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Cross-Organ
Neuroimmunology of Behavior

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Abstract

Here we introduce the Cross-Organ Neuroimmunology of Behavior (CONB) Network, a framework that reconceptualizes behavior as an emergent property of a distributed, whole-body immune–brain network. It builds on knowledge of neuroimmune communication, including cytokine modulation of neural activity and synaptic plasticity, neuroglial–immune interactions, and neuroendocrine pathways, forming a shared language for cross-organ signaling. We examine how peripheral organs function as network nodes, translating local immune or physiological changes into systemic signals that influence brain circuits and behavior. Integrating these axes reveals emergent network properties, such as redundant pathways (degeneracy) that enhance resilience and hub organs that exert disproportionate influence on network stability. This model links complex behavior to multisystem disease cross talk, reframing brain diseases as systemic network dysregulation. Ultimately, the CONB Network perspective informs precision medicine by leveraging immune biomarkers to identify patient subtypes and guide therapeutic strategies to recalibrate cross-organ neuroimmune networks and restore system-wide homeostasis.

INTRODUCTION

The nervous and immune systems maintain a dynamic, bidirectional dialogue throughout the body, enabling the brain to “sense” and respond based on the status of peripheral organs, which in turn secrete factors that shape brain function and behavior profoundly. Classic sickness behavior—characterized by fatigue, anhedonia, and cognitive changes—illustrates how peripheral immune activation triggers central symptoms via cytokines, while neural signals emanating from the brain can conversely regulate the immune system. Recent advances have revealed discrete circuits and molecular mediators linking organs such as the gut, lungs, liver, and heart and immune reservoirs such as the spleen and bone marrow to the central nervous system (CNS), emphasizing the role of both local and long-range neuroimmune interactions (1, 2).

To unify these diverse discoveries, we propose the Cross-Organ Neuroimmunology of Behavior (CONB) Network—a conceptual framework for a distributed system wherein behavior emerges as a network-level output. In this framework, nodes are defined as discrete functional units, such as an organ (e.g., liver, lung), a tissue (e.g., bone marrow), or a specific cell population (e.g., microglia). These nodes are connected by edges, which represent the pathways of information flow, including physical connections such as neural circuits and chemical signaling via circulating immune mediators, such as cytokines, metabolites, or hormones. This concept extends classical psychoneuroimmunology by elevating cross-organ immunoregulation to a primary determinant of behavioral state. Within this network, specific nodes function as hubs, characterized by their high degree of connectivity (high degree centrality) and their critical role in integrating and distributing information. The gut and bone marrow, for example, represent such hubs: The gut integrates vast inputs from diet and microbiota into systemic immune and metabolic signals, while the bone marrow’s hematopoietic output dictates the immune tone of the entire organism. Perturbation at these hubs can thus disproportionately affect the stability and function of the entire network.

In this review, we first establish the molecular and cellular principles that enable the CONB Network (see the section titled Foundational Mechanisms of Neuroimmune Communication). We then examine each peripheral organ axis—the gut, lung, liver, heart, skin, muscle, bone marrow, and spleen—as functional nodes within this network (see the section titled The Organ-Wide Neuroimmune Network: Peripheral Axes Influencing Behavior). Finally, we integrate these axes to illustrate network-level dynamics and discuss emerging therapeutics that target the CONB Network as an integrated whole (see the section titled Systems-Level Integration and Therapeutic Implications).

FOUNDATIONAL MECHANISMS OF NEUROIMMUNE COMMUNICATION

The classical conception of CNS function posits it is an immune-privileged organ operating through a specialized lexicon of neurotransmitters and neuropeptides, largely insulated from immunological insults in the periphery. This view, however, is being supplanted by a paradigm that recognizes a profound and continuous dialogue between the nervous and immune systems—one conducted in a shared molecular language (3, 4). This common lexicon challenges the notion of systemic separation, revealing instead a deeply integrated regulatory network wherein molecules once considered exclusive to one system—such as cytokines, chemokines, and even components of the complement cascade—act directly on neural cells, while classical neural signals reciprocally modulate immune function. The biological meaning encoded by this language is not fixed; rather, it possesses a sophisticated grammar in which the context—including signal concentration, duration, and the specific cellular “listener”—determines the ultimate physiological and behavioral

output (5). Understanding this shared lexicon and its contextual syntax is fundamental to decipher how peripheral states such as infection, metabolic stress, and psychological trauma are translated into adaptive or maladaptive shifts in CNS function and complex behavior.

A primary consequence of this neuroimmune dialogue is the acute and pervasive regulation of brain-wide neurotransmission, a process that functionally reallocates the brain's resources to orchestrate global shifts in behavioral state, such as the induction of sickness behavior. This acute modulation is remarkably comprehensive, targeting all aspects of neurotransmitter and neuropeptide signaling, from synthesis and release to reuptake and degradation. Pro-inflammatory cytokines, for instance, can systemically deplete the foundational precursor for serotonin synthesis by activating the indoleamine 2,3-dioxygenase pathway, which shunts tryptophan toward the production of neuroactive kynurenines, while tumor necrosis factor- α (TNF- α) concurrently enhances serotonin reuptake via the serotonin transporter—a combination that potently contributes to the anhedonic and depressive phenotypes associated with inflammation (6, 7). Simultaneously, these immune signals retune circuits governing motivation and reward by attenuating evoked dopamine release in structures such as the nucleus accumbens (8). This state of diminished motivation is often compounded by a global shift toward neuronal hyperexcitability. Cytokines such as TNF- α and IL-1 β can induce glutamate-mediated excitotoxicity through a dual mechanism: stimulating glutamate release from activated microglia and astrocytes while simultaneously impairing its clearance by downregulating astrocytic transporters such as EAATs (excitatory amino acid transporters) (8, 9). The brain's delicate excitatory-inhibitory balance is further perturbed by context-dependent modulation of GABA (γ -aminobutyric acid)ergic signaling and the induction of a central cholinergic deficit, driven by inhibited acetylcholine synthesis and enhanced degradation (10). This coordinated neurochemical reconfiguration is expanded by neuropeptidergic and neurotransmitter systems governing stress and arousal, such as corticotropin-releasing hormone (CRH) and norepinephrine, which are acutely engaged to orchestrate the broader neuroendocrine components of the sickness response (11, 12). The regulatory network is tuned by chemokines, which, in addition to their canonical chemotactic roles, function as direct neuromodulators. For example, CCL2 (C-C motif chemokine ligand 2) promotes neuronal hyperexcitability, and CX3CL1 (C-X3-C motif chemokine ligand 1) mediates homeostatic synaptic scaling (13–15). These are not stochastic events but rather a highly organized, adaptive program initiated by the immune system to inform the brain of systemic danger signals, thus shifting its operational state away from long-term, resource-intensive goals and toward immediate survival.

While the acute effects of immune signals on neurotransmission are critical for immediate behavioral adaptation, a more profound and lasting consequence of this dialogue emerges when communication becomes chronic or overly intense and leads to long-lasting structural and functional remodeling of neural circuits. Prominent among these changes is the disruption of synaptic plasticity, long thought of as the cellular basis of learning and memory (16). Pro-inflammatory cytokines, such as IL-1 β , can disrupt hippocampal long-term potentiation by activating pathways such as p38 MAPK, which inhibits essential neurotrophic signaling via brain-derived neurotrophic factor (BDNF) and its receptor, TrkB (tropomyosin receptor kinase B) (17). Should the inflammatory stimulus persist, the system can further disrupt synaptic function by physically eliminating synapses via mediation by the complement cascade, a pillar of innate immunity co-opted in the CNS for circuit refinement. In pathological states, pro-inflammatory signals drive the excessive deposition of complement components, particularly C1q and C3, which “tag” synapses for elimination by microglia (18). This mechanism of synaptic pruning is pathologically accelerated in neurodegenerative diseases and implicated in the excessive synaptic loss observed in schizophrenia, leading to irreversible structural damage to the brain (19, 20). Lastly, epigenetic reprogramming mechanisms, encoded by neural and glial cells following immunological insults, can establish a



persistent memory that changes neural circuit function through regulation of gene expression (21). Cytokines orchestrate these modifications by influencing key enzymes, such as by recruiting histone deacetylases to silence plasticity-related genes or by altering DNA methyltransferase activity to repress the expression of genes such as BDNF (22). Concurrently, the regulation of noncoding RNAs, including microRNAs such as miR-146a and miR-124, fine-tunes inflammatory and neuronal gene networks, establishing long-lasting cellular states such as microglial priming, wherein cells become persistently hyperreactive to subsequent stimuli (23). Similarly, astrocytes can develop an epigenetically encoded “memory” of inflammation. For example, Lee et al. (24) showed that repeated inflammatory challenge drives astrocytes to acquire an ACLY (ATP-citrate lyase)- and p300-dependent chromatin signature that primes them for heightened pro-inflammatory responses upon rechallenge. This sequence of events, from functional disruption to structural remodeling to epigenetic modifications for long-term storage, provides a powerful framework for understanding the transition from acute insult or sickness to chronic neuropsychiatric and neurological disease.

These molecular and structural transformations are not abstract processes but are orchestrated by a dynamic and interacting cellular ensemble, consisting of both CNS-resident glia and immune cells recruited from the periphery. Microglia, the primary resident immune cells, act as the first responders, using pattern-recognition receptors to sense danger and release the very cytokines that drive acute neurotransmitter changes. They are also the primary effectors of complement-mediated synaptic pruning, physically engulfing tagged synapses—a function tightly regulated by signals, such as CX3CL1 and CD200, released locally by neurons. Astrocytes, which are often cued by microglial signals, act as crucial partners of the neuroinflammatory response, undergoing reactive astrogliosis to adopt context-dependent phenotypes spanning neurotoxic/pro-inflammatory to neuroprotective states, rather than a binary A1/A2 designation (25–27). They are central executors of excitotoxicity, contributing to both the release and impaired clearance of glutamate (28), and can even upregulate MHC-II to participate in antigen presentation (29). Oligodendrocytes and oligodendrocyte precursor cells (OPCs) are primarily responsible for myelination, which is critical for efficient communication between the brain and the rest of the body. But they also play critical roles in regulating CNS repair and circuit and synaptic plasticity following immune activation. Like other glial cells, OPCs can engulf synapses to regulate synaptic plasticity or can differentiate and remyelinate neural circuits after injury, processes that are regulated by immune–oligodendrocyte interactions (30, 31). Notably, recent work demonstrates that oligodendrocyte-lineage cells can function as antigen-presenting cells in neuroinflammatory conditions. Using single-cell transcriptomics and spatial transcriptomics in experimental autoimmune encephalomyelitis (EAE) and multiple sclerosis (MS) lesions, Falcão and colleagues (32) identified subsets of OPCs and mature oligodendrocytes that upregulate MHC-II core genes (i.e., *H2-aa*, *H2-ab1*, *H2-eb1*, *Cd74*) and confirmed that MHC-II⁺ OPCs can phagocytose antigens and activate CD4⁺ T cells. Complementary analyses by Calabresi’s group (33, 34) show that inflammatory OPCs and immune oligodendroglia upregulate antigen-processing genes for both MHC-I and MHC-II; Cd74-enriched oligodendrocyte clusters were detected in EAE and human MS tissue. These findings indicate that oligodendroglia are active participants in adaptive immunity rather than passive targets.

In addition to local mechanisms of neuroimmune regulation, systemic immune compartments can also contribute to the processes described above. When a threat overwhelms local CNS defenses, a critical phase shift occurs, wherein the recruitment of peripheral immune cells amplifies local CNS resident immune responses. Monocytes are recruited from the blood via chemokines such as CCL2, across a compromised blood-brain barrier (BBB), and differentiate into macrophages that exacerbate neuroinflammation (35). The direct behavioral impact of

this infiltration is profound, as demonstrated by findings that chronic stress elevates circulating myeloid-derived matrix metalloproteinase-8 (MMP-8), which infiltrates the nucleus accumbens to directly drive tissue matrix restructuring, synaptic plasticity, and social avoidance behavior (36). Lymphoid cells introduce further nuance, particularly at the CNS borders. While certain T cell subsets [e.g., T helper 1 cells (Th1)/Th17] can drive autoimmunity, others are integral to behavioral regulation: For instance, meningeal T cells producing IFN- γ can directly influence brain circuits that regulate social behavior (37), while meningeal $\gamma\delta$ T cells producing IL-17 modulate anxiety (38). Recent evidence also reveals that chronic stress can dysregulate B cell homeostasis, leading to the production of brain-reactive autoantibodies, and thereby provides a direct mechanistic link between psychological stress and CNS-targeted autoimmunity (39). This layered choreography, from resident glial activation to peripheral immune trafficking and infiltration, underscores the complex cellular dynamics that translate the shared language of neuroimmunology into lasting changes in brain function and behavior. **Figure 1** presents these mechanisms in a three-panel road map that progresses from peripheral signal entry at the neurovascular interface

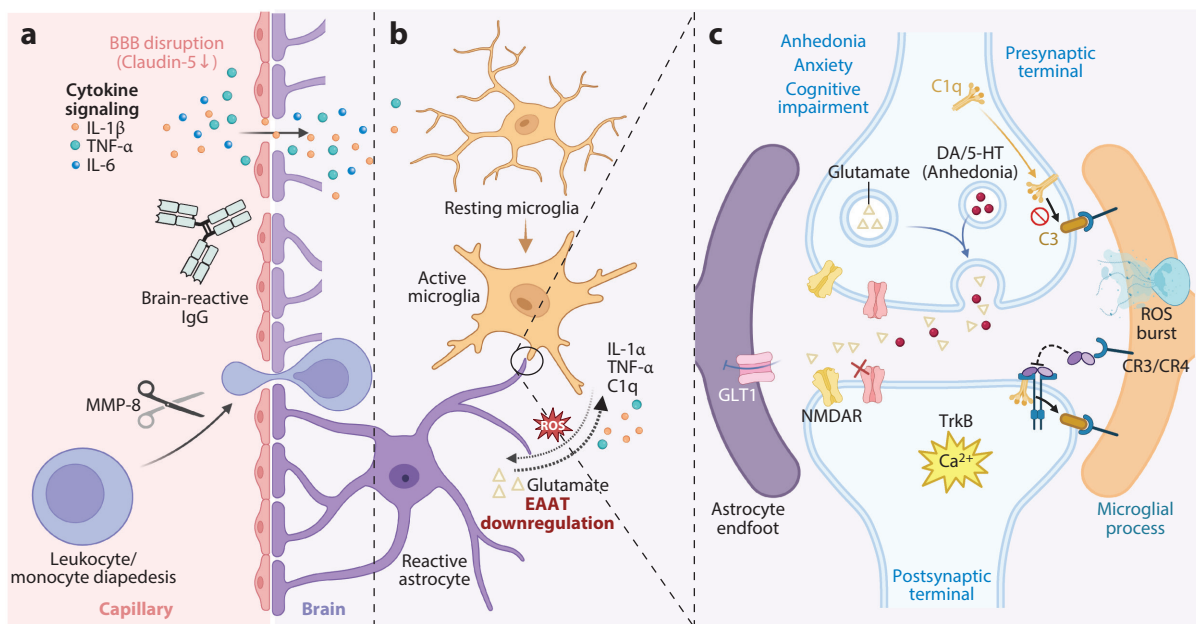


Figure 1

A multi-panel illustration of core cellular and molecular pathways in the central nervous system, linking peripheral immune signals to the glial transduction and synaptic remodeling that underlie behavioral changes. (a) Peripheral signals enter at the neurovascular interface. BBB disruption shows tight junction breakdown by inflammatory mediators. MMP-8 degrades extracellular matrix while brain-reactive autoantibodies (i.e., IgG) breach the barrier. Monocyte diapedesis and release of cytokine (e.g., IL-1 β , TNF- α , IL-6) initiate neuroinflammatory cascades at astrocyte endfeet. (b) Glial activation and signal amplification. Activated microglia release inflammatory mediators (e.g., cytokines, ROS, glutamate), triggering astrocytes to adopt a pro-inflammatory, neurotoxic-reactive phenotype via IL-1 α , TNF- α , and C1q signaling. Reactive astrocytes downregulate EAAT, amplifying glutamate dysregulation. (c) Synaptic alterations and behavioral outcomes. Glutamate excitotoxicity through NMDAR overactivation and complement-mediated synaptic pruning (via complement component C1q and C3) result in synaptic loss. Reduced neurotransmitter (e.g., dopamine, serotonin) signaling and impaired BDNF-TrkB signaling contribute to anhedonia, anxiety, and cognitive impairment. Abbreviations: 5-HT, serotonin; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CR3, complement receptor 3; CR4, complement receptor 4; DA, dopamine; EAAT, excitatory amino acid transporter; GLT1, glutamate transporter 1; MMP-8, matrix metalloproteinase-8; NMDAR, N-methyl-D-aspartate receptor; ROS, reactive oxygen species; TNF- α , tumor necrosis factor- α ; TrkB, tropomyosin receptor kinase B. Figure adapted from images created in BioRender; Guo X. 2025. <https://BioRender.com/s94y7pe>.

(Figure 1a) through glia-mediated transduction (Figure 1b) to activity-dependent synaptic remodeling (Figure 1c) and thereby paves the way for the network-level analysis that follows.

Having established these foundational molecular and cellular principles of neuroimmune communication, we now examine how these universal mechanisms are specifically deployed and integrated within the diverse peripheral organ nodes of the CONB Network. In the next section, we dissect the unique contributions of each central organ axis—from the gut to the lymph nodes—to the overall regulation of behavior.

THE ORGAN-WIDE NEUROIMMUNE NETWORK: PERIPHERAL AXES INFLUENCING BEHAVIOR

Building on the foundational mechanisms outlined above (Figure 1), we now turn to individual organ axes, examining each as a functional node within the CONB Network. Figure 2 offers

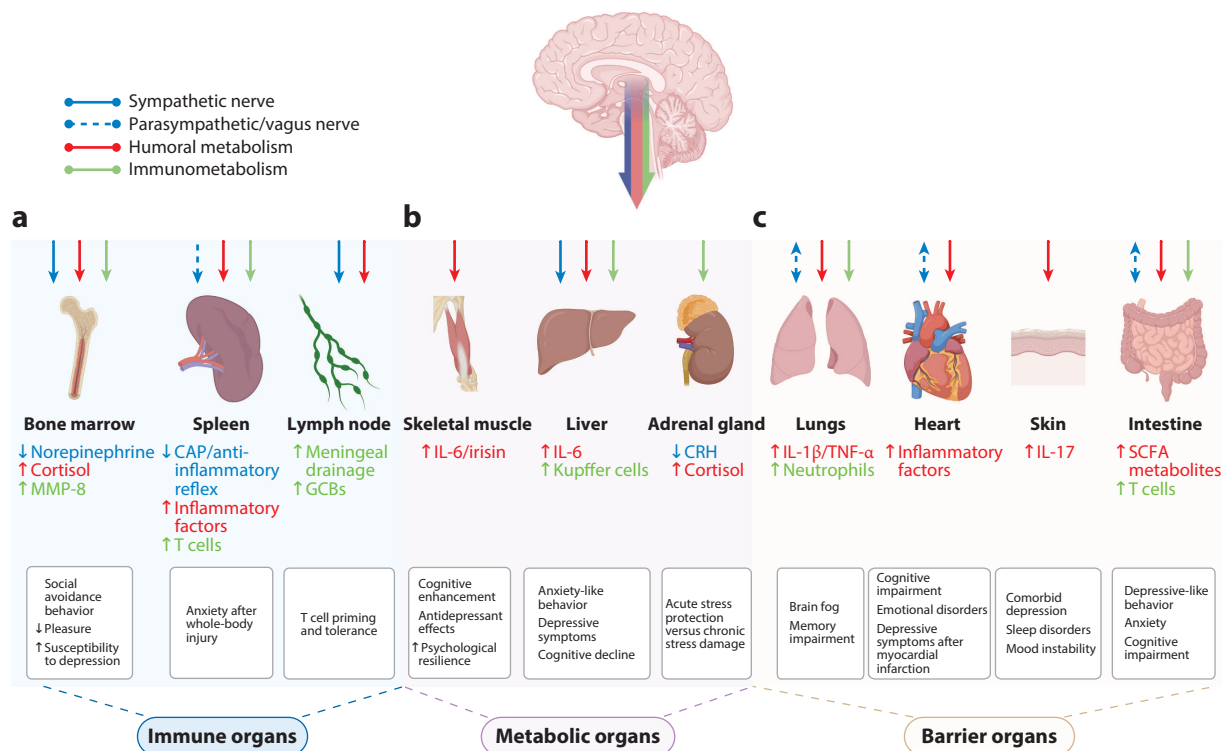


Figure 2

Semi-anatomical overview of the CONB Network, mapping neural and humoral connections between major peripheral organs and the brain as an integrated whole-body framework. (a) Immune organs: The bone marrow, the spleen, and lymph nodes are shown as primary immune-responsive organs involved in immune cell production, trafficking, and inflammatory regulation. (b) Metabolic organs: Skeletal muscle, the liver, and adrenal glands are depicted as key metabolic regulators coordinating neuroimmune signaling through microbial metabolites, hepatic cytokines, and stress hormones. (c) Barrier organs: The lungs, heart, skin, and intestine are represented as tissue interfaces that respond to environmental challenges and mechanical stressors. Color-coded arrows indicate communication modalities: solid blue (sympathetic nerve), dashed blue (parasympathetic/vagus nerve), red (humoral metabolism), and green (immunometabolism). Bidirectional arrows are used to emphasize reciprocal organ–brain communication. Abbreviations: CAP, cholinergic anti-inflammatory pathway; CONB, Cross-Organ Neuroimmunology of Behavior; CRH, corticotropin-releasing hormone; GCB, germinal center B cell; MMP-8, matrix metalloproteinase-8; SCFA, short-chain fatty acid; TNF- α , tumor necrosis factor- α . Figure adapted from images created in BioRender; Guo X. 2025. <https://BioRender.com/hh4s61a>.

a semi-anatomical overview that maps primary and secondary organ nodes, their neural or humoral edges, and the central brain hub, providing readers with a systems-level compass for the subsections that follow.

Intestine (Gut–Brain–Immune Axis)

Within the CONB Network, the intestine functions as a primary contextual modulator and a high-traffic hub that continuously translates microbial and dietary signals into systemic immune responses and that thereby shapes neuroimmune tone throughout life (1). The gut microbiota, a key component of this axis, releases metabolites such as short-chain fatty acids (SCFAs) that are essential for the homeostatic maturation and function of CNS microglia, thereby influencing neurodevelopment, cognition, and mood (40–47). In addition to SCFAs, gut microbes metabolize dietary tryptophan into small-molecule ligands (e.g., indole derivatives) for the aryl hydrocarbon receptor (AHR) expressed by microglia and astrocytes. Activation of the AHR by these microbial metabolites modulates glial inflammatory responses and can ameliorate CNS inflammation in autoimmunity models (48). Perturbations of this hub, such as dysbiosis driven by stress, antibiotics, or even sex hormone fluctuations, can alter systemic immunity via breakdown of epithelial barriers and increased gut permeability (“leaky gut”). This compromised barrier allows microbial products, such as endotoxins, and immune signaling molecules (e.g., those involving Th17/IL-17) to reach the brain via circulation or vagal afferents, contributing to neuroinflammation and alterations in behavior (49–51).

This axis is characterized by robust bidirectional communication. Descending neural circuits, such as the stress-activated pathway from the paraventricular nucleus of the hypothalamus (PVN) CRH⁺ neurons to the enteric nervous system of the colon, can directly drive intestinal inflammation and barrier disruption, demonstrating top-down control over this peripheral node (52). Conversely, ascending signals from the gut have a profound influence on brain states (53, 54). These complex bidirectional interconnections position the gut–brain axis as not merely a contributor to pathology but also a critical interface where other contextual factors, such as early-life programming, stress, and diet, exert their lasting effects on brain health. Consequently, interventions targeting the gut microbiota that affect local immunity [e.g., probiotics, fecal microbiota transplantation (FMT)] represent promising strategies for modulating the entire CONB Network and hold therapeutic potential for a range of brain diseases (40, 55, 56).

Adrenal Glands (Hypothalamic–Pituitary–Adrenal Axis and Stress Immunology)

The adrenal glands are the primary effector nodes of the central stress response, converting neural signals into systemic hormonal cascades that exert potent but time-dependent control over immunity and behavior. Acutely, elevated glucocorticoids (GCs) typically exert potent anti-inflammatory effects, suppressing pro-inflammatory cytokine production, limiting immune cell activity, and thereby protecting the brain from excessive peripheral inflammation—a role highlighted by heightened neuroinflammation in adrenalectomized animals lacking endogenous GCs (1, 57). Concurrently, catecholamines released from the adrenals during acute stress influence leukocyte trafficking and inflammation (58). This neuroendocrine–immune communication is bidirectional, as immune signals also trigger hypothalamic–pituitary–adrenal (HPA) activation, and adrenal hormones such as GCs modulate immune cell functions, including T cell differentiation, which can affect stress resilience (5).

However, chronic or severe stress disrupts this finely tuned system, leading to HPA dysregulation, altering GC receptor sensitivity, and impairing immune homeostasis. Sustained high cortisol levels can induce GC resistance, resulting in a paradoxical failure to suppress inflammation and



even in the exacerbation of stress-related neuroimmune pathology (5, 59). This chronic maladaptation is linked to persistent microglial activation, increased NF- κ B inflammatory signaling within limbic circuits, and subsequent anxiety- and depressive-like behaviors (57, 60). Furthermore, early-life stress can impart lasting epigenetic modifications to GC receptor genes, predisposing individuals to lifelong alterations in stress responsivity and increased risk for developing mood disorders (5, 59, 60). Thus, the adrenal glands serve as a critical neuroimmune nexus—a role complemented by other endocrine nodes, such as the thyroid, where autoimmune dysregulation can also drive neuroinflammation, independent of hormonal status.

Lungs (Pulmonary–Immune–Brain Interaction)

The lungs act as a key sentinel node in the CONB Network: At the body's largest environmental interface, they translate immune challenges—from respiratory infections to airborne pollutants—into systemic inflammatory signals that drive behavioral changes. Chronic respiratory conditions such as chronic obstructive pulmonary disease (COPD) and severe asthma, which are linked clinically to increased rates of depression, anxiety, and cognitive deficits, exemplify this connection. Experimental models have confirmed that chronic allergic lung inflammation elevates systemic cytokines that induce depressive-like behaviors through the central neuroinflammatory pathways discussed in the section titled Foundational Mechanisms of Neuroimmune Communication (61, 62). Acute respiratory infections, such as bacterial pneumonia or severe viral infections, also have a robust impact on the CNS. Pathogens such as *Pseudomonas aeruginosa* provoke a systemic cytokine surge (of IL-1 β , IL-6, and TNF- α) that leads to substantial neuroinflammation and behavioral abnormalities, often mediated by BBB disruption and endothelial activation, even with limited direct pathogen invasion of the brain parenchyma (63, 64).

The COVID-19 pandemic has starkly illuminated these lung–brain neuroimmune interactions. Even mild respiratory SARS-CoV-2 infections can trigger persistent neuroinflammation, the dysregulation of myelin-producing oligodendrocytes, and impaired hippocampal neurogenesis, all of which are linked to enduring cognitive deficits, including memory and attention problems (65–67). Long COVID frequently involves chronic cognitive impairments (e.g., brain fog) that are associated with elevated circulating cytokines (e.g., CCL11) and hippocampal microglial activation and that phenotypically resemble neuroinflammatory syndromes seen after chemotherapy (65). The impact of such pulmonary insults is often exacerbated by aging, as the age-related pro-inflammatory state (“inflammaging”) and primed microglia render the brain more vulnerable to the secondary neuroinflammatory consequences of respiratory distress (68). Furthermore, environmental factors play a significant role: The inhalation of particulates, such as silica, triggers pulmonary inflammation that can induce hippocampal inflammation and disrupt synaptic function, ultimately leading to cognitive deficits (69). These examples highlight multiple pathways—including circulating cytokines, immune cell trafficking, and neural routes such as vagal afferents—through which pulmonary events influence brain health. Therapeutically, effective management of lung inflammation, such as the use of anti-inflammatory biologics (e.g., anti-IL-17A) for asthma, correlates with improvements in mood and cognition, and this correlation underscores the importance of the lung as a key therapeutic target for associated neuropsychiatric conditions (61, 62). These findings position the lung–brain axis as a key modulator of CONB Network-mediated sickness behavior and cognitive fog following infection.

Skin (Cutaneous Neuroimmune System and Behavior)

The skin represents a unique CONB Network node where localized neurogenic inflammation, exemplified by the itch–scratch cycle, can escalate to drive systemic consequences for mood and

sleep. It often participates in a broader gut–lung–skin axis—a concept reflecting the clinical co-occurrence of inflammatory conditions, such as atopic dermatitis (AD) (skin), asthma (lung), and inflammatory bowel disease (gut), across these three significant environmental barriers. Richly innervated by sensory neurons and populated by diverse immune cells (e.g., mast cells, dendritic cells, T cells), the skin mediates local sensations such as itch and pain and contributes to systemic inflammation. Psoriasis, for example, is associated with heightened systemic inflammatory cytokines (e.g., IL-17, TNF- α), which contribute to comorbid depression by engaging the foundational neuroimmune mechanisms outlined above (70, 71). Similarly, AD, characterized by intense itch (pruritus) and chronic inflammation, involves intricate neuroimmune cross talk wherein cytokines such as IL-31 and neuropeptides, released by immune cells and sensory nerves, perpetuate a cycle of itching and inflammation, severely disrupting sleep and mental well-being (72, 73). Specific signaling networks involving neuronal receptors, such as IL-31R and Mrgprs (Mas-related G protein–coupled receptors), are crucial mediators of these chronic itch responses (74, 75).

Neuroimmune communication within the skin involves critical cell–cell interactions. In mast cell–sensory neuron loops, mast cells release histamine and cytokines, stimulating neurons, and neurons modulate mast cell activity, thereby sustaining allergic and inflammatory symptoms (76, 77). Recent findings also suggest that skin-infiltrating neutrophils contribute to chronic itch through CXCR3 (C-X-C motif chemokine receptor 3) signaling (78). Notably, the impact of inflammatory skin diseases extends beyond the site of local neuroimmune activation in the skin, affecting sleep patterns and cognitive functions through mechanisms that are likely to involve increased circulating cytokines and subsequent neuroinflammation. This impact is particularly evident in AD patients, in whom disease severity strongly correlates with sleep disturbances and psychological distress (79). Therapeutically, targeting cutaneous neuroimmune pathways shows significant promise: Biologic therapies inhibiting specific cytokines (e.g., IL-17, IL-4/13, TNF- α) effectively treat skin lesions while concurrently alleviating associated mood disorders, and these effects underscore the direct skin–brain neuroimmune link and reinforce the skin’s integral role in psychoneuroimmunology (70, 71).

Heart (Cardio–Neuro–Immune Interactions)

Within the CONB Network, myocardial infarction (MI) flips the heart from injured target to inflammatory hub: Dying cardiomyocytes alert resident macrophages, while danger signals recruit from circulation neutrophils and CCR2 (C-C motif chemokine receptor 2)⁺ monocytes that release IL-1 β , IL-6, and TNF- α , which are linked with post-MI depression and cognitive decline. These cytokines also circulate to blood–brain interfaces to activate microglia and trigger neuroinflammation, which impairs mood and cognitive function (80). A surge in sympathetic activity post-MI leads to the release of norepinephrine to mobilize immune cells and enhance inflammation via β -adrenergic receptors, while vagal loss disrupts the cholinergic anti-inflammatory pathway (CAP), pushing immune cells toward pro-inflammatory states and reinforcing this cardio–neuro–immune loop (35, 81). Aging, a primary risk factor for cardiovascular events, also primes the neuroimmune system for exaggerated responses, creating a scenario wherein post-MI inflammation leads to more severe neuroinflammatory consequences and behavioral deficits in older individuals (82, 83). MI serves as a critical example, triggering a potent systemic inflammatory response characterized by the mobilization of monocytes and neutrophils from reservoirs, such as the spleen and bone marrow. These cells infiltrate the damaged heart, releasing cytokines (e.g., IL-1 β , IL-6, TNF- α) that drive post-MI depression and cognitive decline; these results are consistent with the established effects of systemic inflammation on central neural circuits (84, 85). Therapeutic targeting of this inflammation, exemplified by minocycline treatment, effectively



reduces brain inflammation and depressive symptoms in preclinical models, and this reduction underscores the cardio–neuroimmune connection (86).

In addition to local inflammatory pathways engaged within the heart, distinct neural pathways connecting cardiac and arterial signals to specific brain areas that govern immune regulation, emotional processing, and stress responses have been revealed in recent work, highlighting a network that integrates multisystem diseases (87). Chronic heart failure further illustrates these neuroimmune dynamics, with persistent elevations in inflammatory cytokines such as TNF- α correlating strongly with cognitive deficits and mood disturbances. The identification of specific mechanisms, such as angiotensin II–driven neuroinflammation in the hippocampus, as contributing to cognitive impairment in heart failure suggests potential therapeutic targets (88). Adding another layer of complexity, recent research has revealed that sleep plays a crucial role in regulating post-MI cardiac inflammation. Sleep quality, modulated by monocytic TNF signaling in brain nuclei, influences cardiac sympathetic output, thereby affecting myocardial inflammation and recovery. Disrupted sleep exacerbates cardiac injury, and this effect emphasizes a vital bidirectional sleep–cardio–neuroimmune interaction (89).

These collective insights pave the way for novel intervention strategies extending beyond traditional cardiovascular care. Treatments targeting neuroinflammation, modulating autonomic function (e.g., via vagal nerve stimulation), and incorporating behavioral factors such as sleep optimization offer promising avenues for synergistically improving cardiovascular and mental health outcomes (90, 91). In summary, the heart has a significant influence on neuroimmune-driven behaviors through complex, bidirectional pathways that involve systemic inflammation, dedicated neural circuits, and autonomic regulation, and this impact thereby establishes the central role of the heart within the broader framework of psychoneuroimmunology.

Muscles (Exercise, Myokines, and Brain Function)

Skeletal muscle functions as a powerful health-promoting node within the CONB Network, primarily through the activity-dependent release of anti-inflammatory and neurotrophic myokines during exercise. Physical exercise stimulates the release of numerous myokines, which have profound neuroimmune effects. Notably, muscle-derived IL-6 acts predominantly as an anti-inflammatory signal by enhancing IL-10 and cortisol secretion while suppressing TNF- α and contributing to the antidepressant and anxiolytic effects of exercise (92, 93). Exercise also activates PGC-1 α (peroxisome proliferator-activated receptor- γ coactivator-1 α)-dependent kynurenine metabolism within muscle, reducing circulating neurotoxic kynurenine and protecting the brain from stress-induced depression (94, 95). Furthermore, myokines such as cathepsin B and FNDC5 (fibronectin type III domain-containing 5) (which can be cleaved to produce irisin) can cross the BBB, stimulate BDNF production, and promote neurogenesis, synaptic plasticity, and cognitive enhancement (92, 96). These mechanisms underlie the broad neuroprotective impacts of regular exercise observed in conditions such as Alzheimer's disease or depression, wherein myokines help counteract pathology and preserve cognition, and contribute to exercise's robust antidepressant effects and influence on psychological resilience (97–99).

Conversely, conditions involving muscle atrophy, disuse, or inflammation (e.g., cachexia, chronic diseases) can negatively affect cognitive function. Under these states, peripheral inflammatory signals originating in muscles may propagate to the CNS, contributing to neuroinflammation and subsequent behavioral impairments and thereby highlighting a bidirectional brain–muscle pathway (100, 101). Thus, a major focus of current research is to develop therapeutics that harness muscle-derived signals to promote brain health. Strategies that involve the use of exercise-mimicking pharmacological agents or muscle-targeted treatments, such as electrical

stimulation, show promise in preclinical models for enhancing hippocampal neurogenesis and cognitive function (102, 103). Collectively, skeletal muscle significantly influences brain health and neuroimmune regulation through dynamic endocrine and immunological pathways, with this influence offering novel therapeutic avenues for treating cognitive decline and mood disorders and reinforcing muscle's essential role in psychoneuroimmunology.

Liver (Metabolic–Immune Interface and Brain Impact)

The liver serves as the central immunometabolic hub of the CONB Network, integrating signals from the gut with the systemic metabolic state to regulate the inflammatory tone that shapes brain function and behavior. Resident hepatic immune cells, especially Kupffer cells, respond to gut-derived signals such as endotoxins by releasing pro-inflammatory cytokines (e.g., IL-6, IL-1 β , TNF- α). These mediators can affect the brain via circulation and impair cognitive and emotional functions. This connection is evident in widespread conditions, such as metabolic dysfunction–associated steatotic liver disease (MASLD); chronic liver inflammation correlates with elevated systemic cytokines, although clinical studies are associative (104, 105), whereas experimental MASLD models demonstrate that hepatic inflammation drives peripheral and central cytokine release and consequent neuroinflammation (104). Animal studies directly link diet-induced hepatic steatosis and inflammation to resultant neuroinflammation, brain hypoxia, and anxiety- or depressive-like behaviors, underlining the neurotoxic potential of hepatic inflammation (106).

Advanced liver dysfunction introduces additional neuroimmune challenges, such as hyperammonemia, a metabolic condition marked by increased ammonia levels in the blood that can significantly exacerbate neuroinflammation and cognitive deficits, and involves mechanisms such as increased peripheral cytokine signaling and direct impairment of astrocyte function (107). Similar pathways operate in hepatic encephalopathy, wherein elevated systemic ammonia and inflammation impair astrocyte autophagy, worsening neuronal dysfunction and cognitive decline (108, 109). Significantly, the gut microbiota profoundly mediates these liver–brain interactions. Modulation of the gut microbiome—for instance, through probiotic supplementation (e.g., *Akkermansia muciniphila*)—can exert neuroprotective effects in liver disease models by reducing inflammation and enhancing brain-supportive pathways involving BDNF and serotonin (110, 111). Therapeutic interventions targeting peripheral inflammation, such as anti-TNF- α treatment, have successfully reversed cognitive impairments in hyperammonemic models, and this reversal confirms a causal role for liver-derived inflammation in neuroimmune dysfunction (107).

Given these complex interactions, targeting hepatic health offers significant therapeutic potential for associated neurological and neuropsychiatric symptoms. Interventions addressing liver inflammation and metabolic disturbances—ranging from dietary modifications and probiotics to bariatric surgery and specific anti-inflammatory therapies—are crucial for achieving broader neurocognitive benefits. Collectively, liver-driven systemic inflammation, metabolic dysregulation (including factors such as ammonia), and modulation via the gut microbiota critically shape brain function and behavior. This metabolic–immune interface is further influenced by the pancreas, where diabetes-associated inflammation and hormones, such as GLP-1 (glucagon-like peptide 1), also affect neuroimmune health (112, 113). This influence reinforces the liver's prominent position in psychoneuroimmunology research and highlights hepatic health as a crucial strategy for maintaining optimal brain function and emotional well-being.

Bone Marrow (Hematopoietic Origins of Neuroimmune Responses)

The bone marrow acts as a primary hematopoietic node of the CONB Network, where central stress signals directly reprogram the production of myeloid cells, and thereby shapes the



nature and intensity of peripheral immune responses that influence the brain. Chronic stress activates sympathetic neuron inputs that innervate bone marrow to release norepinephrine, which skews hematopoietic stem cell (HSC) differentiation toward pro-inflammatory myeloid lineages (36, 114, 115). Especially during aging or under psychological stress, these inflammatory monocytes subsequently infiltrate the brain, where they interact with microglia and the extracellular matrix to drive behavioral alterations (36, 116). This stress-induced shift in myelopoiesis can be programmed by early-life adversity, which establishes a long-term pro-inflammatory bias in hematopoietic output, and creates a lasting vulnerability to stress-related psychopathology (115). Specific molecular pathways underscore this link: Psychological stress elevates vasopressin, which acts on HSCs via the IL-36 γ -IL-1RL2 axis to promote the generation of inflammatory monocytes, and thereby contributes to depressive-like behaviors upon brain homing (117). Furthermore, circulating monocyte-derived factors, such as MMP-8, can infiltrate specific brain regions (e.g., the nucleus accumbens) to modulate synaptic plasticity and can thereby provoke depressive-related behavior in stress-susceptible states (36). The direct influence of the hematopoietic system on emotional states is strongly supported by bone marrow transplant studies, in which the transfer of pro-inflammatory marrow transmits susceptibility to anxiety and depressive-like symptoms, while healthy marrow normalizes behavior in recipients with impaired behavior (118, 119).

Mechanistically, bone marrow-derived monocytes often utilize chemokine signals, such as CCR2, for trafficking to brain compartments. Under severe situations when these cells infiltrate the CNS parenchyma, they can adopt microglia-like phenotypes, amplifying neuroinflammatory cascades and contributing to stress sensitization and cognitive impairments (116, 120). Recent evidence suggests that the skull bone marrow may be a localized source for immune cell trafficking into adjacent meningeal and brain tissues, as supported by both rodent and human imaging studies that link skull marrow inflammation to markers of depression (121, 122). Therapeutic strategies targeting this bone marrow-brain communication axis have shown promise in preclinical models for reducing anxiety and depressive behaviors; these strategies include agents that block sympathetic signaling to marrow, modulating HSC output toward anti-inflammatory lineages, or that pharmacologically inhibit trafficking molecules such as CCR2 (123, 124). In summary, the bone marrow serves as a dynamic interface, translating psychological stress into altered peripheral immunity that directly influences neuroimmune tone and emotional behavior, and this role thereby establishes the bone marrow as a pivotal organ in the field of psychoneuroimmunology.

Spleen (Peripheral Immunity and the Inflammatory Reflex)

The spleen functions as a key neuro-autonomic interface and immune cell reservoir pool within the CONB Network; this role is best exemplified by the CAP, which allows the brain to suppress systemic inflammation directly. The spleen receives sympathetic innervation, modulated by efferent vagus nerve fibers, forming the neural basis of the CAP. In this reflex, vagal signals lead to the release of norepinephrine into the spleen, which acts locally on acetylcholine-producing T cells. The subsequent release of acetylcholine stimulates $\alpha 7$ -nicotinic receptors on splenic macrophages, thereby suppressing the production of TNF- α and other pro-inflammatory cytokines (125). Activation of this “inflammatory reflex” dampens systemic inflammation, thereby reducing sickness behavior and delirium during infection, while its disruption (e.g., via splenic nerve transection) exacerbates inflammatory pathology. Complementing this anti-inflammatory circuit, distinct neural pathways also mediate behaviorally driven immunity: CRH-expressing neurons in the amygdala and PVN connect to the splenic nerve to regulate plasma cell formation, with behavioral or pharmacogenetic stimulation enhancing antigen-specific antibody production via $\alpha 9$ -nicotinic receptors on B cells (126).

Bidirectional communication is also prominent, with the spleen acting as a crucial reservoir and source of immune cells influencing distant organs. Under conditions of stress or injury (e.g., stroke, MI), the spleen mobilizes monocytes that can traffic via circulation to the CNS or heart, where they contribute significantly to sustained inflammation and correlate with worse behavioral outcomes—such as increased anxiety-like behavior and impaired sensorimotor/cognitive function. Consequently, splenectomy can reduce this infiltration and improve recovery in animal models, albeit at the expense of long-term host defense. Furthermore, the spleen functions as a neuroimmune relay in chronic conditions. Specific neuronal populations (e.g., in the somatosensory cortex and amygdala) regulate splenic Th2 immune responses via vagal projections, modulating peripheral inflammation in response to pain states (127). In cardiovascular disease, a heart–brain–spleen reflex involving splenic PIGF (placental growth factor) secretion regulates adaptive cardiac remodeling following pressure overload (128).

Because of these pathways, the spleen is increasingly targeted for therapeutic modulation. Bioelectronic approaches, such as focused ultrasound stimulation of the spleen, activate anti-inflammatory neuroimmune circuits, demonstrating potential in conditions such as pulmonary hypertension (129). Vagus nerve stimulation (VNS), approved for treatment-resistant depression (TRD), stroke rehabilitation, and epilepsy, also leverages splenic pathways to reduce systemic inflammation. In addition, VNS is being investigated for the treatment of several other conditions, including Alzheimer's disease, anxiety disorders, posttraumatic stress disorder (PTSD), heart failure, inflammatory bowel disease, and rheumatoid arthritis. This convergence highlights the spleen as a powerful intermediary among brain states, behavior, and systemic immunity. Overall, the spleen functions dually as both an effector, orchestrating immune tone influenced by the brain, and a sensor/relay, contributing to neuroinflammation; these functions thereby place the spleen centrally in neuroimmune integration, where it has both protective and pathological implications.

Kidneys (Renal Immune Signals and Neurocognitive Effects)

Within the CONB Network, the kidneys modulate neuroimmune responses primarily via immunometabolic pathways. Chronic kidney disease induces systemic inflammation through uremic toxins and cytokines (e.g., IL-1 β) (130, 131), which activate CNS microglia, impair BBB integrity, and contribute to cognitive decline and mood disorders (131, 132). While kidney-derived factors, such as erythropoietin, can be neuroprotective, the primary role of this axis in behavior appears to be driven by the consequences of renal dysfunction for systemic inflammation (133). Future work is needed to disentangle brain–kidney signaling pathways and to determine whether kidneys, like several other organs highlighted above, contribute more broadly to behavioral regulation within the CONB Network.

Lymph Nodes and Meningeal Lymphatics (Immune Cell Trafficking and Brain Drainage)

The discovery of functional meningeal lymphatic vessels (mLVs) lining the dural sinuses has fundamentally reshaped our understanding of CNS immunity and refuted the concept of absolute immune privilege. By draining cerebrospinal fluid (CSF) and interstitial fluid—along with metabolic waste, soluble antigens, and immune cells—into the deep cervical lymph nodes (dCLNs), these vessels enable ongoing peripheral immune surveillance of the CNS (134). This outflow operates in tandem with the glymphatic system [for a review, see “The Glymphatic System: A Beginner's Guide” (135)], is modulated by behavioral states such as sleep, and thereby influences the clearance of proteins including amyloid- β (A β).



The functional integrity of mLV–dCLN drainage proves vital across a range of neurological conditions, from aging-related neurodegeneration to acute injuries. Impaired drainage facilitates the buildup of toxic aggregates (e.g., A β , tau), fueling neuroinflammation and cognitive decline while also hindering CNS-targeted immunotherapies. Conversely, boosting mLV function (e.g., via VEGF-C) improves clearance and pathology in models of Alzheimer’s disease, stroke, and traumatic brain injury. By processing CNS-derived antigens, the dCLNs can shape systemic immune responses relevant to neurodegenerative conditions such as MS. Thus, preserving or restoring meningeal lymphatic flow emerges as a pivotal strategy for maintaining CNS homeostasis and mitigating neuroimmune dysfunction in various disorders. Having dissected the individual functions of these organ-specific nodes, we move to the next section, where we reintegrate them into a cohesive whole-body framework. This final section will analyze the dynamic, network-level properties that emerge from multi-organ interactions within the CONB Network and will explore the therapeutic strategies that target the network as an integrated system.

SYSTEMS-LEVEL INTEGRATION AND THERAPEUTIC IMPLICATIONS

Multi-Organ Cross Talk and Integrated Behavioral Responses

While the above sections have examined individual organ axes as distinct nodes within the CONB Network, the true regulatory power of this system lies in its integrated dynamics. Behavior is not the result of a single organ–brain dialogue; rather, it requires multi-organ network integration that is shaped by the constant cross talk, feedback loops, and signaling convergence among multiple organ systems. This section moves from individual nodes to the edges that connect them, illustrating how multi-organ circuits form complex cycles that drive multidimensional behavioral phenotypes. Before we move to a detailed discussion of this multi-organ integration, let us start with two examples that nicely highlight signaling within the CONB Network, at the edges.

Example 1: the vicious cycle of chronic stress—a brain–adrenal–marrow–spleen axis.

Chronic psychological stress provides a well-established example of a maladaptive feed-forward loop within the CONB Network. The cycle initiates in the brain, where perceived stress triggers activation of the HPA axis and the sympathetic nervous system (125). This central signal propagates to key peripheral nodes and thereby triggers the release of GCs from the adrenal glands, which leads to paradoxical inflammation under chronic exposure. Simultaneously, sympathetic signaling drives pro-inflammatory myelopoiesis in the bone marrow, a process that is amplified by stress hormones, such as vasopressin (114, 117, 136). The spleen then acts as a reservoir pool, mobilizing these primed inflammatory monocytes into circulation (125). The loop closes as these monocytes and their products (e.g., MMP-8) traffic back to the CNS, possibly compromising the BBB in regions such as the nucleus accumbens, driving social avoidance behavior and anhedonia, and perpetuating the initial stress perception (36).

Example 2: the virtuous cycle of physical exercise—a muscle–bone–gut–brain axis.

In stark contrast, physical exercise initiates a protective multi-organ process across the CONB Network (137, 138). The initiating node is skeletal muscle, which releases myokines that promote a systemic anti-inflammatory tone, partly by inducing IL-10 and activating kynurenine-degrading pathways (139). These signals propagate through the network, positively modulating the gut microbiome to enhance the production of beneficial metabolites, such as SCFAs. Exercise also stimulates bones to release factors such as osteocalcin, which crosses the BBB to improve cognitive function. This multi-organ signaling converges on the brain, where myokines and other factors promote the production of BDNF and neurogenesis, creating a positive feedback loop that enhances both physical and mental resilience (140).

Emergent Properties of the Cross-Organ Neuroimmunology of Behavior Network

These examples reveal several key emergent properties of the CONB Network. The first is signaling convergence: Disparate peripheral nodes, such as the skin in psoriasis, the lungs in COPD, or the liver in MASLD, can all generate a standard set of inflammatory mediators (e.g., IL-1 β , IL-6, TNF- α). These signals converge on the brain to produce a remarkably similar behavioral output—sickness behavior, fatigue, and anhedonia—with this similarity demonstrating that the brain responds to a generalized “systemic inflammation” signal regardless of its origin. Second, the CONB Network exhibits profound degeneracy, a core principle of complex biological systems, rather than simple redundancy. While redundancy implies the presence of identical, interchangeable components, degeneracy refers to the phenomenon wherein structurally distinct elements can perform similar functions under specific contexts (141, 142). This property confers enhanced robustness and adaptive potential. Degeneracy is evident at multiple scales within the CONB Network.

At the macrolevel, different peripheral organs (structurally distinct nodes) can trigger similar behavioral outcomes (e.g., sickness behavior) during infection, inflammatory flare, or metabolic disease by releasing functionally convergent, albeit biochemically diverse, combinations of pro-inflammatory cytokines. These combinations represent degenerate pathways leading to a standard functional output.

At the microlevel, the T cell receptor (TCR) repertoire provides a classic example of degeneracy. A single TCR can recognize multiple different peptide–MHC complexes, while multiple distinct TCRs can recognize a single peptide (143). This “many-to-many” mapping ensures robust immune surveillance against a vast array of pathogens with a finite set of receptors.

This property of degeneracy ensures the network’s robustness: If one communication channel is compromised, other structurally different but functionally similar pathways can compensate and thereby ensure that critical information about peripheral state reaches the brain. Finally, the network exhibits vulnerable hubs—for example, organs such as the gut and bone marrow—which process and broadcast high-dimensional immune signals, exerting an outsized influence on the entire network’s tone. Perturbations at these hubs, such as gut dysbiosis or myelopoiesis, can have cascading effects that destabilize the entire system. Recognizing these interconnected pathways and network properties necessitates a holistic, systems-level perspective for both research and therapy. The traditional approach of targeting a single organ or pathway is insufficient. Interventions must be understood through their network-level effects: For example, VNS does not just target the spleen but retunes a brain–spleen circuit (144). Similarly, diet and exercise are powerful therapeutic modalities precisely because they act on multiple nodes of the network simultaneously (145, 146). Therefore, managing complex neuroimmune-related behavioral disorders requires a shift from a single-target paradigm to one focused on restoring equilibrium across the entire CONB Network.

CLINICAL APPLICATIONS AND THERAPEUTIC INTERVENTIONS

Despite advances in conventional psychopharmacology and therapy, substantial unmet needs persist in treating complex behavioral disorders such as stress-related conditions [e.g., major depressive disorder (MDD) and PTSD] and inflammation-associated cognitive dysfunction. High rates of treatment resistance, particularly in MDD subgroups exhibiting peripheral inflammation [e.g., elevated C-reactive protein (CRP), TNF- α , and IL-6], strongly suggest that targeting only central neurotransmitter pathways may be insufficient (147, 148). The robust mechanistic links established herein—which include stress-induced disruption of the BBB in specific regions



such as the nucleus accumbens allowing peripheral IL-6 influx (149); peripheral myeloid cell-derived factors such as MMP-8 directly altering the nucleus accumbens extracellular matrix to drive social avoidance (36); and stress-induced B cell activation leading to potentially pathogenic brain-reactive autoantibodies (39)—provide a compelling rationale for exploring the neuroimmune axis as a source of novel therapeutic targets and biomarkers. Therefore, this section critically evaluates emerging immune-based interventions aimed at restoring neuroimmune homeostasis to alleviate behavioral symptoms and improve mental health outcomes.

Targeting Innate Immunity and Inflammatory Cascades

The clinical need for new psychiatric treatments—especially for TRD—has driven a shift toward neuroimmune targets. In recent years, there has been a clear evolution from broad anti-inflammatory agents to more precise modulators of innate immunity. Cytokine-blocking biologics exemplify this approach. Elevated pro-inflammatory cytokines (e.g., TNF- α , IL-6, IL-17, CRP) are well-documented in major depression, and meta-analyses confirm that adjunctive anti-inflammatories can reduce depressive symptoms (150, 151). However, trials of TNF- α inhibitors (e.g., infliximab) or IL-6 blockers in unselected depressed patients have been largely negative (152). Crucially, benefits of anti-inflammatory treatments appear confined to an “inflammatory biotype”: Patients with high baseline high-sensitivity CRP (hs-CRP) (>5 mg/L) respond selectively to anticytokine therapy (153), whereas patients with low baseline hs-CRP (<5 mg/L) responded worse. This difference in response rates highlights the importance of patient stratification by immune biomarkers, reframing these drugs as precision treatments for inflammation-driven depression. At the same time, modulation of neuroactive cytokine pathways warrants caution: Brodalumab (an IL-17RA antagonist) carries a Food and Drug Administration (FDA) boxed warning for suicidal ideation and behavior on the basis of trial reports, whereas pooled analyses and long-term datasets for IL-17A-neutralizing antibodies (e.g., secukinumab, ixekizumab) have not identified an excess signal for depression, anxiety, or suicidality; this distinction underscores that safety should be judged on a molecule-by-molecule rather than class-wide basis (154, 155).

Janus kinase (JAK) inhibitors offer another intracellular approach, potently blocking multiple cytokine signals via the JAK–STAT pathway. Agents such as tofacitinib and baricitinib have shown potent anti-inflammatory effects, but safety warnings curtail their application in psychiatry. A study published in 2022 in *The New England Journal of Medicine* found that JAK inhibitors carry higher risks of major cardiovascular events, cancers, thromboembolism, and serious infections compared with TNF inhibitors (156). These risks overlap heavily with those seen in the typical TRD population (associated with, e.g., increased age, smoking, comorbidities). Thus, despite a robust development pipeline, regulatory caution limits JAK use in neuropsychiatric disorders (156).

Beyond cytokines, new druggable nodes in innate immunity are emerging. NLRP3 (NLR family pyrin domain-containing 3) inflammasome inhibitors (small molecules such as NT-0796, VTX3232) are novel brain-penetrant compounds and are entering trials, overcoming prior hurdles with BBB penetration. VTX3232 and NT-0796, which completed phase 1, are moving into phase 2 for neurological indications. Because NLRP3 sits at a convergence point for IL-1 β and IL-18 production, these drugs offer a more targeted intracellular blockade than do JAK inhibitors (157). Another innovative target is MMP-8. MMP-8 (neutrophil collagenase) has recently been shown to be upregulated in activated microglia and to act as a TNF- α -converting enzyme, cleaving pro-TNF to its active form (158, 159). Inhibiting MMP-8 in animal models dampens microglial inflammation and preserves the blood–CSF barrier; these findings link peripheral inflammation to CNS effects (159). Although still preclinical, MMP-8 exemplifies

the search for tractable targets downstream of cytokines. Together, these advances illustrate a precision-medicine paradigm, moving from systemic anti-inflammatory agents toward specific immunologic pathways matched to patient subtypes.

Modulating Peripheral–Central Nervous System Communication

Therapies are also emerging that intervene along peripheral–brain axes rather than targeting the CNS directly. The gut–brain axis has been a significant focus. Dysbiosis of the intestinal microbiome is linked to mood disorders, and clinical trials are now testing “psychobiotics”—probiotics formulated to benefit mental health (160). Additionally, dysbiosis of the gut microbiome has been implicated in not only mood disorders but also MS, and probiotic interventions and FMT have shown preliminary benefits for disability, fatigue, and inflammatory biomarkers in MS patients (161, 162). In a landmark 2025 randomized controlled trial (RCT) (the ProDeCa study), a multi-strain psychobiotic improved depression, anxiety, and stress scores compared with a placebo in high-stress surgical patients (163). These live microbes are hypothesized to work via local production of neuroactive compounds (e.g., GABA, serotonin), modulation of gut immunity, and vagal signaling (164). More radical is FMT, wherein whole microbial communities are transferred from healthy donors. Preclinical data and early data from humans indicate that FMT can shift psychiatric phenotypes: Transplanting microbiota from depressed patients induces depressive-like behavior in recipients, whereas healthy-donor transplants can alleviate symptoms (165). These findings underscore the gut’s central role and align with the discussion in the section titled Intestine (Gut–Brain–Immune Axis) regarding gut-derived metabolites and vagal pathways. However, FMT trials remain small and largely uncontrolled; future work must define which specific microbes are responsible for these effects and the specific pathways from gut to brain that mediate their antidepressant effects. There is a growing consensus that larger, well-designed trials are needed to establish the long-term safety and efficacy of therapeutic strains or consortia.

Another peripheral approach is bioelectronic modulation. VNS, which electrically activates the anti-inflammatory “inflammatory reflex” via the vagus nerve, is FDA approved as an adjunct therapy for TRD. Recent data have yielded a complex picture (125). Long-term observational data (from the RESTORE-LIFE study) showed good tolerability and a cumulative therapeutic response of approximately 53% at one year in patients with treatment-resistant conditions (166). However, a rigorous sham-controlled RCT found no significant difference in primary depression outcomes between active and sham VNS (167). Notably, the RCT revealed improvements in secondary measures (i.e., global clinical status and patient-reported symptoms), indicating that conventional trial end points may overlook the full benefits of VNS. One interpretation is that the antidepressant effects of VNS can be slow to emerge and may manifest more in functional recovery and quality of life than in raw symptom scores. The dose–response relationship also appears nonlinear, and this nonlinearity may influence treatment outcomes. Taken together, these data suggest that future VNS studies should focus on how, when, and for whom VNS works—identifying biomarkers of response and using long-term functional end points rather than simply relying on self-report measures.

Adaptive Immunity and Autoimmune Neuropsychiatric Syndromes

A burgeoning area is the role of adaptive immunity in mental illness. Chronic stress, a key psychiatric risk factor, has been shown to dysregulate B cell homeostasis directly. In a 2025 study in mice, chronic stress drove aberrant germinal center B cell expansion and autoantibody production that targeted the brain (39). Clinically, autoimmune encephalitis [e.g., anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis, an established autoimmune condition marked by



overproduction of neuronal autoantibodies against the NMDA receptor] can cause severe deficits in neuronal function, leading to a range of neuropsychiatric symptoms, including psychosis (168). More subtle forms of neuronal autoimmunity are now being uncovered in broader psychiatric populations. For example, higher rates of antithyroid or anti-Ro antibodies have been noted in subsets of depressed or psychotic patients, though some associations may reflect confounders such as smoking (169). Circulating antibodies are correlated with symptoms of anhedonia in MDD subjects as well (39). These converging lines of evidence support the concept of an “autoimmune depression” subtype. In such cases, standard antidepressants are unlikely to suffice; instead, treatment approaches used in neurology or rheumatology may be more appropriate (e.g., plasmapheresis, intravenous immunoglobulin, B cell depletion with rituximab). A key implication of this work is the need for routine autoantibody screening in severe, atypical, or treatment-refractory cases, especially when there is a rapid onset or a personal or family autoimmune history. Identifying these patients could open the way to targeted immunotherapies and avoid years of ineffective trials.

Biomarkers for Patient Stratification and Target Engagement

The success of neuroimmune therapies hinges on precise biomarkers. Peripheral blood biomarkers are the most advanced clinically. Simple assays for inflammatory markers (e.g., hs-CRP, IL-6, TNF- α) are already critical for stratifying trials, as they help to identify the “inflammatory biotype” of depression that better responds to cytokine blockers. These markers are sensitive indicators of systemic immune activation but lack brain or disease specificity. Their utility potentially lies in distinguishing responders to immunotherapy in RCTs with broad enrollment criteria. By contrast, neuronal injury biomarkers, such as neurofilament light chain (NfL), reflect CNS damage more directly. NfL is elevated in severe mental disorders—albeit less than in frank neurodegeneration—and can distinguish neurodegenerative mimics (e.g., frontotemporal dementia) from primary psychiatric illness. In mood disorders, higher NfL correlates with cognitive impairment and brain atrophy, and this correlation suggests that NfL could track “neuroprogression” over time (170, 171).

In vivo neuroimaging offers another tool for diagnosis and trial stratification. Positron emission tomography (PET) imaging of the 18-kDa translocator protein (TSPO) on glial cells is the leading method for visualizing neuroinflammation in humans. A 2023 meta-analysis of 156 TSPO-PET studies found overall elevated glial activation across CNS disorders, with the most significant effects in Alzheimer’s disease and MS (172). Mood disorders showed more minor yet significant increases in TSPO binding within limbic brain regions. Notably, the meta-analysis also highlighted extreme heterogeneity driven by methodological factors (e.g., choice of ligand, quantification model, patient TSPO genotype). As a result, TSPO-PET remains mainly a research tool for confirming target engagement in trials, rather than a routine clinical biomarker.

Next-generation biomarker strategies might benefit by assessing multidimensional signatures. One promising avenue for which this approach is being applied is the gut microbiome, as distinct psychiatric disorders have been shown to have unique microbial compositions. A 2025 study used machine learning on gut sequencing data to diagnose MDD, bipolar disorder, and schizophrenia with 80–97% accuracy based on these dysbiosis signatures (173). If validated, such microbiome profiles could serve as noninvasive diagnostic tools to guide probiotic and FMT therapies. Similarly, autoantibody panels might define an “autoimmune psychiatric” subtype. Discoveries of antibodies against NMDA receptors, muscarinic receptors, or systemic antigens [e.g., anti-Ro52, anti-TPO (anti-thyroid peroxidase) antibodies] in subsets of patients suggest that screening could identify those who may benefit from immunotherapy. Finally, combining these modalities with imaging tools that can stratify psychiatric “biotypes” [i.e., functional magnetic resonance imaging

(functional MRI) or TSPO-PET] could further strengthen biomarker predictions. In summary, the emerging paradigm of multimodal biomarker guidance—which combines markers of peripheral inflammation (e.g., hs-CRP) and neuronal injury (e.g., NFL), neuroinflammation imaging (TSPO-PET), microbiome data, and autoantibody data—might one day be used to identify unique subtypes of patients with neuropsychiatric or neurological diseases and to tailor individualized approaches for treatment. **Figure 3** aligns these immune biotypes with targeted therapies and their anticipated behavioral outcomes, offering a precision-medicine road map for restoring CONB Network homeostasis.

Emerging Technologies and Future Directions

Advances in technology are accelerating psychoneuroimmunology. Single-cell multi-omic platforms now allow mapping of genetic risk to cell type-specific functions. For example, a 2025 study profiled gene expression and chromatin accessibility in induced pluripotent stem cell (iPSC)-derived human neurons under both resting and activated conditions (176). This study revealed thousands of context-dependent eQTLs (expression quantitative trait loci) and caQTLs (chromatin accessibility QTLs), linking psychiatric GWAS (genome-wide association study) variants to specific target genes only evident during neuronal activation (176). Such studies pave the way for identifying precise molecular targets within complex genetic loci.

Humanized disease models are also improving. Brain organoids (3D cultures) and assembloids (fused-region organoids) provide human-specific platforms for studying neuroimmune interactions. Incorporating microglia-like cells into these organoids (neuroimmune organoids) creates a mini human brain environment. Recent work has even transplanted these organoids into rodents to achieve vascularization and maturation, showing that human microglia fully mature only within a native neural context (177, 178). These platforms will enable the testing of neuroimmune drugs in systems that mimic human brain architecture and immune cell interactions. Despite their promise, current iPSC-derived models have notable limitations. Brain organoids often lack key cell types (e.g., microglia, endothelial cells) and vasculature, and this absence limits their ability to model neuroimmune and neurovascular interactions. They typically correspond to early developmental stages and do not recapitulate aging or the systemic environment. Variability between iPSC lines and incomplete maturation also remain challenges. Addressing these limitations—for example, by incorporating vascular and immune components into organoid assembloids or organ-on-chip systems—will be crucial for translating these models into more predictive tools for neuroimmune research (179).

Finally, overcoming the BBB is a significant focus in the delivery of neuroimmune therapies. Novel strategies now harness molecular, cellular, and physical approaches (for a review, see 180). Molecular nanocarriers (e.g., liposomes, polymeric nanoparticles, engineered exosomes) can be decorated with BBB-targeting ligands (e.g., transferrin) to piggyback on endogenous transport routes. Cell-based Trojan horses, such as mesenchymal stem cells, exploit natural homing to deliver payloads across the BBB (181). Physical methods such as MRI-guided focused ultrasound (with microbubble contrast) can transiently open tight junctions in a targeted brain region to allow passage of certain drugs too big to otherwise enter the brain (182). These convergent technologies promise to enable the delivery of large biologics and gene therapies to the CNS, which was previously impossible.

CONCLUSION

The evidence synthesized in this review solidifies a paradigm shift in understanding behavior, moving from isolated organ-brain dialogues to the integrated framework we have termed the



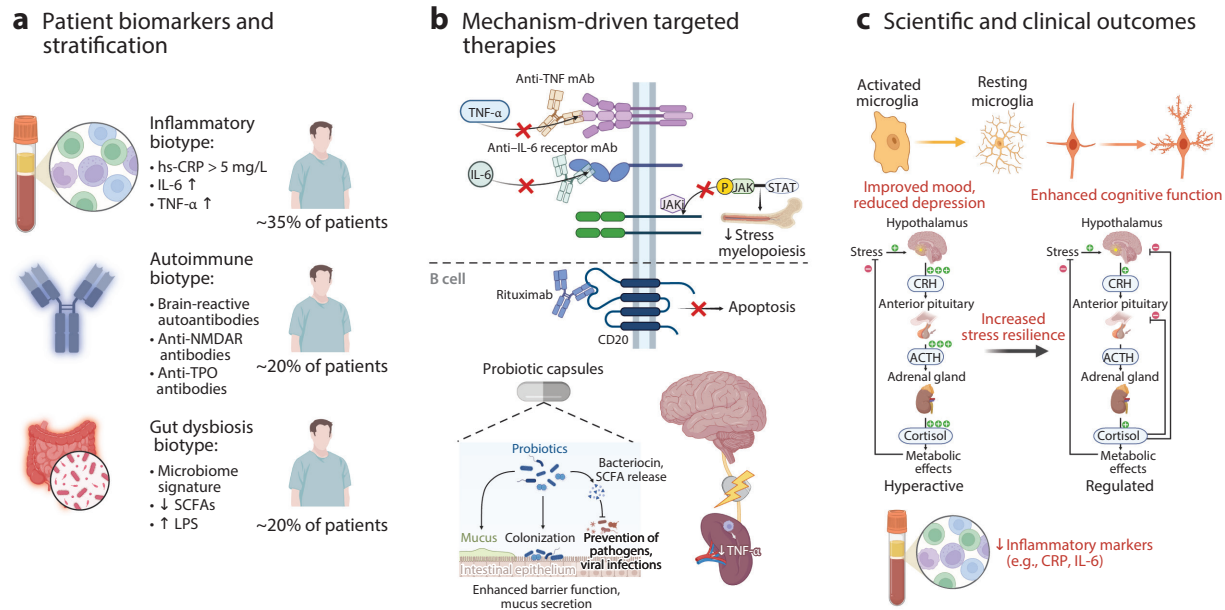


Figure 3

Precision-medicine framework based on the CONB Network, aligning immune-biotype biomarkers for patient stratification with targeted neuroimmune therapies and anticipated behavioral outcomes. (a) Patient immune biotypes are identified based on peripheral biomarker profiles. The inflammatory biotype (approximately 35% of patients), characterized by elevated hs-CRP (> 5 mg/L), IL-6, and TNF- α , represents systemic inflammation-driven neuropsychiatric symptoms. The autoimmune biotype (approximately 20% of patients) is defined by the presence of brain-reactive autoantibodies, anti-NMDAR antibodies, and anti-TPO antibodies, indicating autoimmune-mediated CNS involvement. The gut dysbiosis biotype (approximately 20% of patients), identified through altered microbiome signatures, reduced SCFAs, and elevated LPS levels, reflects gut-brain axis dysfunction (174, 175). (b) Mechanism-driven targeted therapies: Biomarker-guided therapeutic interventions target specific CONB Network components. Anti-cytokine biologics including anti-TNF (infliximab) and anti-IL-6 receptor mAb (tocilizumab) agents block systemic inflammatory pathways in inflammatory biotype patients. JAK inhibitors (tofacitinib) simultaneously suppress cytokine signaling and stress-induced myelopoiesis from bone marrow nodes. B cell depletion therapy (rituximab) eliminates autoantibody-producing cells in autoimmune-biotype patients. Microbiome interventions including psychobiotics (e.g., *Lactobacillus helveticus*, *Bifidobacterium longum*) and FMT restore gut-brain axis homeostasis. VNS activates the cholinergic anti-inflammatory pathway, modulating spleen-mediated immune responses across multiple biotypes. (c) Scientific and clinical outcomes: Targeted interventions aim to restore behavioral homeostasis through distinct but complementary mechanisms. Improved mood and reduced depression result from normalized cytokine signaling and restored monoaminergic neurotransmission. Enhanced cognitive function emerges from reduced neuroinflammation, decreased microglial activation, and improved synaptic plasticity. Increased stress resilience follows HPA axis normalization and enhanced cholinergic anti-inflammatory responses. Reduced anhedonia correlates with restored dopaminergic signaling in reward circuits. Decreased anxiety symptoms accompany normalized glutamate homeostasis and reduced amygdalar hyperactivation. Biomarker normalization, including reduced inflammatory markers (e.g., CRP, IL-6), serves as objective measures of therapeutic efficacy. Abbreviations: ACTH, adrenocorticotropic hormone; CNS, central nervous system; CONB, Cross-Organ Neuroimmunology of Behavior; CRH, corticotropin-releasing hormone; CRP, C-reactive protein; FMT, fecal microbiota transplantation; HPA, hypothalamic-pituitary-adrenal; hs-CRP, high-sensitivity CRP; JAK, Janus kinase; LPS, lipopolysaccharide; mAb, monoclonal antibody; NMDAR, *N*-methyl-D-aspartate receptor; SCFA, short-chain fatty acid; TNF, tumor necrosis factor; TPO, thyroid peroxidase; VNS, vagus nerve stimulation. Figure adapted from images created in BioRender; Guo X. 2025. <https://BioRender.com/tb869pu>.

Cross-Organ Neuroimmunology of Behavior (CONB) Network. By first establishing its fundamental mechanisms and then exploring its constituent organ nodes, we have illustrated how signals from the gut, the bone marrow, the lungs, and beyond converge to regulate neuroinflammation, mood, and cognition. Viewing neuropsychiatric and behavioral disorders through

the lens of the CONB Network reframes them as systemic node-edge dysregulations rather than purely brain-centric conditions. As detailed in our systems-level analysis, future interventions, whether microbiome editing, anticytokine biologics, or bioelectronic modulation—must be evaluated not for their effect on a single component but for their capacity to restore equilibrium across the entire CONB Network. This approach paves the way for a new therapeutic paradigm wherein patients are stratified into immunobiological subtypes—such as “inflammatory depression” versus “autoimmune depression”—and treated with matched, network-level interventions. Embracing this holistic and personalized framework is crucial for ultimately realizing the promise of neuroimmune medicine and enhancing both mental and physical health.

DISCLOSURE STATEMENT

S.J.R. has a pending patent related to the use of dupilumab for the treatment of major depressive disorder.

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LITERATURE CITED

1. Klein Wolterink RGJ, Wu GS, Chiu IM, Veiga-Fernandes H. 2022. Neuroimmune interactions in peripheral organs. *Annu. Rev. Neurosci.* 45:339–60
2. Zhu Y, Duan S, Wang M, Deng Z, Li J. 2022. Neuroimmune interaction: a widespread mutual regulation and the weapons for barrier organs. *Front. Cell Dev. Biol.* 10:906755
3. Castellani G, Croese T, Peralta Ramos JM, Schwartz M. 2023. Transforming the understanding of brain immunity. *Science* 380(6640):eabo7649
4. Leunig A, Gianeselli M, Russo SJ, Swirski FK. 2025. Connection and communication between the nervous and immune systems. *Nat. Rev. Immunol.* 25:912–33
5. Dantzer R. 2018. Neuroimmune interactions: from the brain to the immune system and vice versa. *Physiol. Rev.* 98(1):477–504
6. Correia AS, Vale N. 2022. Tryptophan metabolism in depression: a narrative review with a focus on serotonin and kynurenine pathways. *Int. J. Mol. Sci.* 23(15):8493
7. Dantzer R. 2016. Role of the kynurenine metabolism pathway in inflammation-induced depression: preclinical approaches. In *Inflammation-Associated Depression: Evidence, Mechanisms and Implications*, ed. R Dantzer, L Capuron. Current Topics in Behavioral Neurosciences, Vol. 31. Springer
8. Felger JC, Miller AH. 2012. Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise. *Front. Neuroendocrinol.* 33(3):315–27
9. Takeuchi H, Jin S, Wang J, Zhang G, Kawanokuchi J, et al. 2006. Tumor necrosis factor- α induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner. *J. Biol. Chem.* 281(30):21362–68
10. Miller AH, Haroon E, Raison CL, Felger JC. 2013. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. *Depress. Anxiety* 30(4):297–306
11. Black PH. 2002. Stress and the inflammatory response: a review of neurogenic inflammation. *Brain Behav. Immun.* 16(6):622–53
12. Finnell JE, Moffitt CM, Hesser LA, Harrington E, Melson MN, et al. 2019. The contribution of the locus coeruleus-norepinephrine system in the emergence of defeat-induced inflammatory priming. *Brain Behav. Immun.* 79:102–13
13. Ji E, Zhang Y, Li Z, Wei L, Wu Z, et al. 2024. The chemokine CCL2 promotes excitatory synaptic transmission in hippocampal neurons via GluA1 subunit trafficking. *Neurosci. Bull.* 40(11):1649–66



14. Sheridan GK, Wdowicz A, Pickering M, Watters O, Halley P, et al. 2014. CX3CL1 is up-regulated in the rat hippocampus during memory-associated synaptic plasticity. *Front. Cell. Neurosci.* 8:233
15. Sowa JE, Tokarski K. 2021. Cellular, synaptic, and network effects of chemokines in the central nervous system and their implications to behavior. *Pharmacol. Rep.* 73(6):1595–625
16. Citri A, Malenka RC. 2008. Synaptic plasticity: multiple forms, functions, and mechanisms. *Neuropharmacology* 33(1):18–41
17. Tong L, Prieto GA, Kramár EA, Smith ED, Cribbs DH, et al. 2012. Brain-derived neurotrophic factor-dependent synaptic plasticity is suppressed by interleukin-1 β via p38 mitogen-activated protein kinase. *J. Neurosci.* 32(49):17714–24
18. Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, et al. 2012. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* 74(4):691–705
19. Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, et al. 2016. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* 352(6286):712–16
20. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, et al. 2016. Schizophrenia risk from complex variation of complement component 4. *Nature* 530(7589):177–83
21. Wendeln A-C, Degenhardt K, Kaurani L, Gertig M, Ulas T, et al. 2018. Innate immune memory in the brain shapes neurological disease hallmarks. *Nature* 556(7701):332–38
22. Karpova NN. 2014. Role of BDNF epigenetics in activity-dependent neuronal plasticity. *Neuropharmacology* 76(Part C):709–18
23. Yang R, Yang B, Liu W, Tan C, Chen H, Wang X. 2023. Emerging role of non-coding RNAs in neuroinflammation mediated by microglia and astrocytes. *J. Neuroinflamm.* 20(1):173
24. Lee H-G, Rone JM, Li Z, Akl CF, Shin SW, et al. 2024. Disease-associated astrocyte epigenetic memory promotes CNS pathology. *Nature* 627(8005):865–72
25. Escartin C, Galea E, Lakatos A, O’Callaghan JP, Petzold GC, et al. 2021. Reactive astrocyte nomenclature, definitions, and future directions. *Nat. Neurosci.* 24(3):312–25
26. Giovannoni F, Quintana FJ. 2020. The role of astrocytes in CNS inflammation. *Trends Immunol.* 41(9):805–19
27. Lee H-G, Wheeler MA, Quintana FJ. 2022. Function and therapeutic value of astrocytes in neurological diseases. *Nat. Rev. Drug Discov.* 21(5):339–58
28. Mahmoud S, Gharagozloo M, Simard C, Gris D. 2019. Astrocytes maintain glutamate homeostasis in the CNS by controlling the balance between glutamate uptake and release. *Cells* 8(2):184
29. Rostami J, Fotaki G, Sirois J, Mzezewa R, Bergström J, et al. 2020. Astrocytes have the capacity to act as antigen-presenting cells in the Parkinson’s disease brain. *J. Neuroinflamm.* 17(1):119
30. Auguste YSS, Ferro A, Kahng JA, Xavier AM, Dixon JR, et al. 2022. Oligodendrocyte precursor cells engulf synapses during circuit remodeling in mice. *Nat. Neurosci.* 25(10):1273–78
31. Madeira MM, Hage Z, Tsirka SE. 2022. Beyond myelination: possible roles of the immune proteasome in oligodendroglial homeostasis and dysfunction. *Front. Neurosci.* 16:867357
32. Falcão AM, van Bruggen D, Marques S, Meijer M, Jäkel S, et al. 2018. Disease-specific oligodendrocyte lineage cells arise in multiple sclerosis. *Nat. Med.* 24(12):1837–44
33. Harrington EP, Bergles DE, Calabresi PA. 2020. Immune cell modulation of oligodendrocyte lineage cells. *Neurosci. Lett.* 715:134601
34. Harrington EP, Catenacci RB, Smith MD, Heo D, Miller CE, et al. 2023. MHC class I and MHC class II reporter mice enable analysis of immune oligodendroglia in mouse models of multiple sclerosis. *eLife* 12:e82938
35. D’Mello C, Le T, Swain MG. 2009. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factor α signaling during peripheral organ inflammation. *J. Neurosci.* 29(7):2089–102
36. Cathomas F, Lin H-Y, Chan KL, Li L, Parise LF, et al. 2024. Circulating myeloid-derived MMP8 in stress susceptibility and depression. *Nature* 626(8001):1108–15
37. Filiano AJ, Xu Y, Tustison NJ, Marsh RL, Baker W, et al. 2016. Unexpected role of interferon- γ in regulating neuronal connectivity and social behavior. *Nature* 535(7612):425–29
38. Alves de Lima K, Rustenhoven J, Da Mesquita S, Wall M, Salvador AF, et al. 2020. Meningeal $\gamma\delta$ T cells regulate anxiety-like behavior via IL-17a signaling in neurons. *Nat. Immunol.* 21(11):1421–29



39. Shimo Y, Cathomas F, Lin H, Chan KL, Parise LF, et al. 2023. Social stress induces autoimmune responses against the brain. *PNAS* 120(49):e2305778120
40. Cryan JF, O’Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, et al. 2019. The microbiota-gut-brain axis. *Physiol. Rev.* 99(4):1877–2013
41. Erny D, de Angelis ALH, Jaitin D, Wieghofer P, Staszewski O, et al. 2015. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat. Neurosci.* 18(7):965–77
42. Fung TC, Olson CA, Hsiao EY. 2017. Interactions between the microbiota, immune and nervous systems in health and disease. *Nat. Neurosci.* 20(2):145–55
43. Leonardi I, Gao IH, Lin W-Y, Allen M, Li XV, et al. 2022. Mucosal fungi promote gut barrier function and social behavior via type 17 immunity. *Cell* 185(5):831–46.e14
44. Matta SM, Hill-Yardin EL, Crack PJ. 2019. The influence of neuroinflammation in autism spectrum disorder. *Brain Behav. Immun.* 79:75–90
45. Medina-Rodríguez EM, Martínez-Raga J, Sanz Y. 2024. Intestinal barrier, immunity and microbiome: partners in the depression crime. *Pharmacol. Rev.* 76(5):956–69
46. Ritz NL, Draper LA, Bastiaanssen TFS, Turkington CJR, Peterson VL, et al. 2024. The gut virome is associated with stress-induced changes in behaviour and immune responses in mice. *Nat. Microbiol.* 9(2):359–76
47. Wang S, van de Pavert SA. 2022. Innate lymphoid cells in the central nervous system. *Front. Immunol.* 13:837250
48. Rothhammer V, Borucki DM, Tjon EC, Takenaka MC, Chao C-C, et al. 2018. Microglial control of astrocytes in response to microbial metabolites. *Nature* 557(7707):724–28
49. Girolamo F, Coppola C, Ribatti D. 2017. Immunoregulatory effect of mast cells influenced by microbes in neurodegenerative diseases. *Brain Behav. Immun.* 65:68–89
50. Vanuytsel T, Bercik P, Boeckxstaens G. 2023. Understanding neuroimmune interactions in disorders of gut–brain interaction: from functional to immune-mediated disorders. *Gut* 72(4):787–98
51. Yuan C, He Y, Xie K, Feng L, Gao S, Cai L. 2023. Review of microbiota gut brain axis and innate immunity in inflammatory and infective diseases. *Front. Cell. Infect. Microbiol.* 13:1282431
52. Russo S, Chan K, Li L, Parise L, Cathomas F, et al. 2023. Stress-activated brain-gut circuits disrupt intestinal barrier integrity and social behaviour. Preprint, Research Square. <https://doi.org/10.21203/rs.3.rs-3459170/v1>
53. Margolis KG, Shea-Donohue T, Cummings DM, Greenwel P, Lunsford RD, et al. 2024. 2023 workshop: neuroimmune crosstalk in the gut – impact on local, autonomic and gut–brain function. *Gastroenterology* 167(2):223–30
54. Wallrapp A, Chiu IM. 2024. Neuroimmune interactions in the intestine. *Annu. Rev. Immunol.* 42:489–519
55. Jordan KR, Loman BR, Bailey MT, Pyter LM. 2018. Gut microbiota-immune-brain interactions in chemotherapy-associated behavioral comorbidities. *Cancer* 124(20):3990–99
56. Loh JS, Mak WQ, Tan LKS, Ng CX, Chan HH, et al. 2024. Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases. *Signal Transduct. Target. Ther.* 9:37
57. Bellavance M-A, Rivest S. 2014. The HPA – immune axis and the immunomodulatory actions of glucocorticoids in the brain. *Front. Immunol.* 5:136
58. Ince LM, Weber J, Scheiermann C. 2018. Control of leukocyte trafficking by stress-associated hormones. *Front. Immunol.* 9:3143
59. Nusslock R, Miller GE. 2016. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. *Biol. Psychiatry* 80(1):23–32
60. Calcia MA, Bonsall DR, Bloomfield PS, Selvaraj S, Barichello T, Howes OD. 2016. Stress and neuroinflammation: a systematic review of the effects of stress on microglia and the implications for mental illness. *Psychopharmacology* 233(9):1637–50
61. Dill-McFarland KA, Altman MC, Esnault S, Jarjour NN, Busse WW, Rosenkranz MA. 2024. Molecular pathways underlying lung-brain axis signaling in asthma: relevance for psychopathology and neuroinflammation. *J. Allergy Clin. Immunol.* 153(1):111–21
62. Kanaya A, Yang M, Emala C, Mikami M. 2022. Chronic allergic lung inflammation negatively influences neurobehavioral outcomes in mice. *J. Neuroinflamm.* 19(1):210



63. Vanderheiden A, Klein RS. 2022. Neuroinflammation and COVID-19. *Curr. Opin. Neurobiol.* 76:102608
64. Villalba N, Ma Y, Gahan SA, Joly-Amado A, Spence S, et al. 2023. Lung infection by *Pseudomonas aeruginosa* induces neuroinflammation and blood–brain barrier dysfunction in mice. *J. Neuroinflamm.* 20(1):127
65. Fernández-Castañeda A, Lu P, Geraghty AC, Song E, Lee M-H, et al. 2022. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. *Cell* 185(14):2452–68.e16
66. Radke J, Meinhardt J, Aschman T, Chua RL, Farztdinov V, et al. 2024. Proteomic and transcriptomic profiling of brainstem, cerebellum and olfactory tissues in early- and late-phase COVID-19. *Nat. Neurosci.* 27(3):409–20
67. Yang AC, Kern F, Losada PM, Agam MR, Maat CA, et al. 2021. Dysregulation of brain and choroid plexus cell types in severe COVID-19. *Nature* 595(7868):565–71
68. Demuth L, Ohm M, Michaelsen-Preusse K, Schulze K, Riese P, et al. 2023. Influenza vaccine is able to prevent neuroinflammation triggered by H7N7 IAV infection. *Front. Pharmacol.* 14:1142639
69. Suman PR, Souza LS, Kincheski GC, Melo HM, Machado MN, et al. 2022. Lung inflammation induced by silica particles triggers hippocampal inflammation, synapse damage and memory impairment in mice. *J. Neuroinflamm.* 19(1):303
70. Armstrong AW, Read C. 2020. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. *JAMA* 323(19):1945–60
71. Katamanin OM, Tan IJ, Barry J, Jafferany M. 2025. Role of inflammation and cytokine dysregulation in depression in patients with inflammatory skin conditions. *Am. J. Clin. Dermatol.* 26(1):35–43
72. Datsi A, Steinhoff M, Ahmad F, Alam M, Buddenkotte J. 2021. Interleukin-31: the “itchy” cytokine in inflammation and therapy. *Allergy* 76(10):2982–97
73. Steinhoff M, Ahmad F, Pandey A, Datsi A, AlHammadi A, et al. 2022. Neuroimmune communication regulating pruritus in atopic dermatitis. *J. Allergy Clin. Immunol.* 149(6):1875–98
74. Choi JE, Di Nardo A. 2018. Skin neurogenic inflammation. *Semin. Immunopathol.* 40(3):249–59
75. Kim B, Rothenberg ME, Sun X, Bachert C, Artis D, et al. 2024. Neuroimmune interplay during type 2 inflammation: symptoms, mechanisms, and therapeutic targets in atopic diseases. *J. Allergy Clin. Immunol.* 153(4):879–93
76. Bao C, Abraham SN. 2024. Mast cell–sensory neuron crosstalk in allergic diseases. *J. Allergy Clin. Immunol.* 153(4):939–53
77. Mack MR, Kim BS. 2018. The itch-scratch cycle: a neuroimmune perspective. *Trends Immunol.* 39(12):980–91
78. Walsh CM, Hill RZ, Schwendinger-Schreck J, Deguine J, Brock EC, et al. 2019. Neutrophils promote CXCR3-dependent itch in the development of atopic dermatitis. *eLife* 8:e48448
79. Cameron S, Donnelly A, Broderick C, Arichi T, Bartsch U, et al. 2024. Mind and skin: exploring the links between inflammation, sleep disturbance and neurocognitive function in patients with atopic dermatitis. *Allergy* 79(1):26–36
80. Thackeray JT, Hupe HC, Wang Y, Bankstahl JP, Berding G, et al. 2018. Myocardial inflammation predicts remodeling and neuroinflammation after myocardial infarction. *JACC* 71(3):263–75
81. Bellinger DL, Lorton D. 2014. Autonomic regulation of cellular immune function. *Auton. Neurosci.* 182:15–41
82. Bochaton T, Leboube S, Paccalet A, Crola Da Silva C, Buisson M, et al. 2022. Impact of age on systemic inflammatory profile of patients with ST-segment–elevation myocardial infarction and acute ischemic stroke. *Stroke* 53(7):2249–59
83. Johansen MC, Ye W, Gross A, Gottesman RF, Han D, et al. 2023. Association between acute myocardial infarction and cognition. *JAMA Neurol.* 80(7):723–31
84. Perry VH, Holmes C. 2014. Microglial priming in neurodegenerative disease. *Nat. Rev. Neurol.* 10(4):217–24
85. Swirski FK, Nahrendorf M, Etzrodt M, Wildgruber M, Cortez-Retamozo V, et al. 2009. Identification of splenic reservoir monocytes and their deployment to inflammatory sites. *Science* 325(5940):612–16
86. Jinawong K, Apaijai N, Chattipakorn N, Chattipakorn SC. 2021. Cognitive impairment in myocardial infarction and heart failure. *Acta Physiol.* 232(1):e13642



87. Mohanta SK, Yin C, Weber C, Godinho-Silva C, Veiga-Fernandes H, et al. 2023. Cardiovascular brain circuits. *Circ. Res.* 132(11):1546–65
88. Althammer F, Roy RK, Kirchner MK, Campos-Lira E, Whitley KE, et al. 2023. Angiotensin II–mediated neuroinflammation in the hippocampus contributes to neuronal deficits and cognitive impairment in heart failure rats. *Hypertension* 80(6):1258–73
89. Huynh P, Hoffmann JD, Gerhardt T, Kiss MG, Zuraikat FM, et al. 2024. Myocardial infarction augments sleep to limit cardiac inflammation and damage. *Nature* 635(8037):168–77
90. Hu MX, Penninx BWJH, de Geus EJC, Lamers F, Kuan DC-H, et al. 2018. Associations of immunometabolic risk factors with symptoms of depression and anxiety: the role of cardiac vagal activity. *Brain Behav. Immun.* 73:493–503
91. Iseger TA, Van Bueren NER, Kenemans JL, Gevartz R, Arns M. 2020. A frontal–vagal network theory for Major Depressive Disorder: implications for optimizing neuromodulation techniques. *Brain Stimul.* 13(1):1–9
92. Pedersen BK. 2019. Physical activity and muscle–brain crosstalk. *Nat. Rev. Endocrinol.* 15(7):383–92
93. Severinsen MCK, Pedersen BK. 2020. Muscle–organ crosstalk: the emerging roles of myokines. *Endocr. Rev.* 41(4):594–609
94. Agudelo LZ, Ferreira DMS, Cervenka I, Bryzgalova G, Dadvar S, et al. 2018. Kynurenic acid and Gpr35 regulate adipose tissue energy homeostasis and inflammation. *Cell Metab.* 27(2):378–92.e5
95. Cervenka I, Agudelo LZ, Ruas JL. 2017. Kynurenines: tryptophan’s metabolites in exercise, inflammation, and mental health. *Science* 357(6349):eaaf9794
96. Moon HY, Becke A, Berron D, Becker B, Sah N, et al. 2016. Running-induced systemic cathepsin B secretion is associated with memory function. *Cell Metab.* 24(2):332–40
97. Choi SH, Bylykbashi E, Chatila ZK, Lee SW, Pulli B, et al. 2018. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer’s mouse model. *Science* 361(6406):eaan8821
98. Kandola A, Ashdown-Franks G, Hendrikse J, Sabiston CM, Stubbs B. 2019. Physical activity and depression: towards understanding the antidepressant mechanisms of physical activity. *Neurosci. Biobehav. Rev.* 107:525–39
99. Valenzuela PL, Castillo-García A, Morales JS, de la Villa P, Hampel H, et al. 2020. Exercise benefits on Alzheimer’s disease: state-of-the-science. *Ageing Res. Rev.* 62:101108
100. Liu X, Viswanadhappalli S, Kumar S, Lee T-K, Moore A, et al. 2022. Targeting LIPA independent of its lipase activity is a therapeutic strategy in solid tumors via induction of endoplasmic reticulum stress. *Nat. Cancer* 3:866–84
101. Yang S, Tian M, Dai Y, Wang R, Yamada S, et al. 2024. Infection and chronic disease activate a systemic brain–muscle signaling axis. *Sci. Immunol.* 9(97):eadm7908
102. Hendrikse J, Kandola A, Coxon J, Rogasch N, Yücel M. 2017. Combining aerobic exercise and repetitive transcranial magnetic stimulation to improve brain function in health and disease. *Neurosci. Biobehav. Rev.* 83:11–20
103. Sleijser-Koehorst MLS, Koop MA, Coppieters MW, Lutke Schipholt IJ, Radisic N, et al. 2023. The effects of aerobic exercise on neuroimmune responses in animals with traumatic peripheral nerve injury: a systematic review with meta-analyses. *J. Neuroinflamm.* 20(1):104
104. Kjaergaard M, Lindvig KP, Thorhauge KH, Andersen P, Hansen JK, et al. 2023. Using the ELF test, FIB-4 and NAFLD fibrosis score to screen the population for liver disease. *J. Hepatol.* 79(2):277–86
105. Mikkelsen ACD, Kjaergaard K, Schapira AHV, Mookerjee RP, Thomsen KL. 2025. The liver–brain axis in metabolic dysfunction-associated steatotic liver disease. *Lancet Gastroenterol. Hepatol.* 10(3):248–58
106. Hadjihambi A, Konstantinou C, Klohs J, Monsorno K, Le Guennec A, et al. 2023. Partial MCT1 invalidation protects against diet-induced non-alcoholic fatty liver disease and the associated brain dysfunction. *J. Hepatol.* 78(1):180–90
107. Izquierdo-Altarejos P, Cabrera-Pastor A, Martínez-García M, Sánchez-Huertas C, Hernández A, et al. 2023. Extracellular vesicles from mesenchymal stem cells reduce neuroinflammation in hippocampus and restore cognitive function in hyperammonemic rats. *J. Neuroinflamm.* 20(1):1
108. Dhanda S, Gupta S, Halder A, Sunkaria A, Sandhir R. 2018. Systemic inflammation without gliosis mediates cognitive deficits through impaired BDNF expression in bile duct ligation model of hepatic encephalopathy. *Brain Behav. Immun.* 70:214–32



109. Lu K, Zimmermann M, Görg B, Bidmon H-J, Biermann B, et al. 2019. Hepatic encephalopathy is linked to alterations of autophagic flux in astrocytes. *EBioMedicine* 48:539–53
110. Kang EJ, Cha M-G, Kwon G-H, Han SH, Yoon SJ, et al. 2024. *Akkermansia muciniphila* improve cognitive dysfunction by regulating BDNF and serotonin pathway in gut-liver-brain axis. *Microbiome* 12(1):181
111. Sun X, Shukla M, Wang W, Li S. 2024. Unlocking gut-liver-brain axis communication metabolites: energy metabolism, immunity and barriers. *NPJ Biofilms Microbiomes* 10:136
112. Drucker DJ, Holst JJ. 2023. The expanding incretin universe: from basic biology to clinical translation. *Diabetologia* 66(10):1765–79
113. Kellar D, Craft S. 2020. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. *Lancet Neurol.* 19(9):758–66
114. Heidt T, Sager HB, Courties G, Dutta P, Iwamoto Y, et al. 2014. Chronic variable stress activates hematopoietic stem cells. *Nat. Med.* 20(7):754–58
115. Powell ND, Sloan EK, Bailey MT, Arevalo JMG, Miller GE, et al. 2013. Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via β -adrenergic induction of myelopoiesis. *PNAS* 110(41):16574–79
116. Hu H, Yang X, He Y, Duan C, Sun N. 2022. Psychological stress induces depressive-like behavior associated with bone marrow-derived monocyte infiltration into the hippocampus independent of blood-brain barrier disruption. *J. Neuroinflamm.* 19(1):208
117. Mou R, Ma J, Ju X, Wu Y, Chen Q, et al. 2024. Vasopressin drives aberrant myeloid differentiation of hematopoietic stem cells, contributing to depression in mice. *Cell Stem Cell* 31(12):1794–812.e10
118. Hodes GE, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, et al. 2014. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. *PNAS* 111(45):16136–41
119. Wohleb ES, Powell ND, Godbout JP, Sheridan JF. 2013. Stress-induced recruitment of bone marrow-derived monocytes to the brain promotes anxiety-like behavior. *J. Neurosci.* 33(34):13820–33
120. Biltz RG, Sawicki CM, Sheridan JF, Godbout JP. 2022. The neuroimmunology of social-stress-induced sensitization. *Nat. Immunol.* 23(11):1527–35
121. Cugurra A, Mamuladze T, Rustenhoven J, Dykstra T, Beroshvili G, et al. 2021. Skull and vertebral bone marrow are myeloid cell reservoirs for the meninges and CNS parenchyma. *Science* 373(6553):eabf7844
122. Eiff B, Bullmore ET, Clatworthy MR, Fryer TD, Pariante CM, et al. 2025. Extra-axial inflammatory signal and its relationship to peripheral and central immunity in depression. *Brain* 148(2):635–46
123. McKim DB, Yin W, Wang Y, Cole SW, Godbout JP, Sheridan JF. 2018. Social stress mobilizes hematopoietic stem cells to establish persistent splenic myelopoiesis. *Cell Rep.* 25(9):2552–62.e3
124. Sawada A, Niiyama Y, Ataka K, Nagaishi K, Yamakage M, Fujimiya M. 2014. Suppression of bone marrow-derived microglia in the amygdala improves anxiety-like behavior induced by chronic partial sciatic nerve ligation in mice. *Pain* 155(9):1762–72
125. Kelly MJ, Breathnach C, Tracey KJ, Donnelly SC. 2022. Manipulation of the inflammatory reflex as a therapeutic strategy. *Cell Rep. Med.* 3(7):100696
126. Zhang X, Lei B, Yuan Y, Zhang L, Hu L, et al. 2020. Brain control of humoral immune responses amenable to behavioural modulation. *Nature* 581(7807):204–8
127. Zhu X, Huang J-Y, Dong W-Y, Tang H-D, Xu S, et al. 2024. Somatosensory cortex and central amygdala regulate neuropathic pain-mediated peripheral immune response via vagal projections to the spleen. *Nat. Neurosci.* 27(3):471–83
128. Perrotta S, Carnevale L, Perrotta M, Pallante F, Mikołajczyk TP, et al. 2025. A heart-brain-spleen axis controls cardiac remodeling to hypertensive stress. *Immunity* 58(3):648–65.e7
129. Zafeiropoulos S, Ahmed U, Bekiaridou A, Jayaprakash N, Mughrabi IT, et al. 2024. Ultrasound neuromodulation of an anti-inflammatory pathway at the spleen improves experimental pulmonary hypertension. *Circ. Res.* 135(1):41–56
130. Bronas UG, Puzantian H, Hannan M. 2017. Cognitive impairment in chronic kidney disease: vascular milieu and the potential therapeutic role of exercise. *BioMed Res. Int.* 2017:2726369
131. Zimmermann S, Mathew A, Bondareva O, Elwakiel A, Waldmann K, et al. 2024. Chronic kidney disease leads to microglial potassium efflux and inflammasome activation in the brain. *Kidney Int.* 106(6):1101–16



132. Bugnicourt J-M, Godefroy O, Chillon J-M, Choukroun G, Massy ZA. 2013. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. *J. Am. Soc. Nephrol.* 24(3):353–63
133. Thompson B, Waterhouse M, English DR, McLeod DS, Armstrong BK, et al. 2023. Vitamin D supplementation and major cardiovascular events: D-Health randomised controlled trial. *BMJ* 381:e075230
134. Mesquita SD, Fu Z, Kipnis J. 2018. The meningeal lymphatic system: a new player in neurophysiology. *Neuron* 100(2):375–88
135. Jessen NA, Munk ASF, Lundgaard I, Nedergaard M. 2015. The glymphatic system: a beginner's guide. *Neurochem. Res.* 40(12):2583–99
136. Reader BF, Jarrett BL, McKim DB, Wohleb ES, Godbout JP, Sheridan JF. 2015. Peripheral and central effects of repeated social defeat stress: monocyte trafficking, microglial activation, and anxiety. *Neuroscience* 289:429–42
137. Khrimian L, Obri A, Karsenty G. 2017. Modulation of cognition and anxiety-like behavior by bone remodeling. *Mol. Metab.* 6(12):1610–15
138. Qi X-S, He X, Peng Y, He X-H, Yang Q-Y, et al. 2024. Roles of osteocalcin in the central nervous system. *CNS Neurosci. Ther.* 30(9):e70016
139. Pedersen BK, Febbraio MA. 2012. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat. Rev. Endocrinol.* 8(8):457–65
140. Voss MW, Nagamatsu LS, Liu-Ambrose T, Kramer AF. 2011. Exercise, brain, and cognition across the life span. *J. Appl. Physiol.* 111(5):1505–13
141. Edelman GM, Gally JA. 2001. Degeneracy and complexity in biological systems. *PNAS* 98(24):13763–68
142. Whitacre JM. 2010. Degeneracy: a link between evolvability, robustness and complexity in biological systems. *Theor. Biol. Med. Model.* 7(1):6
143. Colf LA, Bankovich AJ, Hanick NA, Bowerman NA, Jones LL, et al. 2007. How a single T cell receptor recognizes both self and foreign MHC. *Cell* 129(1):135–46
144. Mota CMD, Madden CJ. 2022. Neural control of the spleen as an effector of immune responses to inflammation: mechanisms and treatments. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 323(4):R375–84
145. Ashcroft SP, Stocks B, Egan B, Zierath JR. 2024. Exercise induces tissue-specific adaptations to enhance cardiometabolic health. *Cell Metab.* 36(2):278–300
146. Townsend JR, Kirby TO, Sapp PA, Gonzalez AM, Marshall TM, Esposito R. 2023. Nutrient synergy: definition, evidence, and future directions. *Front. Nutr.* 10:1279925
147. Mancuso E, Sampogna G, Boiano A, Rocca BD, Vincenzo MD, et al. 2023. Biological correlates of treatment resistant depression: a review of peripheral biomarkers. *Front. Psychiatry* 14:1291176
148. Miller AH, Raison CL. 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat. Rev. Immunol.* 16(1):22–34
149. Menard C, Pfau ML, Hodes GE, Kana V, Wang VX, et al. 2017. Social stress induces neurovascular pathology promoting depression. *Nat. Neurosci.* 20(12):1752–60
150. Köhler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, et al. 2014. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 71(12):1381–91
151. Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM, Pariante CM, Howes OD. 2020. Inflammatory markers in depression: a meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. *Brain Behav. Immun.* 87:901–9
152. Miller AH, Pariante CM. 2020. Trial failures of anti-inflammatory drugs in depression. *Lancet Psychiatry* 7(10):837
153. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, et al. 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* 70(1):31–41
154. Chiricozzi A, Romanelli M, Saraceno R, Torres T. 2016. No meaningful association between suicidal behavior and the use of IL-17A-neutralizing or IL-17RA-blocking agents. *Expert Opin. Drug Saf.* 15(12):1653–59



155. Deodhar A, Mease PJ, McInnes IB, Baraliakos X, Reich K, et al. 2019. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. *Arthritis Res. Ther.* 21(1):111
156. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, et al. 2022. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N. Engl. J. Med.* 386(4):316–26
157. Harrison D, Billinton A, Bock MG, Doedens JR, Gabel CA, et al. 2023. Discovery of clinical candidate NT-0796, a brain-penetrant and highly potent NLRP3 inflammasome inhibitor for neuroinflammatory disorders. *J. Med. Chem.* 66(21):14897–911
158. Lee E-J, Han JE, Woo M-S, Shin JA, Park E-M, et al. 2014. Matrix metalloproteinase-8 plays a pivotal role in neuroinflammation by modulating TNF- α activation. *J. Immunol.* 193(5):2384–93
159. Vandenbroucke RE, Dejonckheere E, Van Lint P, Demeestere D, Van Wouterghem E, et al. 2012. Matrix metalloprotease 8-dependent extracellular matrix cleavage at the blood–CSF barrier contributes to lethality during systemic inflammatory diseases. *J. Neurosci.* 32(29):9805–16
160. Dinan TG, Stanton C, Cryan JF. 2013. Psychobiotics: a novel class of psychotropic. *Biol. Psychiatry* 74(10):720–26
161. Correale J, Hohlfeld R, Baranzini SE. 2022. The role of the gut microbiota in multiple sclerosis. *Nat. Rev. Neurol.* 18(9):544–58
162. Tsogka A, Kitsos DK, Stavrogianni K, Giannopapas V, Chasiotis A, et al. 2023. Modulating the gut microbiome in multiple sclerosis management: a systematic review of current interventions. *J. Clin. Med.* 12(24):7610
163. Tzikos G, Chamalidou E, Christopoulou D, Apostolopoulou A, Gkarmiri S, et al. 2025. Psychobiotics ameliorate depression and anxiety status in surgical oncology patients: results from the ProDeCa study. *Nutrients* 17(5):857
164. Sampson TR, Mazmanian SK. 2015. Control of brain development, function, and behavior by the microbiome. *Cell Host Microbe* 17(5):565–76
165. Chinna Meyyappan A, Forth E, Wallace CJK, Milev R. 2020. Effect of fecal microbiota transplant on symptoms of psychiatric disorders: a systematic review. *BMC Psychiatry* 20:299
166. Young AH, Juruena MF, De Zwaef R, Demyttenaere K. 2020. Vagus nerve stimulation as adjunctive therapy in patients with difficult-to-treat depression (RESTORE-LIFE): study protocol design and rationale of a real-world post-market study. *BMC Psychiatry* 20:471
167. Conway CR, Aaronson ST, Sackeim HA, George MS, Zajecka J, et al. 2025. Vagus nerve stimulation in treatment-resistant depression: a one-year, randomized, sham-controlled trial. *Brain Stimul.* 18(3):676–89
168. Kayser MS, Dalmau J. 2016. Anti-NMDA receptor encephalitis, autoimmunity, and psychosis. *Schizophr. Res.* 176(1):36–40
169. Hansen N, Lipp M, Vogelgsang J, Vukovich R, Zindler T, et al. 2020. Autoantibody-associated psychiatric symptoms and syndromes in adults: a narrative review and proposed diagnostic approach. *Brain Behav. Immun. Health* 9:100154
170. Bavato F, Barro C, Schnider LK, Simrén J, Zetterberg H, et al. 2024. Introducing neurofilament light chain measure in psychiatry: current evidence, opportunities, and pitfalls. *Mol. Psychiatry* 29(8):2543–59
171. Kang MJY, Grewal J, Eratne D, Malpas C, Chiu W-H, et al. 2025. Neurofilament light and glial fibrillary acidic protein in mood and anxiety disorders: a systematic review and meta-analysis. *Brain Behav. Immun.* 123:1091–102
172. De Picker LJ, Morrens M, Branchi I, Haarman BCM, Terada T, et al. 2023. TSPO PET brain inflammation imaging: a transdiagnostic systematic review and meta-analysis of 156 case-control studies. *Brain Behav. Immun.* 113:415–31
173. Ma Z (S), Qiao Y, Li L. 2025. Comparative medical ecology of gut microbiomes in major neurodegenerative, neurodevelopmental, and psychiatric (NNP) disorders. Preprint, medRxiv. <https://www.medrxiv.org/content/10.1101/2025.03.16.25324039v1>
174. Jha MK, Leboyer M, Pariante CM, Miller AH. 2025. Should inflammation be a specifier for major depression in the DSM-6? *JAMA Psychiatry* 82(6):549–50
175. Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM. 2019. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychol. Med.* 49(12):1958–70



176. Liang L, Zhang S, Wang Z, Zhang H, Li C, et al. 2025. Single-cell multiomics of neuronal activation reveals context-dependent genetic control of brain disorders. Preprint, bioRxiv. <https://www.biorxiv.org/content/10.1101/2025.02.17.638682v1>
177. Schafer ST, Mansour AA, Schlachetzki JCM, Pena M, Ghassemzadeh S, et al. 2023. An in vivo neuroimmune organoid model to study human microglia phenotypes. *Cell* 186(10):2111–26.e20
178. Tian A, Bhattacharya A, Muffat J, Li Y. 2025. Expanding the neuroimmune research toolkit with in vivo brain organoid technologies. *Dis. Model. Mech.* 18(4):dmm052200
179. Huang R, Gao F, Yu L, Chen H, Zhu R. 2025. Generation of neural organoids and their application in disease modeling and regenerative medicine. *Adv. Sci.* 12(29):e01198
180. Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. 2023. The blood–brain barrier: structure, regulation, and drug delivery. *Signal Transduct. Target. Ther.* 8:217
181. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. 2021. Engineering precision nanoparticles for drug delivery. *Nat. Rev. Drug Discov.* 20(2):101–24
182. Jolesz FA. 2009. MRI-guided focused ultrasound surgery. *Annu. Rev. Med.* 60:417–30

