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GUEST EDITORIAL

From peripheral blood neutrophils and monocytes to microglia in the brain: Converging evidence for innate immune activation in schizophrenia and major depression

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Major depressive disorder (MDD) and schizophrenia (SCZ) are traditionally treated as distinct diagnoses, yet converging evidence suggests that some pathophysiological mechanisms span the affective–psychosis spectrum (1). Innate immune activation has emerged as a potential link between peripheral myeloid alterations and microglia-related processes in the brain (1). This perspective provides a framework for integrating blood-based inflammatory findings with central nervous system dysfunction and supports stratified treatment approaches.

Genetic and epidemiological studies further link prenatal and lifetime infections, as well as autoimmune disease, to later risk of schizophrenia and mood disorders (2-4). In schizophrenia, the major histocompatibility complex locus on chromosome 6 represents one of the strongest common variant signals (4). Peripheral inflammatory proteins such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) are elevated in both disorders, although effect sizes, heterogeneity, and study designs vary (5).

This editorial integrates evidence from differential blood counts, positron emission tomography (PET) imaging, cerebrospinal fluid (CSF), and postmortem studies to examine whether a shared innate immune pathway links peripheral blood changes to microglia-related alterations in the brain. Proposed mechanisms include cytokine signaling, blood–brain barrier (BBB) dysfunction, complement-related pathways, and immune cell trafficking (Fig. 1). Peripheral cytokines (e.g., IL-1) can activate vagal afferents and the cholinergic anti-inflammatory reflex, enabling rapid immune-to-brain signaling. Complement components (C1q, C3, C4) may bridge peripheral innate immune activation and microglial synapse tagging in the central nervous system (CNS) (6). However, these data are largely cross-sectional and correlational and should be considered a working model rather than evidence of a causal sequence (1, 7-9).

PERIPHERAL INNATE IMMUNE ACTIVATION

Most psychiatric immunology research has focused on cytokines and mononuclear cells, but

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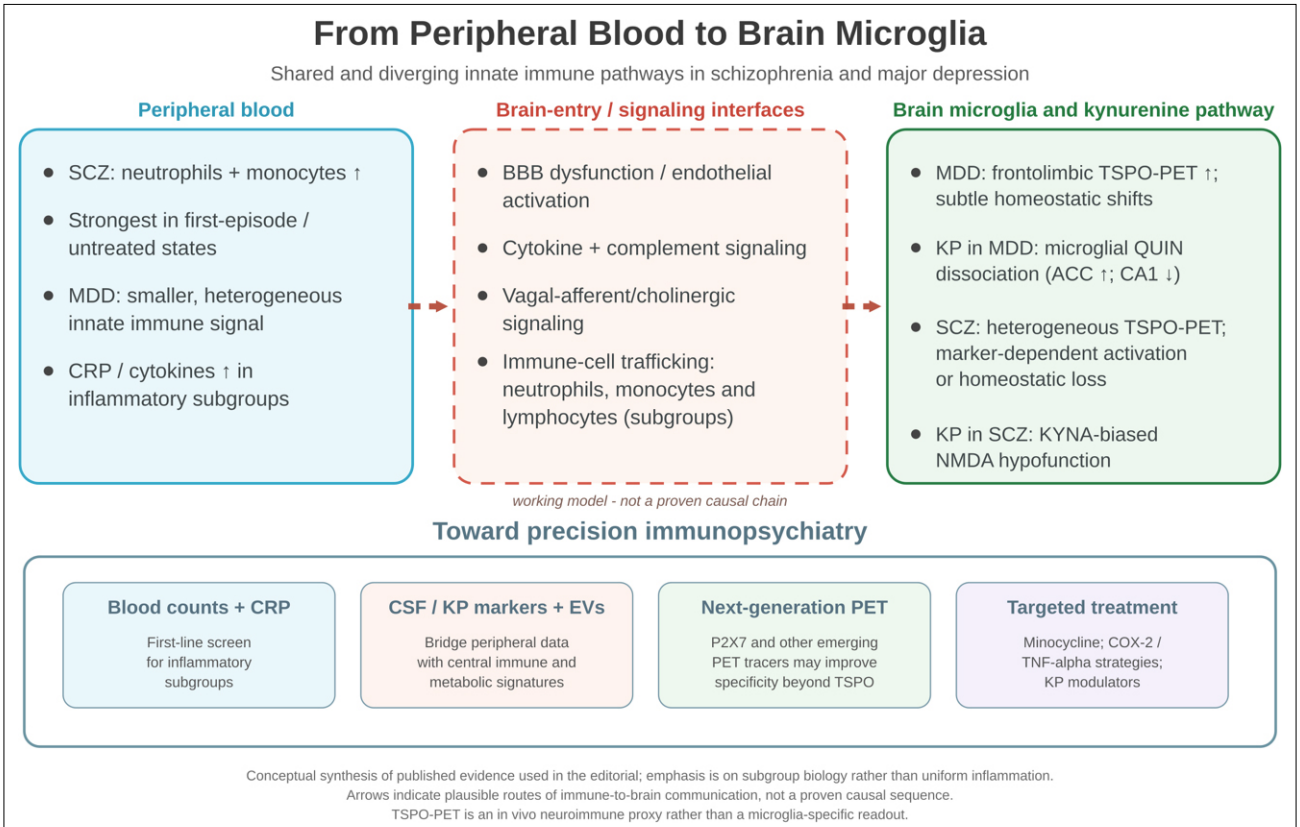

Figure 1. Conceptual bridge linking peripheral innate immune activation with central microglial and kynurenine pathway alterations in schizophrenia and major depression. Proposed routes of immune-to-brain communication include blood–brain barrier (BBB) dysfunction and endothelial activation, cytokine and complement signaling, vagal afferent/cholinergic anti-inflammatory pathways, and trafficking of peripheral innate immune cells (neutrophils and monocytes) and lymphocytes in selected subgroups. Downstream signatures appear to be partly disorder-specific. Major depressive disorder (MDD) is characterized by reproducible frontolimbic translocator protein positron emission tomography (TSPO-PET) elevations, subtle postmortem shifts in homeostatic microglial markers without a consistent classical activation pattern, and regionally dissociated microglial quinolinic acid (QUIN) signals (increased in anterior cingulate subregions and reduced in hippocampal cornu ammonis 1 [CA1]). Schizophrenia (SCZ) is associated with heterogeneous TSPO-PET findings, marker-dependent activation or homeostatic loss in postmortem studies, and a kynurenic acid (KYNA)-biased N-methyl-D-aspartate (NMDA)-hypofunction profile. TSPO-PET should be interpreted as an in vivo neuroimmune proxy rather than a microglia-specific readout. Arrows indicate plausible pathways within a conceptual working model rather than a uniform or established causal chain.

ACC: Anterior cingulate cortex; BBB: Blood–brain barrier; CA1: Cornu ammonis 1; COX-2: Cyclooxygenase-2; CRP: C-reactive protein; CSF: Cerebrospinal fluid; EVs: Extracellular vesicles; KP: Kynurenine pathway; KYNA: Kynurenic acid; MDD: Major depressive disorder; NMDA: N-methyl-D-aspartate; P2X7: Purinergic P2X7 receptor; PET: Positron emission tomography; QUIN: Quinolinic acid; SCZ: Schizophrenia; TNF-α: Tumor necrosis factor alpha; TSPO: Translocator protein.

granulocytes also deserve attention. In the largest meta-analysis to date, we found significantly elevated neutrophil and monocyte counts in schizophrenia, whereas other leukocyte populations were not consistently altered. This pattern suggests selective activation of innate immunity rather than generalized inflammation (9). The effects were strongest in first-episode and antipsychotic-naïve patients and attenuated with treatment (8, 9). Peripheral measures are also influenced by smoking, body mass index, acute stress, infection, and medication use (8).

In MDD, peripheral immune activation appears less specific and more heterogeneous. Meta-analyses demonstrate elevated neutrophil and monocyte counts, although lymphocyte findings are less consistent (10). In stage-sensitive clinical studies, we observed increased neutrophil counts and CRP levels during acute depressive episodes, with smaller effect sizes than those observed in schizophrenia (7).

Peripheral signals may also relate to brain alterations. In first-episode psychosis, higher neutrophil counts were associated with reduced gray matter volume and enlarged ventricles (11).

Mechanistically, neutrophils may transmigrate across a disrupted BBB into the brain parenchyma, contributing to neuroinflammation through chemokine-mediated pathways (12).

CENTRAL IMMUNE ACTIVATION: MICROGLIA

In addition to immune defense, microglia regulate synaptic pruning, neurotransmission, myelination, and BBB integrity. Our recent systematic review integrating translocator protein positron emission tomography (TSPO-PET) imaging, kynurenine pathway metabolism, and postmortem microglial markers across the affective–psychosis spectrum found that microglia-related alterations may map more closely onto symptom dimensions and biologically defined subgroups than onto conventional diagnostic categories (1).

In MDD, meta-analyses of TSPO-PET studies have reported increased binding, particularly in the hippocampus, cingulate, and prefrontal regions (13). In contrast, findings in schizophrenia are more heterogeneous and often non-significant, reflecting biological and cohort variability, as well as methodological differences (1, 14).

Postmortem findings further refine this distinction. In MDD, several studies suggest that microglia do not exhibit a classical pro-inflammatory phenotype. Instead, they demonstrate altered expression or compensatory shifts in homeostatic markers such as TMEM119, P2Y12/P2RY12, and CX3CR1 (15). We found increased quinolinic acid (QUIN)-positive microglia in subregions of the anterior cingulate cortex in patients with severe depression, indicating that region-specific and functionally relevant microglial alterations can occur in the absence of global classical activation (16).

In schizophrenia, one study reported increases in activation markers (17), whereas another found no overall increase in density but a reduction in mature microglial markers, suggesting impaired homeostatic identity rather than uniform classical activation (18). These findings may partly reflect infiltrating macrophages rather than resident microglia.

Findings in bipolar disorder are more limited but appear to place the disorder between the MDD and schizophrenia patterns, consistent with a dimensional rather than categorical interpretation (1). Overall, these findings suggest that microglial alterations vary according to brain region, disease stage, and biological subgroup.

THE KYNURENINE PATHWAY

The kynurenine pathway links immune signaling to glutamatergic neurotransmission. Inflammatory cytokines induce indoleamine 2,3-dioxygenase (IDO), diverting serotonin synthesis toward kynurenine metabolism (19, 20). Microglial kynurenine-3-monooxygenase (KMO) activity converts kynurenine into quinolinic acid, an N-methyl-D-aspartate (NMDA) receptor agonist with excitotoxic potential. Astrocytes lack KMO and instead metabolize kynurenine into kynurenic acid (KYNA), an NMDA receptor antagonist.

In MDD, evidence suggests region-specific increases in QUIN rather than global pathway activation. Elevated QUIN-positive microglia have been documented in anterior cingulate subregions, whereas reduced immunoreactivity has been observed in the hippocampus; CSF findings remain inconsistent (16, 21). This regional dissociation may reflect differential microglial KMO activity and local IDO-mediated kynurenine pathway activation within stress-sensitive circuits. In schizophrenia, the pattern shifts toward increased KYNA production (22), consistent with NMDA receptor hypofunction, a proposed feature of schizophrenia pathophysiology.

This distinction may have clinical relevance. MDD appears to involve regionally circumscribed, microglia-associated QUIN alterations within frontolimbic circuits, whereas schizophrenia is characterized more strongly by KYNA-related hypoglutamatergic signaling.

IMMUNE HETEROGENEITY AND BIOMARKER STRATIFICATION

A central finding across studies is heterogeneity. Only approximately 30% of patients with MDD exhibit elevated inflammatory markers or broader immune signatures (10). In schizophrenia, postmortem and transcriptomic studies have identified high-inflammation subgroups rather than a universal inflammatory phenotype, again in approximately one-third of cases (23). Consistent with these findings, increased densities of T and B lymphocytes have been observed in subsets of brains from patients with schizophrenia and mood disorders, suggesting that BBB dysfunction or immune cell trafficking occurs in some individuals (24). Analyses of such studies should carefully account for clinical variables including sex, illness phase, medication status, smoking, and metabolic factors, which may function more appropriately as stratifiers than as confounders.

This variability suggests that anti-inflammatory or microglia-targeted strategies are unlikely to benefit all patients. Adjunctive minocycline has shown some efficacy, particularly for negative symptoms in schizophrenia (25). Anti-inflammatory agents such as celecoxib and infliximab have demonstrated benefits in treatment-resistant depression among subgroups with elevated CRP levels (26, 27). Kynurenine pathway modulators are also attractive candidates because they directly target the immune-glutamate interface (20).

Future approaches should emphasize biomarker-guided stratification. Candidate biomarkers include differential blood counts, CRP, cytokines, CSF metabolites, microglia-derived extracellular vesicles, and next-generation PET tracers targeting microglial receptors (1). Integration with clinical phenotyping, dimensional symptom assessment, and computational clustering will also be essential for identifying biologically coherent subgroups.

OUTLOOK

Among currently available measures, differential blood counts represent the most pragmatic entry point for clinical application. In schizophrenia, elevated neutrophil and monocyte counts, particularly early in the disease course or before treatment, may serve as accessible markers of innate immune activation (9). In MDD, immune cell alterations appear more subtle and heterogeneous but may still support subgroup identification (7, 10).

The broader goal is the development of precision immunopsychiatry by linking peripheral profiles with BBB integrity, microglial phenotypes, and kynurenine pathway signatures to guide targeted interventions. Achieving this goal will require longitudinal studies, harmonized protocols, microglia-selective biomarkers, and biomarker-enriched clinical trials.

Future research should aim to identify which patients exhibit clinically relevant immune dysregulation. If successful, this approach could facilitate a transition from syndrome-based diagnosis toward mechanism-informed care in psychiatry.

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