympathetic nervous system, leading to increased production of glucocorticoids and catecholamines. These hormones can suppress adaptive immunity while promoting inflammation [5].

Conclusion

Neuroimmune crosstalk represents a transformative lens through which to understand psychiatric disorders. From inflammation-driven depression to immune-linked psychosis and neurodevelopmental disruptions in autism, the immune system plays a pivotal role in shaping brain function and behavior. As evidence mounts, integrating immunology into psychiatry promises to enhance diagnosis, personalize treatment, and ultimately improve outcomes for millions affected by mental illness.

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