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NEUROIMMUNE CROSSTALK IN BRAIN HEALTH AND DISEASE: EMERGING ROLES AND THERAPEUTIC TARGETS

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ABSTRACT

The brain and immune system talk constantly, swapping chemical whispers and electrical nudges that decide whether to stay sharp, forget, or fall apart. Here, we piece together the conversation: antigens seep from cerebrospinal fluid into dural sinuses where quiet T cells peek without triggering chaos; microglia slip lysosomal enzymes into neurons to keep lipid clocks ticking, but if the exchange stalls GM2 ganglioside piles up and lights the fuse of neurodegeneration; astrocytes ship cholesterol to remyelinating oligodendrocytes, yet in male mice the same cargo becomes a roadblock unless luteolin opens the efflux hatch. Danger signals ATP, HMGB1, misfolded proteins flip purinergic and TLR switches that weld NLRP3 inflammasomes, releasing IL-1β waves that travel from cortex to coronary arteries, linking stroke risk to mood dips. When the chatter derails, autism brains show IL-17 graffiti, lupus neutrophils spew NETs that shred the blood–brain barrier, Parkinson's mitochondria leak ROS that become microglia, and depressed hippocampi drowned in kynurenine. Vagus-nerve stimulation, SIRT1 boosters, NET-cutting DNase I, CGRP silencers, and programmable bioelectronic implants can reduce or increase the volume, but human trials remain small, short, and noisy.

KEYWORDS: neuroimmune crosstalk; microglia; astrocytes; vagus nerve; NLRP3 inflammasome; blood–brain barrier; neuroinflammation; bioelectronic medicine; Parkinson's disease; major depressive disorder.

1. INTRODUCTION

The Bidirectional Dialogue Between the Nervous and Immune Systems

The central nervous system (CNS) and immune system engage in a continuous and highly dynamic bidirectional dialogue that is fundamental for maintaining brain homeostasis, responding to infection, and orchestrating repair mechanisms. Neurons not only sense immune-derived mediators but also actively regulate immune functions through direct and indirect mechanisms. Neuronal receptors detect cytokines, chemokines, and other inflammatory mediators released by immune cells, enabling the rapid detection of local or systemic inflammation and communication with higher brain centers or local neural circuits.[1],[2],[3] In the gastrointestinal tract, cytokines stimulate enteroendocrine cells to release serotonin and other signaling molecules that activate enteric neurons to modulate gut motility and immune defense.[4] Thus, the immune system functions as an additional sensory organ that informs the nervous system of internal inflammatory cues, allowing coordinated and adaptive physiological responses.[5]

Conversely, neural outputs regulate immune cell activity through classical neurotransmitters and neuropeptides such as acetylcholine, norepinephrine, calcitonin gene-related peptide (CGRP), and substance P. These signaling molecules influence immune cell migration, cytokine synthesis, and differentiation.[1],[3] A well-characterized example is the vagus nerve–mediated "inflammatory reflex," where vagal efferent activity suppresses the overproduction of pro-inflammatory cytokines, thus limiting systemic inflammation and promoting tissue recovery.[2],[3] Both sympathetic and parasympathetic circuits contribute to this regulatory balance and can either amplify or suppress immunity depending on the receptor context, target tissue, and disease state.[2],[3],[5]

In addition, sensory neurons, including nociceptors, extend their roles beyond pain perception to actively shape adaptive immune responses within the peripheral organs. Sensory innervation of lymphoid structures, such as the presence of sensory fibers in splenic B cell zones, has been shown to enhance germinal center formation and antibody production through the release of CGRP and related neuropeptides.[6] In barrier tissues such as the skin, lungs, and gastrointestinal tract, sensory neurons detect pathogenic insults and instruct local

immune cells, contributing to protective immunity or, when dysregulated, to chronic inflammation and autoimmunity.[1],[7]

The defining features of this neuroimmune dialogue include speed, specificity, and bidirectional control. Neural modulation occurs within milliseconds, providing anatomically localized immune regulation that complements slower endocrine and paracrine pathways.[3,9] Depending on the neuronal circuit activated, the outcome may be immunosuppressive, such as vagus-driven inhibition of cytokine release, or immunopotentiating, as seen in sympathetic or sensory stimulation under certain contexts.[2],[3],[5] Moreover, neuroimmune interactions influence both the innate and adaptive immune arms by modulating macrophage activation, NK cell cytotoxicity, T cell priming, and B cell antibody responses.[6],[8],[9] Importantly, these effects are highly organ- and disease-specific; neural signaling that is protective in infection can become maladaptive in chronic inflammatory states, cancer, or neurodegeneration.[6],[10]

Mechanistic evidence supporting this phenomenon has been extensive in preclinical research. Animal models have delineated key cellular and circuit-level mechanisms, identifying the neurotransmitters, receptors, and intracellular pathways involved in neuroimmune regulation.[6],[7],[9] Systematic reviews and translational studies have further synthesized these findings and emphasized the potential of bioelectronic medicine and pharmacological neuromodulation to restore immune balance in diseases.[1,9,10] However, its clinical translation remains in its early stages, with only limited human trials confirming its consistent immunomodulatory outcomes. Interspecies differences in neural innervation, receptor expression, and immune architecture underscore the need for cautious interpretation and further validation in human systems.[3],[6],[10],[11]

In light of these insights, the present study aimed to comprehensively elucidate the concept, mechanisms, and translational implications of neuroimmune crosstalk. By integrating current mechanistic and clinical evidence, this study explored how neural and immune systems cooperate to preserve brain integrity and systemic equilibrium. This review further traces the historical evolution of the concept, from the outdated notion of immune privilege to the modern understanding of neuroimmune integration, and delineates the principal cellular and molecular mediators involved, including neurons, glial cells, cytokines, chemokines, and neuropeptides. Finally, it highlights the physiological importance of homeostatic neuroimmune signaling in maintaining brain plasticity, cognition, and neuroprotection, and

introduces experimental and clinical models that have shaped our understanding of this complex intersystem communication.

Section 2: Cellular and Molecular Mechanisms of Neuroimmune Crosstalk in the CNS

Neuroimmune crosstalk in the central nervous system (CNS) operates through multilayered mechanisms that encompass anatomical interfaces, cellular signaling, and receptor-mediated molecular pathways. Three major axes underpin this bidirectional communication.[12] anatomically privileged interfaces that enable immune surveillance and antigen sampling.[13] parenchymal cell–cell signaling networks linking microglia, astrocytes, and oligodendrocytes; and[14] pattern recognition and purinergic receptor–driven pathways that translate damage signals into inflammatory and neuromodulatory responses.

Anatomical interfaces as functional immune gateways At the CNS borders, the dural sinuses and meningeal niches act as regulated immunological portals. Rustenhoven et al.[13] demonstrated that cerebrospinal fluid (CSF) antigens accumulate adjacent to dural sinuses, where local antigen-presenting cells (APCs) engage patrolling T cells. These interactions are scaffolded by endothelial and mural stromal niches, which facilitate antigen capture and presentation. This spatial compartmentalization explains how peripheral adaptive immunity can monitor CNS-derived antigens without inducing widespread parenchymal inflammation. Such border immunology provides a mechanistic framework for T cell–glia communication in neuroinflammatory diseases, such as the multiple sclerosis (MS) models cited by the authors. These studies offer strong anatomical and mechanistic evidence through imaging, phenotyping, and functional assays; however, the absence of human quantitative data limits clinical extrapolation.

Microglia as enzymatic and trophic partners. Microglia serve as immune sentinels and metabolic regulators. Frosch et al.[15] identified a bidirectional biochemical mechanism by which microglia deliver β-hexosaminidase (HEXB) to neurons to control GM2 ganglioside turnover. In HEXB deficiency, neuronal GM2 accumulation activates microglial MGL2 via GalNAc residues, thereby triggering neurodegeneration. This discovery reframes microglia–neuron homeostasis as a metabolic partnership dependent on lysosomal enzyme transfer. The evidence encompassing lipidomics, spatial lipid imaging, single-cell transcriptomics, and cell-type-specific mutants in mice was corroborated by parallels in human Sandhoff disease. This study established microglia as active metabolic partners rather than passive immune

cells. However, while mechanistically robust, the generalizability beyond monogenic neurodegenerative diseases remains to be tested.

Microglia–astrocyte paracrine regulation Wheeler et al.[16] employed a droplet-based forward genetic screening platform (SPEAC-seq) to identify ligands that mediate astrocyte–microglia communication. This study revealed microglial amphiregulin (AREG) as a paracrine suppressor of disease-promoting astrocyte states in MS models and patient samples. This discovery links microglial trophic signaling to astrocytic immune phenotype modulation. Methodological rigor—high-throughput perturbation, functional co-culture assays, and in vivo validation— conferred causal weight to the findings. Although human quantification remains limited, this approach marks a transition from correlative cell-state mapping to mechanistic ligand–receptor axis identification.

Astrocyte–oligodendrocyte metabolic coupling in remyelination Astrocytes also modulate oligodendrocyte survival and remyelination via metabolic signaling. Molina-Gonzalez et al.[12] demonstrated that astrocytic Nrf2 activation and associated cholesterol biosynthesis/efflux pathways support oligodendrocyte regeneration. Persistent Nrf2 activation, however, impaired remyelination in male mice, an effect reversed pharmacologically (e.g., luteolin) or by stimulating cholesterol efflux. These findings define a metabolicredox axis that couples astrocyte homeostasis with myelin repair. The study integrates transcriptomics, functional assays, and human lesion analyses, although the reported sex-specific differences require further replication and patient-level confirmation.

Pattern recognition and purinergic receptor signaling Donnelly et al.[17] and Wang et al.[14] compiled evidence identifying pattern-recognition receptors (TLR4, Mincle), purinergic receptors (P2X7), and inflammasome components (NLRP3, TREM2) as central mediators linking metabolic and pathogen-associated danger signals to glial activation and neuronal modulation. Inflammasome-driven cytokine cascades, especially IL-1β release, mediate downstream neuroinflammatory responses. Notably, Wang et al. connected microglial activation pathways (TLR4, HMGB1, NLRP3, TREM2) to systemic cardiovascular effects, underscoring bidirectional neuroimmune coupling between the CNS and peripheral systems. Although these studies relied largely on animal and in vitro models, their convergence across diverse systems highlights the conserved architecture of neuroimmune signal transduction.

Section 3: Dysregulated Neuroimmune Interactions in Neurological and Psychiatric Disorders

Pavlov et al.[2] provided a foundational mechanistic framework describing bidirectional neuroimmune reflexes in which sensory neurons detect inflammatory cues and autonomic efferents modulate systemic immune responses. This model establishes a theoretical basis for bioelectronic and neuroimmunomodulatory interventions. While conceptually robust, the evidence is primarily narrative and mechanistic, and lacks definitive human causal trials.

Peripheral immune activation and maternal immune dysregulation have repeatedly been implicated in neurodevelopmental and psychiatric phenotypes. Han et al.[18] summarized the associations between maternal inflammatory states and offspring neurodevelopmental disorders, highlighting microglial priming and epigenetic imprinting as potential mediators. However, these studies are largely correlated with limited quantitative human data. Th17/IL-17 signaling has emerged as a pivotal mechanistic pathway; a systematic review of 28 rodent models reported consistently elevated IL-17 levels in autism spectrum disorder (ASD) paradigms. These findings strongly support preclinical causality but suffer from construct heterogeneity and a lack of longitudinal human cytokine datasets for validation.

In autoimmune and inflammatory CNS conditions, innate immune products, such as neutrophil extracellular traps (NETs), directly compromise BBB integrity. Guan et al.[19] synthesized evidence implicating NET-mediated endothelial injury and sterile inflammation in neuropsychiatric systemic lupus erythematosus (NPSLE), establishing a coherent molecular chain from peripheral inflammation to CNS pathology. Despite the strong mechanistic plausibility, no clinical trials have yet tested NET inhibition as a therapeutic strategy for NPSLE.

Human molecular profiling offers high-resolution insights into the neuroimmune landscape. Brase et al.[20] conducted single-nucleus RNA sequencing on approximately 300,000 nuclei from the parietal cortex of patients with Alzheimer’s disease (AD) and risk-variant carriers, uncovering distinct transcriptional immune and metabolic states in microglia, oligodendrocytes, and neurons. These data provide unprecedented evidence linking genetic susceptibility to cell-type–specific immune dysregulation. Nonetheless, the postmortem, cross-sectional design precludes the inference of temporal causality, and subject-level clinical correlations remain limited.

Tan et al.[21] integrated clinical, genetic, and experimental data implicating immune dysfunction in Parkinson's disease (PD) pathogenesis. Although immune activation is consistently observed, whether it represents a primary driver or secondary response remains debated. Similarly, Sarno et al.[22] reviewed immune alterations in major depressive disorder (MDD), noting proinflammatory cytokine activation, hypothalamic–pituitary–adrenal (HPA) axis crosstalk, and meningeal immune involvement. Although inflammatory subtypes of depression are increasingly recognized, clinical trials of immunomodulatory therapies have yielded modest and heterogeneous results, underscoring the need for biomarker-based patient stratification.

Emerging data also implicate the autonomic and gut–brain axes as amplifiers of neuroimmune dysregulation. Beopoulos et al.[23] proposed that autonomic nervous system (ANS) imbalance in ASD contributes to gut dysbiosis and sustained intestinal immune activation. This concept aligns with the vagal anti-inflammatory reflex outlined by Pavlov et al.[2], although direct interventional evidence in humans remains limited.

From a therapeutic perspective, multiple mechanistic nodes have been identified as potential targets, including the Th17/IL-17 axis, NET inhibition, SIRT1 activation, and neuropeptide modulation. Sharma et al.[24] reported that SIRT1 upregulation exerts neuroprotective and immunomodulatory effects in preclinical models, while Lu et al.[25] demonstrated that nociceptor-derived calcitonin gene-related peptide (CGRP) regulates neutrophil and macrophage responses to promote tissue repair. Although these findings provide valuable mechanistic insights, translation to the CNS context remains unproven and requires disease-specific validation.

4. Therapeutic Modulation of Neuroimmune Crosstalk — From Bench to Bedside

What is neuroimmune communication and why it matters

Neuroimmune communication refers to bidirectional signaling between the nervous system—including the brain, peripheral nerves, and glial cells—and the immune system, comprising microglia, macrophages, circulating leukocytes, and cytokines. These pathways orchestrate the initiation, propagation, and resolution of inflammation, as well as repair processes such as remyelination and synaptic remodeling. Dysregulated neuroimmune signaling is increasingly recognized as a central determinant of the disease trajectory in conditions characterized by neuroinflammation, including multiple sclerosis (MS), Parkinson's disease (PD), mood disorders with neuroinflammatory features, and other neurodegenerative disorders.

How modulation of neuroimmune communication alters disease course

Evidence from preclinical and translational studies has identified several consistent mechanisms whereby neuroimmune modulation can influence pathology.

1. Neural circuit modulation restrains inflammation

Dedicated neural reflexes, such as the vagus nerve-mediated "inflammatory reflex," can limit systemic inflammation. In experimental autoimmune encephalomyelitis (EAE), a well-established rat model of MS, vagus nerve stimulation (VNS) reduces clinical disease severity, decreases immune cell infiltration into the CNS, limits blood–brain barrier disruption, and alters microglial activation states. Notably, VNS also modulates gene expression linked to myelin synthesis, demonstrating both anti-inflammatory and pro-repair effects.[26]

2. Peripheral immune states influence central disease

Peripheral immune dysregulation can precede and shape CNS pathologies. Genetic progranulin deficiency, a risk factor for frontotemporal dementia, induces early changes in macrophage gene and protein expression (e.g., GPNMB), which in turn suppress stimulation-dependent cytokine release and disrupt central immune–neuronal interactions. These findings highlight peripheral immune cells as potential early therapeutic targets.[27]

3. Glia–immune cell interactions amplify neuroinflammation

Microglia and astrocytes coordinate CNS inflammatory responses and respond to mediators released by peripheral immune cells and tissue-resident mast cells. Maladaptive crosstalk between mast cells and glia can exacerbate neuroinflammation, promote neuronal sensitization, and accelerate disease pathways. Interventions that disrupt these maladaptive interactions may blunt disease progression and mitigate symptoms.[28]

4. Convergent oxidative/metabolic stress and immune activation

In PD and other neurodegenerative disorders, mitochondrial dysfunction, oxidative stress, and immune activation form interacting pathological loops. Reviews suggest that combined antioxidant and immune-modulating strategies—such as glutathione supplementation, N-acetylcysteine, lifestyle measures, and anti-inflammatory drugs—may slow disease progression, although clinical confirmation remains limited.[29]

5. Influence on psychiatric disease outcomes and treatment response

In mood disorders, elevated inflammatory markers are correlated with reduced antidepressant responsiveness. Mechanistic pathways include altered tryptophan/kynurenine metabolism, impaired neuroplasticity, and dysregulated T-cell responses. Prospective studies, such as those on bipolar disorder, link cerebrospinal inflammatory markers to subsequent clinical outcomes, but their predictive value is heterogeneous, emphasizing the need for individualized immune profiling.[30]

Mechanistic pathways of therapeutic modulation

Therapeutic modulation affects disease progression and treatment outcomes through several mechanisms.

- **Dampening pro-inflammatory signaling:** reduces microglial M1-like activation and bystander neuronal injury, preserving network integrity.
- **Enhancing pro-resolution pathways:** Promotes debris clearance and supports remyelination and synaptic repair via anti-inflammatory cytokines and M2-like microglial phenotypes.
- **Preserving blood–brain barrier integrity:** Limits peripheral immune cell infiltration and secondary damage.
- **Neural circuit modulation:** Vagal and autonomic interventions rapidly reshape systemic and central immune responses, yielding both symptomatic and structural benefits.[26],[30]
- **Peripheral immune interventions:** Targeting macrophages, T cells, or molecules such as progranulin/GPNMB can prevent or delay central inflammatory cascades if applied early.[27]

Limitations and gaps

Despite strong preclinical rationale, high-quality randomized clinical trial evidence for the disease-modifying effects of neuroimmune modulation in humans is scarce. Critical gaps include:

- Optimal timing of intervention (prodromal vs. late-stage disease).
- Patient heterogeneity (inflammatory phenotype, genetics, comorbidities) necessitates precision medicine approaches.
- Safety and off-target effects of chronic immune or neural modulation.
- Incomplete temporal mapping of causal links between peripheral immune changes and central pathology in humans.

CONCLUSIONS

Neuroimmune crosstalk has emerged as a master regulator of brain fate, translating peripheral infections, metabolic stress, and emotional states into glial activation patterns that can either protect or dismantle synapses. The same microglial receptor that clears debris during development can seed proteinopathy in disease; the vagal spike that tames cytokine storms in sepsis may also rescue memory in early Alzheimer's disease, yet these powerful levers remain blunt instruments outside of animal models. Closing the translation gap requires longitudinal human maps that couple real-time neural recordings with single-cell immune phenotyping, clinical-grade closed-loop stimulators that titrate cytokines instead of heart rate, and trial designs that randomize patients by inflammatory endotype rather than diagnosis. If we succeed, tomorrow's neurology wards will look more like hybrid electro-immune operating rooms, where neurologists and immunologists co-program implants that speak fluent chemokines and deliver timed bursts of neuroprotection—turning chronic neurodegeneration into a preventable, tunable network disorder.

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