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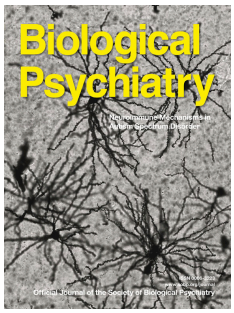

Cytokines as neuromodulators: insights from experimental studies in humans and non-human primates

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PII: S0006-3223(25)01315-0

DOI: https://doi.org/10.1016/j.biopsych.2025.06.037

Reference: BPS 15876

To appear in: *Biological Psychiatry*

Received Date: 18 February 2025

Revised Date: 19 June 2025

Accepted Date: 22 June 2025

Please cite this article as: Martins D. & Harrison N.A, Cytokines as neuromodulators: insights from experimental studies in humans and non-human primates *Biological Psychiatry* (2025), doi: https://doi.org/10.1016/j.biopsych.2025.06.037.

Special Issue: Brain – immune communication in Health and Disease

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Running title: Cytokines as neuromodulators

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Type: Review article

Abstract

Beyond their role in immune signalling, cytokines have emerged as key neuromodulators influencing processes including neurotransmitter function, neuronal excitability, synaptic plasticity, neurogenesis, myelination, and cortical sleep-state. These roles are observed in both the healthy brain and during infections when they reorient motivational, cognitive, and emotional responses. Experimental evidence from human and non-human primate immune challenge studies has been pivotal to understanding these effects. By showing that elevated cytokines readily induce transdiagnostic symptoms, including anhedonia, social withdrawal, psychomotor slowing, and cognitive impairment, they have also helped demonstrate that inflammation contributes to the shared neural dysfunction observed across psychiatric and neurological disorders. Cytokines modulate glutamatergic and GABAergic neurotransmission, impair dopaminergic and serotonergic signalling, and regulate homeostatic synaptic scaling, leading to altered network connectivity and behavioural deficits. While research has often focused on single cytokines in isolation, neuroimmune signalling occurs through combinatorial cytokine codes, requiring systems-level approaches to understand their interactive effects. Advances in neuroimaging, molecular neuroscience, and biophysical modelling offer opportunities to link cellular cytokine action with macroscale network dysfunction, enabling mechanistic insights into cytokine-mediated neuromodulation. Clinically, cytokine-targeting therapies hold promise for treating inflammation-driven cognitive and mood disorders, but their long-term impact on neuroplasticity remains uncertain. Future research should characterize immune signatures predictive of neuropsychiatric symptoms, identify cell-type-specific cytokine effects, and integrate multiscale modelling to refine understanding of neuroimmune interactions. Reconceptualising cytokines as fundamental regulators of neural function rather than merely inflammatory mediators is crucial for developing precision medicine to mitigate immune-driven brain dysfunction and improve mental health outcomes.

Key-words: Cytokines; Neuromodulation; Behavioural integration; Imaging Biomarkers; Immunopsychiatry; Precision Psychiatry

1. Introduction

Cytokines are central to inter-cellular communication, particularly within the immune system. Traditionally known for coordinating responses to infection, injury, and inflammation, recent reviews/perspectives highlight their roles as neuromodulators (1-3). Cytokine receptors are widely expressed in the central nervous system (CNS), facilitating actions on neuronal excitability, synaptic plasticity, and network stability(4) which govern cognition, motivation, and emotion(1-3), even in the noninflamed state.

Neuromodulators are broadly defined as substances that modulate neuronal excitability and synaptic plasticity over slower timescales - typically acting at nanomolar to picomolar concentrations - and exerting their effects on distributed circuits rather than discrete synapses. Cytokines meet these criteria and have therefore been increasingly recognized as bona fide neuromodulators. For example, IL-17A has been shown to directly increase the excitability of human sensory neurons, providing compelling evidence of direct neuromodulatory actions in primates(5). Recent work has also demonstrated that IL-17E (also known as IL-25) and its receptor IL17RB are expressed across the brain and regulate neuronal activity, highlighting an unexpected neuroimmune axis with regionally organized functional roles(6). Additionally, immune checkpoint inhibitors have been shown to regulate hippocampal neuron activity in nonhuman brain slices(7). Unlike classical neurotransmitters, which mediate rapid, localized communication, cytokines function as long-range modulators that can shape neural activity over extended spatial and temporal scales(8). By altering synaptic strength, neurotransmitter release, and neuroplasticity, cytokines also serve as a critical interface between peripheral immune activity and CNS function(3). These multifaceted roles in fundamental neuronal processes not only help maintain brain homeostasis but also enable rapid reorientation of behavioral responses during infection or inflammation(1, 3, 9).

Emerging research links elevated cytokine levels to transdiagnostic symptoms, including cognitive dysfunction, mood disturbances, anhedonia, social withdrawal, and psychomotor slowing, suggesting a shared mechanism across psychiatric and neurological disorders(9-11). Experimental studies in humans and non-human primates using immune challenge paradigms, such as interferon-alpha (IFN-α), lipopolysaccharide (LPS), and typhoid vaccination, provide causal evidence that inflammation alters neural circuits involved in motivation, executive function, and reward processing(9, 11).

Here, we focus on how experimental studies in humans and non-human primates, combined with knowledge of cytokine production, receptor distribution and mechanisms of action within the CNS, have provided new insights into their neuromodulatory roles and established cytokines as fundamental regulators of neural function, beyond their classical roles in immunity. We cover their influence on neurotransmission, synaptic plasticity, and neural network dynamics, highlighting clinical implications for immune-driven neural

dysfunction. The recognition of cytokines as fundamental regulators of brain function is placing immune-brain interactions at the center of neuropsychiatric research and emerging precision therapies.

2. Cytokines production and its regulation in the CNS

Within the central nervous system (CNS), cytokines are produced by a diverse range of cellular sources, including glial cells (microglia, astrocytes, and oligodendrocytes) (12), neurons(13, 14), endothelial cells at the blood-brain barrier (BBB)(15), meningeal immune cells(16), the skull bone marrow(17), and the choroid plexus(18) (see Supplementary material for an extended review and Figure 1). Single-cell transcriptomics integrating receptor and ligand expression data, such as those in the Allen Human Brain Atlas efforts(19, 20), have shed light on the highly specialized roles of different CNS cell populations in cytokine-mediated signalling (Supplementary Figure 1). Rapid advances in producing a human cell atlas and discovery that humans consist of thousands (not hundreds) of individual cell types will undoubtedly advance this still further in the coming years(21, 22).

3. Cytokine receptor signalling and distribution within the CNS

Within the CNS, cytokine receptors are expressed across diverse cell types, including neurons, glia, and the endothelial cells of the blood-brain barrier (BBB)(23). The distinct distribution of cytokine receptor families, such as Type I and Type II cytokine receptors, the TNF receptor superfamily, IL-1 and TGF-β receptor families, and chemokine receptors(24) varies substantially across brain and spinal cord regions, thereby shaping region and circuit-specific cytokine sensitivity. This aligns closely with network-based models for the pathophysiology of psychiatric disorders (see Supplementary material for extended review and Figure 2).

4. Mechanisms of Neuromodulation by Cytokines

As illustrated below, cytokines exert neuromodulatory effects through a complex interplay of mechanisms that regulate neuronal excitability, neurotransmitter balance and synaptic plasticity and remodelling(2, 3) (Figure 3).

4.1. Ion Channel Modulation

Ion channels regulate neuronal excitability, synaptic transmission, and network dynamics, making them key targets of cytokine neuromodulation. Cytokines modulate voltage-gated sodium (Na^+), calcium (Ca^{2+}), and potassium (K^+) channels through receptor interactions, intracellular signalling cascades, and post-translational modifications, with effects that can be direct, opposing, and context-dependent (4, 25). For example, in vitro patch-clamp studies in rat hippocampal neurons have shown IL-1β enhances sodium channel conductance, resulting in lowering of activation thresholds and an increase in neuronal excitability, particularly in circuits involving top-down and bottom-up regulation of emotion like the prefrontal cortex,

and amygdala(4, 25, 26). TNF-α, IL-6, and IL-1β inhibit voltage-gated calcium channels (VGCCs), reducing presynaptic Ca^{2+} influx and limiting neurotransmitter release through TNFR1-PKC signalling(27). This mechanism is proposed to protect against excitotoxicity, however, of potential importance to depression, it also impairs synaptic plasticity and cognition by disrupting synaptic vesicle fusion(4, 25). IL-1β further suppresses voltage-gated K^+ channels, prolonging depolarization and increasing microglial activation. This sustained excitability fosters a pro-inflammatory environment exacerbating neuroinflammation in disorders such as Alzheimer's disease. This imbalance is also thought to contribute to the excitation-inhibition deficits observed in schizophrenia, bipolar disorder and autism spectrum disorder(2, 4, 28). Cytokines also modulate transient receptor potential (TRP) channels such as TRPV1 and TRPA1, which are key to nociceptive signalling and central pain amplification but less explored in the context of neuropsychiatric disorders(29).

4.2. Regulation of neurotransmitter and monoaminergic neuromodulatory systems

Cytokines can also alter neurotransmission by disrupting excitatory-inhibitory neurotransmission and modulating monoaminergic systems(2). Pro-inflammatory cytokines like TNF-α can enhance glutamate release and impair astrocytic reuptake, increasing extracellular glutamate and excitatory drive, contributing to neuroinflammatory conditions such as schizophrenia and depression(30-32). This might represent an important mechanism of resistance to conventional treatment in subsets of patients with elevated inflammatory markers(33), where innovative therapeutics such as ketamine might hold particular promise(34). In vitro studies in rat hippocampal neurons found that IL-6, however, inhibits excitatory transmission by upregulating adenosine A1 receptors and downregulating mGluR2/3, potentially modulating stress-induced excitotoxicity but at the cost of cognitive function(35, 36).

Cytokines also impair GABAergic signalling. TNF-α reduces GABA-A receptor expression, weakening inhibition and promoting hyperexcitability linked to anxiety, cognitive rigidity, and seizures. In contrast, IFN-γ increases GABA release in prefrontal cortex, while IL-1β upregulates α5-GABA-A receptors, contributing to inflammation-induced memory deficits(37-39). Preclinical in vivo rodent studies indicate that positive and negative modulators of α5-GABA-A receptors have antidepressant-like actions, likely involving improved signal-to-noise ratio in cortical microcircuits(40). While involvement of α5-GABA-A receptors in inflammation-induced mood impairment remains to be established, these agents could potentially offer new alternatives for treating depression and cognitive impairment in inflamed subgroups.

Relevant to inflammation-associated depression and psychomotor slowing, IL-6 and TNF-α downregulate tyrosine hydroxylase, reducing dopamine synthesis in the striatum (50-52). They also decrease D2 receptor availability and increase dopamine transporter expression, leading to accelerating dopamine clearance and anhedonia in non-human

primates (41-43). Similarly, IL-1β and TNF-α enhance serotonin transporter activity(44, 45), depleting extracellular serotonin and contributing to depression, as observed in patients under IFN-α therapy(46, 47). The kynurenine pathway (KP), which diverts tryptophan from serotonin synthesis toward neuroactive metabolites, is a key link between immune activation and neurotransmitter disruption(48). Quinolinic acid, an NMDA receptor agonist, exacerbates excitotoxic glutamate signalling, further impairing neural function in inflammatory conditions(49). Interestingly, psychedelics, which are attracting increasing attention in neuropsychiatry, appear to modulate the KP directly through enzyme regulation and indirectly through the gut-brain axis and immune interactions(50).

4.3. Synaptic Plasticity and Pruning

Cytokine influences on long-term potentiation (LTP) and long-term depression (LTD), key to synaptic functional plasticity, learning and memory, provide another mechanism for adaptive and maladaptive changes in neural circuits relevant to psychiatry (2). At low levels, IL-1β enhances synaptic plasticity by increasing NMDA receptor phosphorylation and calcium influx. However, excessive IL-1β inhibits LTP, promotes LTD, and weakens synapses, contributing to memory deficits in late-life depression and Alzheimer's disease(2, 51-53). Homeostatic synaptic scaling, which stabilizes network activity, is also cytokine-dependent(54). Here, TNF-α regulates AMPA receptor trafficking, increasing receptor insertion under low synaptic activity to restore excitability and promoting receptor internalization under excessive activity to reduce excitatory drive. Chronic TNF-α elevation disrupts this balance contributing to the synaptic dysregulation seen in schizophrenia, epilepsy and multiple sclerosis(55). Cytokines also influence synaptic pruning, a microglia-mediated process implicated in schizophrenia and neurodevelopment disorders(56). Here, microglia eliminate weak synapses via complement-mediated tagging, with proteins like C1q and C3 marking synapses for removal(57). IL-6 enhances complement expression, accelerating synaptic elimination. Moreover, interferons, for instance, regulate a broad array of interferon-stimulated genes (ISGs) involved in metabolism, synaptic pruning, and oxidative stress(58, 59).

5. Experimental Evidence from Human and Primate Studies with Immune Challenges

Controlled immune modulation models, including IFN-α, LPS, typhoid vaccination, and anti-TNF-α therapy, enable precise manipulation of inflammatory signalling, offering insights into cytokine-driven neuromodulation(11, 60, 61). IFN-α (interferon-alpha) has been shown to cross the BBB, allowing it to directly influence brain function(62). LPS is a prototypical pathogen-associated molecular pattern that activates the innate immune system through a Toll-like receptor 4-dependent pathway(63). LPS administration and typhoid vaccination in humans induce peripheral IL-6, TNF-α, and IL-1β elevations, with downstream effects on CNS activation, though direct CNS measurements in humans remain limited(59, 62, 64-66). When combined with neuroimaging (fMRI, PET, EEG), these models reveal inflammation-induced

brain changes affecting mood, cognition, and behaviour. Studies in humans (Supplementary Table S1) demonstrate how acute immune activation mirrors symptoms of psychiatric and neurological disorders, while primate studies (Supplementary Table S2) provide mechanistic insights into cytokine effects on neural circuits. Below, we review key findings from both.

5.1. Human Studies

Human immune challenge studies demonstrate that acute inflammation affects motivation**,** cognition**,** social behaviour, mood, sleep, pain perception**,** and interoception, mirroring symptoms in disorders with chronic immune dysregulation (Supplementary Table S1). These effects are linked to changes in neurotransmission, network connectivity, and metabolic activity within key brain circuits (summarized in Figure 4), similarly observed across patients with neurological and psychiatric disorders.

5.1.1. Motivation and Reward: Cytokines regulate motivation and reward sensitivity, a key factor in depression, fatigue-related disorders, and anhedonia**.** Individuals undergoing immune activation, whether due to infection, chronic illness, or therapeutic cytokine administration, exhibit blunted reward anticipation, reduced effort-based decision-making, and heightened avoidance behaviours -hallmarks of sickness behaviour that closely resemble motivational deficits in psychiatric disorders**.** A striking example is the use of interferon-alpha (IFN-α) in hepatitis-C and melanoma, which frequently induces anhedonia, psychomotor slowing, and social withdrawal(67, 68). These behavioural effects correlate with increased proinflammatory cytokine levels (IL-6, TNF-α, and IL-1β) and disrupted dopaminergic signalling(41, 69), suggesting that neuroimmune interactions shape motivational impairments in inflammation-associated depression.

Neuroimaging studies provide converging evidence: [18F]FDG-PET scans reveal reduced glucose metabolism in prefrontal cortex alongside increased basal ganglia activity, indicative of impaired reward processing after IFN-α(70, 71). Functional MRI (fMRI) studies confirm blunted striatal responses during reward anticipation associated with increased circulating IL-6 and TNF-α, consistent with cytokine-induced alterations in dopaminergic transmission(72). Even milder immune challenges, such as typhoid vaccination**,** transiently reduce ventral striatal activity and shift motivation from approach to avoidance behaviour**,** reinforcing the idea that immune activation biases decision-making toward threat avoidance at the expense of goal-directed reward-seeking(73, 74). This effect extends to effort-based decision-making, where inflammation increases the perceived cost of exerting effort, contributing to fatigue, anergia, and amotivation seen in chronic inflammatory conditions, major depression, and schizophrenia(75, 76). These findings support a cytokine-dopamine interaction model, where inflammation-induced glial activation, kynurenine pathway shifts, and altered dopamine synthesis lead to functional impairments in the striatum and prefrontal cortex.

Understanding how cytokines reconfigure motivational circuits provides a neurobiological basis for targeting neuroinflammation in psychiatric conditions, offering potential therapeutic avenues such as anti-inflammatory treatments, neuromodulation, and pro-dopaminergic interventions to restore motivational processing in affected individuals(75).

5.1.2. Cognition and Executive Function: Inflammation impairs cognitive flexibility, working memory, and executive control, reflecting disrupted network integration(77). LPS administration slows cognition and weakens attentional control. PET studies confirm increased glial activation (evidenced by increased TSPO PET binding using multiple tracers, such as [^{11}C]PBR28 or [^{18}F]DPA-714) in limbic and cortical regions, reinforcing the role of pro-inflammatory cytokines in cognitive dysfunction. Time-frequency analyses of EEG signals reveal reduced theta power, impairing cognitive control(78), and increased beta power, shifting attentional states(79). These changes, also seen in disorders like schizophrenia and neurodegeneration, highlight inflammation's impact on neural efficiency and connectivity.

5.1.3. Mood and Emotional Regulation: Cytokine-induced inflammation contributes to low mood, heightened negative affect, and emotional reactivity, central to depression and anxiety. IFN-α therapy frequently induces depressive symptoms, including sadness, fatigue, and emotional blunting. Similarly, LPS administration increases negative mood(80). Functional MRI data links these effects to amygdala hyperactivity and subgenual anterior cingulate cortex (sACC) dysfunction, both implicated in affective disorders(81, 82). IFN-α heightens amygdala reactivity, while anti-TNF-α therapy dampens it, suggesting cytokine modulation of emotional processing and psychosocial stress reactivity(83). Evidence from in vivo human IFN-α therapy studies confirms increased cerebrospinal fluid (CSF) concentrations of serotonin metabolites (5-HIAA), reflecting disrupted serotonergic turnover, alongside worsening depressive symptoms(48). Noteworthy, symptoms improve with specific serotonin reuptake inhibitors(47). IFN-α and LPS administration enhance serotonin transporter (SERT) activity, increasing serotonin reuptake and depleting synaptic serotonin, a mechanism linked to the onset of depression during cytokine therapy(84). In vivo PET imaging human studies confirm that TNF-α inhibition reduces SERT binding ([^{123}I]-CIP), supporting the hypothesis that inflammatory blockade can restore serotonergic homeostasis and mitigate affective symptoms(45).

5.1.4. Social Behaviour: Cytokines influence social behaviour, promoting withdrawal and reduced social interest. IFN-α-treated individuals report diminished social motivation(37), while LPS administration increases perceived social disconnection(85). Functional MRI shows blunted striatal responses to social rewards, suggesting inflammation disrupts social reinforcement processing(86). Increased amygdala reactivity to social threats may drive avoidance behaviour, contributing to social withdrawal in depression and schizophrenia.

5.1.5. Pain and Interoception: Inflammation amplifies pain perception and interoceptive awareness(87). Functional task-based MRI studies show that LPS and IFN-α administration heighten activity in pain-processing regions like the anterior insula, mid-cingulate cortex, and thalamus, increasing pain unpleasantness even without altered thresholds(88-91). These effects extend to social and emotional pain, with fMRI studies showing decreased empathy(92). Additional correlational evidence has shown that increases in CSF and peripheral IP-10 (CXCL10) and IL-8 are associated with increased pain sensitivity(93).

5.1.6. Sleep: Inflammation disrupts sleep architecture, likely through cytokine effects on serotonergic and homeostatic regulation. Elevated peripheral IL-6 levels have been associated with reduced sleep continuity and increased nighttime awakenings in both clinical and experimental studies. In contrast, central administration of IL-1β enhances non-rapid eye movement (NREM) sleep and increases EEG delta (0.5–4 Hz) power, a marker of sleep intensity, across multiple species including rodents, cats, primates, and humans(94-96). Immune challenge models using IFN-α or LPS further show increased wakefulness, reduced slow-wave sleep (SWS), and prolonged REM latency, leading to fragmented, non-restorative sleep patterns(97-99).

Beyond global changes in sleep stages, recent work suggests that cytokines may also influence “local sleep” dynamics - a phenomenon where specific brain regions enter sleep-like states independently of global vigilance(100). IL-1 and TNF-α have been shown to modulate local delta power in cortical areas, reflecting use-dependent sleep regulation and neuronal recovery at the circuit level(94-96). This may be particularly relevant in inflammation, where regional cytokine gradients and receptor expression patterns vary. Aberrant local sleep induction during wakefulness may contribute to lapses in attention, fatigue, and slowed cognition(101), while impaired local NREM expression in task-relevant areas during sleep could hinder neural replay and consequently memory consolidation and emotional processing(102, 103). Thus, cytokine-induced alterations in local sleep homeostasis may represent a key mechanism linking inflammation to the neurocognitive symptoms observed in depression, chronic fatigue, and neurodegenerative conditions.

5.2. Primate Studies

Non-human primates (NHPs) provide a critical translational model for studying the neuromodulatory role of cytokines. Their close phylogenetic relationship to humans, including similarities in brain structure, immune response, and behavioural repertoire, makes them uniquely suited to bridge the gap between basic research and clinical applications. A significant advantage of NHP models is the possibility of precisely controlled experimental conditions, enabling rigorous investigation into how specific cytokines influence neural activity, connectivity patterns, and resulting behaviors. Such controlled experimental manipulations are typically infeasible or unethical in human studies, underscoring the value of NHP research for elucidating cytokine-driven neuromodulation(104).

Administration of lipopolysaccharide (LPS), a potent immune stimulant, in baboons provides an established experimental model to study systemic inflammation and neuroimmune interactions. Such inflammatory challenges induce marked neuroinflammation characterized by elevated translocator protein (TSPO) expression(105) ([^{11}C]PBR28) and colony-stimulating factor 1 receptor (CSF1R) binding ([^{11}C]CPPC) (106), reflecting activated microglia in the central nervous system. This robust neuroinflammatory response closely parallels findings from human PET imaging studies, thus validating the translational utility of NHP models for understanding immune–CNS interactions in psychiatric and neurological disorders.

Studies in rhesus monkeys further illustrate the translational relevance of NHP to help us dissect further mechanisms of cytokine-induced neuromodulation. For instance, administration of interferon-alpha (IFN-α) - a cytokine commonly used therapeutically in humans - results in decreased striatal dopamine release. This reduction in dopamine availability is associated with pronounced anhedonia and anxiety-like behaviors, symptoms that mirror depressive phenotypes frequently observed in patients receiving IFN-α treatment(107). Critically, these behavioral and neurochemical changes can be partially reversed by dopamine precursors such as L-DOPA(107), providing mechanistic insights into immune-induced mood dysregulation and potential therapeutic avenues(108) (Supplementary Table S2)**.** Advanced neuroimaging and neurochemical techniques, such as PET imaging combined with microdialysis, have confirmed cytokine-mediated disruptions in dopamine neurotransmission within the striatum of rhesus monkeys(107). These findings directly link peripheral immune activation to alterations in central reward circuitry, offering strong translational evidence that cytokines modulate mood, motivation, and reward processing through specific neurochemical pathways.

6. Clinical Implications: Inflammation-driven neural dysfunction as a transdiagnostic factor

A core set of transdiagnostic symptoms emerges in response to cytokine dysregulation, including anhedonia, psychomotor slowing, cognitive impairment, social withdrawal, fatigue,

and altered sleep patterns. These symptoms are consistently reported in neuropsychiatric conditions such as depression, psychosis, chronic fatigue, Parkinson's disease, and multiple sclerosis, where immune dysregulation is also often observed(109). That experimental immune challenges can reliably induce similar symptoms in healthy individuals provides compelling evidence that cytokine signalling is not merely a secondary consequence of disease but might be an active participant in shaping neuropsychiatric dysfunction in a way that transcend traditional disease boundaries(110, 111), at least in subsets of patients with heightened inflammation.

These insights position a cytokine-driven framework as a potential unifying model for understanding psychiatric disorders, with significant implications for diagnosis and treatment(61). Traditional classifications rely on broad symptom clusters, but stratifying patients based on inflammatory markers may better help refine therapeutic approaches(111). However, not all neuropsychiatric patients show elevated inflammatory markers, which vary according to genetic predisposition, early-life exposures(112), and comorbidities(113). Integrating immune biomarkers into clinical assessments could enable a more mechanistically informed and personalized approach to mental health care, improving outcomes for patients with immune-related neuropsychiatric symptoms.

By restoring cytokine-mediated homeostatic brain function, future treatments may address not only symptomatic relief but also the underlying neural dysfunction. Pharmacological strategies targeting neuroinflammation include cytokine inhibitors such as TNF-α and IL-6 blockers, which have shown promise in treating inflammation-associated depression and cognitive dysfunction in patients with elevated inflammatory markers(111). Modulation of microglial activity through agents like TSPO ligands, minocycline, and CSF1R inhibitors may also alleviate mood and cognitive symptoms, while antidepressants with anti-inflammatory properties, such as SSRIs, bupropion, and ketamine, could offer dual benefits by addressing both neurotransmitter imbalances and immune dysfunction(111).

Beyond pharmacological treatments, non-pharmacological interventions play a crucial role in mitigating inflammation-driven neuropsychiatric symptoms. Regular physical activity and anti-inflammatory diets rich in omega-3 fatty acids and polyphenols have been shown to reduce systemic inflammation and improve mood and cognition (114). Vagus nerve stimulation, which modulates inflammatory responses, has demonstrated efficacy in treatment-resistant depression and cognitive disorders(115). Mind-body interventions, including mindfulness, meditation, and cognitive-behavioural therapy, can help counteract stress-induced inflammation, promoting emotional and cognitive resilience(116). Irrespectively of the type of intervention though, treatments must reduce pathological inflammation without disrupting immune functions essential for neurodevelopment and plasticity.

7. Outstanding Questions and Directions for Future Research

Despite progress, key gaps remain in understanding cytokine neuromodulation, particularly in integrating immune-brain models with patient-specific variability for targeted therapies. Research has largely focused on individual cytokines, overlooking their dynamic interactions within broader immune networks. Cytokine effects depend on combinatorial signalling, timing, spatial distribution, and receptor crosstalk(117, 118). A systems-level approach incorporating longitudinal multi-cytokine profiling and network modelling is needed to clarify how immune signals shape neural function in health and disease.

A major challenge is determining cell-type specificity in cytokine action. While microglia are key immune sensors, astrocytes, oligodendrocytes, and neurons also respond to cytokines, influencing neuroplasticity, metabolism, and synaptic remodelling(1, 2). The same cytokine can have opposing effects depending on cell type and receptor expression. Single-cell RNA sequencing and spatial proteomics will be important for clarifying how cytokine responses differ across microglia, astrocytes, and neurons.

Bridging molecular immune mechanisms with macroscale neural activity remains another hurdle. While neuroimaging shows inflammation disrupts networks governing motivation, cognition, and emotion, these findings lack mechanistic clarity. Multiscale biophysical modelling(119) integrating cytokine signalling with neural oscillations, neurotransmitter dynamics, and network connectivity could clarify causal links between immune activation and neuropsychiatric symptoms. For instance, computational frameworks like The Virtual Brain(120) or Human Neocortical Neurosolver(121) could be extended to include cytokine signalling nodes that modulate excitatory/inhibitory balance or plasticity thresholds. In parallel, human PET imaging of cytokine receptors combined with fMRI and EEG could help validate model predictions. Additionally, comparing acute vs. chronic inflammatory states across immune challenge paradigms may clarify how transient vs. sustained cytokine exposure differentially reshapes network topology. Ultimately, this multilevel integration could identify mechanistic pathways by which specific immune profiles produce distinct symptom clusters.

Despite their value in identifying the neural circuits most sensitive to inflammation, and their relationship with discrete symptoms, most immune challenge models allow only a brief snapshot into the effects of systemic inflammation on the brain. For example, most studies only investigate effects 3-8 hours after immune challenge, thus in their current guise they may be less useful for providing insights into inter-individual differences in response to more chronic immune activation. This is important, as many neuropsychiatric and neurodegenerative disorders involve persistent, low-grade inflammation rather than acute immune responses. To date, relatively few studies have investigated how brain and behavioural responses to acute inflammatory challenges relate to changes observed with more chronic inflammation or whether characterisation of acute responses can predict the

longer-term consequences of sustained inflammation(83, 122). Future studies should investigate whether responses to acute inflammation constitute good experimental models by examining their predictive power for outcomes in chronic conditions.

Related to this, there is limited understanding of the duration and reversibility of inflammation-induced neural changes. While acute immune activation causes temporary cognitive and mood disruptions, long-term effects may involve maladaptive plasticity, microglial priming, and persistent neurotransmitter imbalances(123). Longitudinal studies leveraging recent advances in machine learning and artificial intelligence for identifying individuals at risk for prolonged impairments and determining whether early interventions can prevent chronic neuropsychiatric and neurodegenerative conditions is essential.

Age-related differences in immune-neural interactions also require study. Older adults exhibit heightened cognitive and mood disturbances following immune activation, likely due to increased microglial reactivity and weakened neuroprotection(124, 125). Whether inflammation accelerates neurodegeneration or interacts with pre-existing vulnerabilities remains uncertain. Understanding these processes is crucial for designing interventions to mitigate inflammation-driven cognitive decline.

8. Conclusions

Experimental and clinical evidence now supports cytokines as neuromodulators that influence neural excitability, connectivity, and behaviour. Immune challenge studies in humans and non-human primates show that transient inflammation can trigger neuropsychiatric symptoms resembling those in chronic disorders, urging a shift from viewing cytokines as mere inflammatory byproducts to recognizing their direct role in brain function. Reframing cytokines as neuromodulators invites novel therapeutic strategies that restore immune–neural balance, moving beyond symptom relief to address core neurophysiological dysfunction. Advances in neuroimaging, transcriptomics, and computational modelling now allow detailed examination of cytokine effects at cellular and circuit levels, potentially uncovering novel therapeutic targets. Although anti-inflammatory therapies have shown some promise in reducing depressive symptoms, their long-term impact on neural plasticity and cognition remains uncertain. Clinical heterogeneity must be acknowledged explicitly, as not all forms of depression or other psychiatric conditions will necessarily have inflammatory underpinnings. Recognizing this variability is crucial for precision psychiatry, ensuring targeted interventions tailored to individual neuroimmune profiles.

Acknowledgments: DM is supported by the NIHR Maudsley Biomedical Research Centre, South London and Maudsley NHS Trust. DM conceptualized the review, coordinated the literature search, and drafted the initial manuscript. NH provided critical revisions, contributed to data interpretation, and assisted with final manuscript preparation. Both authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflicts of Interest: The authors report no biomedical financial interests or potential conflicts of interest.

Supplement Description:

Supplement Text and Tables S1-S2

References:

1. Vitkovic L, Bockaert J, Jacque C (2000): "Inflammatory" cytokines: neuromodulators in normal brain? *J Neurochem*. 74:457-471.
2. Zipp F, Bittner S, Schafer DP (2023): Cytokines as emerging regulators of central nervous system synapses. *Immunity*. 56:914-925.
3. Salvador AF, de Lima KA, Kipnis J (2021): Neuromodulation by the immune system: a focus on cytokines. *Nat Rev Immunol*. 21:526-541.
4. Vezzani A, Viviani B (2015): Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. *Neuropharmacology*. 96:70-82.
5. Luo X, Chen O, Wang Z, Bang S, Ji J, Lee SH, et al. (2021): IL-23/IL-17A/TRPV1 axis produces mechanical pain via macrophage-sensory neuron crosstalk in female mice. *Neuron*. 109:2691-2706 e2695.
6. Lee Y, Ishikawa T, Lee H, Lee B, Ryu C, Davila Mejia I, et al. (2025): Brain-wide mapping of immune receptors uncovers a neuromodulatory role of IL-17E and the receptor IL-17RB. *Cell*. 188:2203-2217 e2217.
7. Zhao J, Bang S, Furutani K, McGinnis A, Jiang C, Roberts A, et al. (2023): PD-L1/PD-1 checkpoint pathway regulates hippocampal neuronal excitability and learning and memory behavior. *Neuron*. 111:2709-2726 e2709.
8. Alcedo J, Prahlad V (2020): Neuromodulators: an essential part of survival. *J Neurogenet*. 34:475-481.
9. Miller AH, Haroon E, Felger JC (2017): The Immunology of Behavior-Exploring the Role of the Immune System in Brain Health and Illness. *Neuropsychopharmacology*. 42:1-4.
10. Goldsmith DR, Bekhbat M, Mehta ND, Felger JC (2023): Inflammation-Related Functional and Structural Dysconnectivity as a Pathway to Psychopathology. *Biol Psychiatry*. 93:405-418.
11. Lasselin J, Lekander M, Benson S, Schedlowski M, Engler H (2021): Sick for science: experimental endotoxemia as a translational tool to develop and test new therapies for inflammation-associated depression. *Mol Psychiatry*. 26:3672-3683.
12. Vezzani A, Ravizza T, Balosso S, Aronica E (2008): Glia as a source of cytokines: implications for neuronal excitability and survival. *Epilepsia*. 49 Suppl 2:24-32.
13. Bledsoe AW, Jackson CA, McPherson S, Morrow CD (2000): Cytokine production in motor neurons by poliovirus replicon vector gene delivery. *Nat Biotechnol*. 18:964-969.
14. Schluter D, Deckert M, Hof H, Frei K (2001): Toxoplasma gondii infection of neurons induces neuronal cytokine and chemokine production, but gamma interferon- and tumor necrosis factor-stimulated neurons fail to inhibit the invasion and growth of T. gondii. *Infect Immun*. 69:7889-7893.
15. Verma S, Nakaoke R, Dohgu S, Banks WA (2006): Release of cytokines by brain endothelial cells: A polarized response to lipopolysaccharide. *Brain Behav Immun*. 20:449-455.
16. Wieseler-Frank J, Jekich BM, Mahoney JH, Bland ST, Maier SF, Watkins LR (2007): A novel immune-to-CNS communication pathway: cells of the meninges surrounding the spinal cord CSF space produce proinflammatory cytokines in response to an inflammatory stimulus. *Brain Behav Immun*. 21:711-718.
17. Mazzitelli JA, Pulous FE, Smyth LCD, Kaya Z, Rustenhoven J, Moskowitz MA, et al. (2023): Skull bone marrow channels as immune gateways to the central nervous system. *Nat Neurosci*. 26:2052-2062.
18. Cui J, Xu H, Lehtinen MK (2021): Macrophages on the margin: choroid plexus immune responses. *Trends Neurosci*. 44:864-875.

19. Shen EH, Overly CC, Jones AR (2012): The Allen Human Brain Atlas: comprehensive gene expression mapping of the human brain. *Trends Neurosci*. 35:711-714.
20. Chen X, Huang Y, Huang L, Huang Z, Hao ZZ, Xu L, et al. (2024): A brain cell atlas integrating single-cell transcriptomes across human brain regions. *Nat Med*. 30:2679-2691.
21. Heimberg G, Kuo T, DePianto DJ, Salem O, Heigl T, Diamant N, et al. (2024): A cell atlas foundation model for scalable search of similar human cells. *Nature*.
22. Rood JE, Wynne S, Robson L, Hupalowska A, Randell J, Teichmann SA, et al. (2025): The Human Cell Atlas from a cell census to a unified foundation model. *Nature*. 637:1065-1071.
23. Dantzer R (1996): Expanding the range of cytokines and cytokine receptors in the brain. *Mol Psychiatry*. 1:98.
24. Wang X, Lupardus P, Laporte SL, Garcia KC (2009): Structural biology of shared cytokine receptors. *Annu Rev Immunol*. 27:29-60.
25. Viviani B, Gardoni F, Marinovich M (2007): Cytokines and neuronal ion channels in health and disease. *Int Rev Neurobiol*. 82:247-263.
26. Zhang P, Bi RY, Gan YH (2018): Glial interleukin-1beta upregulates neuronal sodium channel 1.7 in trigeminal ganglion contributing to temporomandibular joint inflammatory hypernociception in rats. *J Neuroinflammation*. 15:117.
27. Ma SH, Li B, Huang HW, Peng YP, Qiu YH (2012): Interleukin-6 inhibits L-type calcium channel activity of cultured cerebellar granule neurons. *J Physiol Sci*. 62:385-392.
28. Cocozza G, Garofalo S, Capitani R, D'Alessandro G, Limatola C (2021): Microglial Potassium Channels: From Homeostasis to Neurodegeneration. *Biomolecules*. 11.
29. Martins D, Tavares I, Morgado C (2014): "Hotheaded": the role OF TRPV1 in brain functions. *Neuropharmacology*. 85:151-157.
30. Carmen J, Rothstein JD, Kerr DA (2009): Tumor necrosis factor-alpha modulates glutamate transport in the CNS and is a critical determinant of outcome from viral encephalomyelitis. *Brain Res*. 1263:143-154.
31. Pickering M, Cumiskey D, O'Connor JJ (2005): Actions of TNF-alpha on glutamatergic synaptic transmission in the central nervous system. *Exp Physiol*. 90:663-670.
32. Taylor MJ, Godlewska B, Near J, Christmas D, Potokar J, Collier J, et al. (2014): Effect of interferon-alpha on cortical glutamate in patients with hepatitis C: a proton magnetic resonance spectroscopy study. *Psychol Med*. 44:789-795.
33. Haroon E, Miller AH (2017): Inflammation Effects on Brain Glutamate in Depression: Mechanistic Considerations and Treatment Implications. *Curr Top Behav Neurosci*. 31:173-198.
34. Nikkheslat N (2021): Targeting inflammation in depression: Ketamine as an anti-inflammatory antidepressant in psychiatric emergency. *Brain Behav Immun Health*. 18:100383.
35. Biber K, Pinto-Duarte A, Wittendorp MC, Dolga AM, Fernandes CC, Von Frijtag Drabbe Kunzel J, et al. (2008): Interleukin-6 upregulates neuronal adenosine A1 receptors: implications for neuromodulation and neuroprotection. *Neuropsychopharmacology*. 33:2237-2250.
36. Vereyken EJ, Bajova H, Chow S, de Graan PN, Gruol DL (2007): Chronic interleukin-6 alters the level of synaptic proteins in hippocampus in culture and in vivo. *Eur J Neurosci*. 25:3605-3616.
37. Filiano AJ, Xu Y, Tustison NJ, Marsh RL, Baker W, Smirnov I, et al. (2016): Unexpected role of interferon-gamma in regulating neuronal connectivity and social behaviour. *Nature*. 535:425-429.

38. Flood L, Korol SV, Ekselius L, Birnir B, Jin Z (2019): Interferon-gamma potentiates GABA(A) receptor-mediated inhibitory currents in rat hippocampal CA1 pyramidal neurons. *J Neuroimmunol*. 337:577050.
39. Wang DS, Zurek AA, Lecker I, Yu J, Abramian AM, Avramescu S, et al. (2012): Memory deficits induced by inflammation are regulated by alpha5-subunit-containing GABAA receptors. *Cell Rep*. 2:488-496.
40. Luscher B, Maguire JL, Rudolph U, Sibille E (2023): GABA(A) receptors as targets for treating affective and cognitive symptoms of depression. *Trends Pharmacol Sci*. 44:586-600.
41. Felger JC, Miller AH (2012): Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise. *Front Neuroendocrinol*. 33:315-327.
42. Bekhbat M, Block AM, Dickinson SY, Tharp GK, Bosinger SE, Felger JC (2025): Neurotransmitter and metabolic effects of interferon-alpha in association with decreased striatal dopamine in a Non-Human primate model of Cytokine-Induced depression. *Brain Behav Immun*. 125:308-318.
43. Felger JC, Treadway MT (2017): Inflammation Effects on Motivation and Motor Activity: Role of Dopamine. *Neuropsychopharmacology*. 42:216-241.
44. Dwarkasing JT, Witkamp RF, Boekschoten MV, Ter Laak MC, Heins MS, van Norren K (2016): Increased hypothalamic serotonin turnover in inflammation-induced anorexia. *BMC Neurosci*. 17:26.
45. Krishnadas R, Nicol A, Sassarini J, Puri N, Burden AD, Leman J, et al. (2016): Circulating tumour necrosis factor is highly correlated with brainstem serotonin transporter availability in humans. *Brain Behav Immun*. 51:29-38.
46. Lai JY, Ho JX, Kow ASF, Liang G, Tham CL, Ho YC, et al. (2023): Interferon therapy and its association with depressive disorders - A review. *Front Immunol*. 14:1048592.
47. Jiang HY, Deng M, Zhang YH, Chen HZ, Chen Q, Ruan B (2014): Specific serotonin reuptake inhibitors prevent interferon-alpha-induced depression in patients with hepatitis C: a meta-analysis. *Clin Gastroenterol Hepatol*. 12:1452-1460 e1453.
48. Capuron L, Neurauter G, Musselman DL, Lawson DH, Nemeroff CB, Fuchs D, et al. (2003): Interferon-alpha-induced changes in tryptophan metabolism. relationship to depression and paroxetine treatment. *Biol Psychiatry*. 54:906-914.
49. Campbell BM, Charych E, Lee AW, Moller T (2014): Kynurenines in CNS disease: regulation by inflammatory cytokines. *Front Neurosci*. 8:12.
50. Campanale A, Inserra A, Comai S (2024): Therapeutic modulation of the kynurenine pathway in severe mental illness and comorbidities: A potential role for serotonergic psychedelics. *Prog Neuropsychopharmacol Biol Psychiatry*. 134:111058.
51. Prieto GA, Smith ED, Tong L, Nguyen M, Cotman CW (2019): Inhibition of LTP-Induced Translation by IL-1beta Reduces the Level of Newly Synthesized Proteins in Hippocampal Dendrites. *ACS Chem Neurosci*. 10:1197-1203.
52. Hoshino K, Uchinami Y, Uchida Y, Saito H, Morimoto Y (2021): Interleukin-1beta Modulates Synaptic Transmission and Synaptic Plasticity During the Acute Phase of Sepsis in the Senescence-Accelerated Mouse Hippocampus. *Front Aging Neurosci*. 13:637703.
53. Shaftel SS, Griffin WS, O'Banion MK (2008): The role of interleukin-1 in neuroinflammation and Alzheimer disease: an evolving perspective. *J Neuroinflammation*. 5:7.
54. Turrigiano G (2012): Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. *Cold Spring Harb Perspect Biol*. 4:a005736.

55. Heir R, Stellwagen D (2020): TNF-Mediated Homeostatic Synaptic Plasticity: From in vitro to in vivo Models. *Front Cell Neurosci*. 14:565841.
56. Mordelt A, de Witte LD (2023): Microglia-mediated synaptic pruning as a key deficit in neurodevelopmental disorders: Hype or hope? *Curr Opin Neurobiol*. 79:102674.
57. Zhang MM, Guo MX, Zhang QP, Chen XQ, Li NZ, Liu Q, et al. (2022): IL-1R/C3aR signaling regulates synaptic pruning in the prefrontal cortex of depression. *Cell Biosci*. 12:90.
58. Lang R, Li H, Luo X, Liu C, Zhang Y, Guo S, et al. (2022): Expression and mechanisms of interferon-stimulated genes in viral infection of the central nervous system (CNS) and neurological diseases. *Front Immunol*. 13:1008072.
59. Calvano SE, Xiao W, Richards DR, Felciano RM, Baker HV, Cho RJ, et al. (2005): A network-based analysis of systemic inflammation in humans. *Nature*. 437:1032-1037.
60. Schedlowski M, Engler H, Grigoleit JS (2014): Endotoxin-induced experimental systemic inflammation in humans: a model to disentangle immune-to-brain communication. *Brain Behav Immun*. 35:1-8.
61. Capuron L, Miller AH (2011): Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol Ther*. 130:226-238.
62. Raison CL, Borisov AS, Majer M, Drake DF, Pagnoni G, Woolwine BJ, et al. (2009): Activation of central nervous system inflammatory pathways by interferon-alpha: relationship to monoamines and depression. *Biol Psychiatry*. 65:296-303.
63. Beutler B (2002): TLR4 as the mammalian endotoxin sensor. *Curr Top Microbiol Immunol*. 270:109-120.
64. van der Bruggen T, Nijenhuis S, van Raaij E, Verhoef J, van Asbeck BS (1999): Lipopolysaccharide-induced tumor necrosis factor alpha production by human monocytes involves the raf-1/MEK1-MEK2/ERK1-ERK2 pathway. *Infect Immun*. 67:3824-3829.
65. Ishijima T, Nakajima K (2021): Inflammatory cytokines TNFalpha, IL-1beta, and IL-6 are induced in endotoxin- stimulated microglia through different signaling cascades. *Sci Prog*. 104:368504211054985.
66. Engler H, Brendt P, Wischermann J, Wegner A, Rohling R, Schoemberg T, et al. (2017): Selective increase of cerebrospinal fluid IL-6 during experimental systemic inflammation in humans: association with depressive symptoms. *Mol Psychiatry*. 22:1448-1454.
67. Majer M, Welberg LA, Capuron L, Pagnoni G, Raison CL, Miller AH (2008): IFN-alpha-induced motor slowing is associated with increased depression and fatigue in patients with chronic hepatitis C. *Brain Behav Immun*. 22:870-880.
68. Malaguarnera M, Laurino A, Di Fazio I, Pistone G, Castorina M, Guccione N, et al. (2001): Neuropsychiatric effects and type of IFN-alpha in chronic hepatitis C. *J Interferon Cytokine Res*. 21:273-278.
69. Capuron L, Pagnoni G, Drake DF, Woolwine BJ, Spivey JR, Crowe RJ, et al. (2012): Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Arch Gen Psychiatry*. 69:1044-1053.
70. Capuron L, Pagnoni G, Demetrashvili MF, Lawson DH, Fornwalt FB, Woolwine B, et al. (2007): Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy. *Neuropsychopharmacology*. 32:2384-2392.
71. Juengling FD, Ebert D, Gut O, Engelbrecht MA, Rasenack J, Nitzsche EU, et al. (2000): Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. *Psychopharmacology (Berl)*. 152:383-389.
72. Brydon L, Harrison NA, Walker C, Steptoe A, Critchley HD (2008): Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. *Biol Psychiatry*. 63:1022-1029.

73. Harrison NA, Voon V, Cercignani M, Cooper EA, Pessiglione M, Critchley HD (2016): A Neurocomputational Account of How Inflammation Enhances Sensitivity to Punishments Versus Rewards. *Biol Psychiatry*. 80:73-81.
74. Harrison NA, Cercignani M, Voon V, Critchley HD (2015): Effects of inflammation on hippocampus and substantia nigra responses to novelty in healthy human participants. *Neuropsychopharmacology*. 40:831-838.
75. Bekhbat M, Li Z, Mehta ND, Treadway MT, Lucido MJ, Woolwine BJ, et al. (2022): Functional connectivity in reward circuitry and symptoms of anhedonia as therapeutic targets in depression with high inflammation: evidence from a dopamine challenge study. *Mol Psychiatry*. 27:4113-4121.
76. Lambregts B, Vassena E, Jansen A, Stremmelaar DE, Pickkers P, Kox M, et al. (2023): Fatigue during acute systemic inflammation is associated with reduced mental effort expenditure while task accuracy is preserved. *Brain Behav Immun*. 112:235-245.
77. Dipasquale O, Cooper EA, Tibble J, Voon V, Baglio F, Baselli G, et al. (2016): Interferon-alpha acutely impairs whole-brain functional connectivity network architecture - A preliminary study. *Brain Behav Immun*. 58:31-39.
78. Tan E, Troller-Renfree SV, Morales S, Buzzell GA, McSweeney M, Antunez M, et al. (2024): Theta activity and cognitive functioning: Integrating evidence from resting-state and task-related developmental electroencephalography (EEG) research. *Dev Cogn Neurosci*. 67:101404.
79. Morillas-Romero A, Tortella-Feliu M, Bornas X, Putman P (2015): Spontaneous EEG theta/beta ratio and delta-beta coupling in relation to attentional network functioning and self-reported attentional control. *Cogn Affect Behav Neurosci*. 15:598-606.
80. Strike PC, Wardle J, Steptoe A (2004): Mild acute inflammatory stimulation induces transient negative mood. *J Psychosom Res*. 57:189-194.
81. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD (2009): Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol Psychiatry*. 66:407-414.
82. Kullmann JS, Grigoleit JS, Lichte P, Kobbe P, Rosenberger C, Banner C, et al. (2013): Neural response to emotional stimuli during experimental human endotoxemia. *Hum Brain Mapp*. 34:2217-2227.
83. Davies KA, Cooper E, Voon V, Tibble J, Cercignani M, Harrison NA (2021): Interferon and anti-TNF therapies differentially modulate amygdala reactivity which predicts associated bidirectional changes in depressive symptoms. *Mol Psychiatry*. 26:5150-5160.
84. Shapiro PA, Sloan RP, Deochand C, Franceschi AM, Delorenzo C, Mann JJ, et al. (2014): Quantifying serotonin transporters by PET with [11C]-DASB before and after interferon-alpha treatment. *Synapse*. 68:548-555.
85. Kullmann JS, Grigoleit JS, Wolf OT, Engler H, Oberbeck R, Elsenbruch S, et al. (2014): Experimental human endotoxemia enhances brain activity during social cognition. *Soc Cogn Affect Neurosci*. 9:786-793.
86. Inagaki TK, Muscatell KA, Irwin MR, Moieni M, Dutcher JM, Jevtic I, et al. (2015): The role of the ventral striatum in inflammatory-induced approach toward support figures. *Brain Behav Immun*. 44:247-252.
87. Benson S, Labrenz F, Kotulla S, Brotte L, Rodder P, Tebbe B, et al. (2023): Amplified gut feelings under inflammation and depressed mood: A randomized fMRI trial on interoceptive pain in healthy volunteers. *Brain Behav Immun*. 112:132-137.
88. Hannestad J, Subramanyam K, Dellagioia N, Planeta-Wilson B, Weinzimmer D, Pittman B, et al. (2012): Glucose metabolism in the insula and cingulate is affected by systemic inflammation in humans. *J Nucl Med*. 53:601-607.

89. Harrison NA, Cooper E, Voon V, Miles K, Critchley HD (2013): Central autonomic network mediates cardiovascular responses to acute inflammation: relevance to increased cardiovascular risk in depression? *Brain Behav Immun*. 31:189-196.
90. Lacourt TE, Houtveen JH, Veldhuijzen van Zanten JJ, Bosch JA, Drayson MT, Van Doornen LJ (2015): Negative affectivity predicts decreased pain tolerance during low-grade inflammation in healthy women. *Brain Behav Immun*. 44:32-36.
91. Benson S, Rebernik L, Wegner A, Kleine-Borgmann J, Engler H, Schlamann M, et al. (2015): Neural circuitry mediating inflammation-induced central pain amplification in human experimental endotoxemia. *Brain Behav Immun*. 48:222-231.
92. Flasbeck V, Dersch N, Engler H, Schedlowski M, Brune M (2024): Acute experimental inflammation in healthy women attenuates empathy for psychological pain. *Brain Behav Immun*. 119:1-5.
93. Bjurstrom MF, Bodelsson M, Irwin MR, Orbjorn C, Hansson O, Mattsson-Carlgren N (2022): Decreased pain sensitivity and alterations of cerebrospinal fluid and plasma inflammatory mediators after total hip arthroplasty in patients with disabling osteoarthritis. *Pain Pract*. 22:66-82.
94. Krueger JM, Majde JA, Rector DM (2011): Cytokines in immune function and sleep regulation. *Handb Clin Neurol*. 98:229-240.
95. Krueger JM (2008): The role of cytokines in sleep regulation. *Curr Pharm Des*. 14:3408-3416.
96. Krueger JM, Obal FJ, Fang J, Kubota T, Taishi P (2001): The role of cytokines in physiological sleep regulation. *Ann N Y Acad Sci*. 933:211-221.
97. Raison CL, Rye DB, Woolwine BJ, Vogt GJ, Bautista BM, Spivey JR, et al. (2010): Chronic interferon-alpha administration disrupts sleep continuity and depth in patients with hepatitis C: association with fatigue, motor slowing, and increased evening cortisol. *Biol Psychiatry*. 68:942-949.
98. Pollmacher T, Schreiber W, Gudewill S, Vedder H, Fassbender K, Wiedemann K, et al. (1993): Influence of endotoxin on nocturnal sleep in humans. *Am J Physiol*. 264:R1077-1083.
99. Mullington J, Korth C, Hermann DM, Orth A, Galanos C, Holsboer F, et al. (2000): Dose-dependent effects of endotoxin on human sleep. *Am J Physiol Regul Integr Comp Physiol*. 278:R947-955.
100. Krueger JM, Nguyen JT, Dykstra-Aiello CJ, Taishi P (2019): Local sleep. *Sleep Med Rev*. 43:14-21.
101. Andrillon T, Burns A, Mackay T, Windt J, Tsuchiya N (2021): Predicting lapses of attention with sleep-like slow waves. *Nat Commun*. 12:3657.
102. Lipinska G, Thomas KGF (2019): Rapid eye movement fragmentation, not slow-wave sleep, predicts neutral declarative memory consolidation in posttraumatic stress disorder. *J Sleep Res*. 28:e12846.
103. Yuksel C, Denis D, Coleman J, Ren B, Oh A, Cox R, et al. (2025): Both slow wave and rapid eye movement sleep contribute to emotional memory consolidation. *Commun Biol*. 8:485.
104. Miller AH (2009): Norman Cousins Lecture. Mechanisms of cytokine-induced behavioral changes: psychoneuroimmunology at the translational interface. *Brain Behav Immun*. 23:149-158.
105. Hannestad J, Gallezot JD, Schafbauer T, Lim K, Kloczynski T, Morris ED, et al. (2012): Endotoxin-induced systemic inflammation activates microglia: [(1)(1)C]PBR28 positron emission tomography in nonhuman primates. *Neuroimage*. 63:232-239.

106. Horti AG, Naik R, Foss CA, Minn I, Misheneva V, Du Y, et al. (2019): PET imaging of microglia by targeting macrophage colony-stimulating factor 1 receptor (CSF1R). *Proc Natl Acad Sci U S A*. 116:1686-1691.
107. Felger JC, Hernandez CR, Miller AH (2015): Levodopa reverses cytokine-induced reductions in striatal dopamine release. *Int J Neuropsychopharmacol*. 18.
108. Felger JC, Mun J, Kimmel HL, Nye JA, Drake DF, Hernandez CR, et al. (2013): Chronic interferon-alpha decreases dopamine 2 receptor binding and striatal dopamine release in association with anhedonia-like behavior in nonhuman primates. *Neuropsychopharmacology*. 38:2179-2187.
109. Gibney SM, Drexhage HA (2013): Evidence for a dysregulated immune system in the etiology of psychiatric disorders. *J Neuroimmune Pharmacol*. 8:900-920.
110. Fourrier C, Singhal G, Baune BT (2019): Neuroinflammation and cognition across psychiatric conditions. *CNS Spectr*. 24:4-15.
111. Miller AH, Berk M, Bloch G, Briquet-Laugier V, Brouillon C, Cuthbert BN, et al. (2025): Advancing precision psychiatry and targeted treatments: Insights from immunopsychiatry. *Brain Behav Immun*. 125:319-329.
112. Lawn RB, Murchland AR, Kim Y, Chibnik LB, Tworoger SS, Rimm EB, et al. (2022): Trauma, psychological distress and markers of systemic inflammation among US women: A longitudinal study. *Psychoneuroendocrinology*. 145:105915.
113. Capuron L, Lasselin J, Castanon N (2017): Role of Adiposity-Driven Inflammation in Depressive Morbidity. *Neuropsychopharmacology*. 42:115-128.
114. Suneson K, Soderberg Veiback G, Lindahl J, Tjernberg J, Stahl D, Ventorp S, et al. (2024): Omega-3 fatty acids for inflamed depression - A match/mismatch study. *Brain Behav Immun*. 118:192-201.
115. Lesperance P, Desbeaumes Jodoin V, Drouin D, Racicot F, Miron JP, Longpre-Poirier C, et al. (2024): Vagus Nerve Stimulation Modulates Inflammation in Treatment-Resistant Depression Patients: A Pilot Study. *Int J Mol Sci*. 25.
116. Kucukosmanoglu HS, Cramer H, Tavakoly R, Moosburner A, Bilc MI (2024): Mind-Body Medicine in the Treatment of Depression: A Narrative Review of Efficacy, Safety and Mechanisms. *Curr Psychiatry Rep*. 26:729-740.
117. Takahama M, Patil A, Richey G, Cipurko D, Johnson K, Carbonetto P, et al. (2024): A pairwise cytokine code explains the organism-wide response to sepsis. *Nat Immunol*. 25:226-239.
118. Cappuccio A, Jensen ST, Hartmann BM, Sealfon SC, Soumelis V, Zaslavsky E (2020): Deciphering the combinatorial landscape of immunity. *Elife*. 9.
119. D'Angelo E, Jirsa V (2022): The quest for multiscale brain modeling. *Trends Neurosci*. 45:777-790.
120. Hashemi M, Depannemaecker D, Saggio M, Triebkorn P, Rabuffo G, Fousek J, et al. (2025): Principles and Operation of Virtual Brain Twins. *IEEE Rev Biomed Eng*. PP.
121. Neymotin SA, Daniels DS, Caldwell B, McDougal RA, Carnevale NT, Jas M, et al. (2020): Human Neocortical Neurosolver (HNN), a new software tool for interpreting the cellular and network origin of human MEG/EEG data. *Elife*. 9.
122. Dowell NG, Cooper EA, Tibble J, Voon V, Critchley HD, Cercignani M, et al. (2016): Acute Changes in Striatal Microstructure Predict the Development of Interferon-Alpha Induced Fatigue. *Biol Psychiatry*. 79:320-328.
123. Peters van Ton AM, Leijte GP, Franssen GM, Bruse N, Booij J, Doorduin J, et al. (2021): Human in vivo neuroimaging to detect reprogramming of the cerebral immune response following repeated systemic inflammation. *Brain Behav Immun*. 95:321-329.

124. Finger CE, Moreno-Gonzalez I, Gutierrez A, Moruno-Manchon JF, McCullough LD (2022): Age-related immune alterations and cerebrovascular inflammation. *Mol Psychiatry*. 27:803-818.
125. Silva AR, Regueira P, Peres A, Cardoso AL, Baldeiras I, Santana I, et al. (2022): In vivo molecular imaging of the neuroinflammatory response to peripheral acute bacterial infection in older patients with cognitive dysfunction: A cross-sectional controlled study. *Front Aging Neurosci*. 14:984178.
126. Alexander B, Loh WY, Matthews LG, Murray AL, Adamson C, Beare R, et al. (2019): Desikan-Killiany-Tourville Atlas Compatible Version of M-CRIB Neonatal Parcellated Whole Brain Atlas: The M-CRIB 2.0. *Front Neurosci*. 13:34.

Legends for tables and figures

Figure 1. Sources of Cytokines in the CNS. Cytokines in the brain are produced by a diverse range of cell types, including microglia, astrocytes, neurons, endothelial cells of the blood-brain barrier (BBB), meningeal immune cells, and the skull bone marrow. Microglia are the primary cytokine producers, releasing both pro- and anti-inflammatory cytokines that shape synaptic plasticity and neuronal health. Astrocytes and neurons also contribute to cytokine signalling, mainly under conditions of stress and injury but at basal conditions too. The blood-brain barrier acts as a key interface, regulating cytokine exchange between the periphery and the CNS. Cytokines released into the periphery during systemic inflammation stimulate afferent fibbers of the vagus nerve, which relays these immune signals to the brainstem. During health, these molecules play vital roles in maintaining neural health by supporting synaptic plasticity, neurogenesis, and metabolic homeostasis(2, 23). However, triggering of neuroinflammation through stress, injury, or infection rapidly perturbs brain function and when severe or chronic contributes to neuropsychiatric disorders.

Figure 2. Cytokine Receptor Distribution Across Brain Regions (Allen Human Brain Atlas). Gene expression was measured in multiple samples across the whole brain using microarray as part of the Human Brain Atlas. Data can be downloaded from https://human.brain-map.org/. Samples were mapped to parcels of the Desikan-Killiany atlas(126), after normalization, using the *abagen* toolbox (https://abagen.readthedocs.io). Only parcels of the left brain are displayed as gene expression data is only available for two donors in the atlas. Warmer colours indicate higher expression (Z-score), while cooler colours represent lower expression levels. The right panel shows principal component analysis (PCA) scores derived from cytokine receptor expression patterns, summarizing dominant spatial variance in cytokine-related neurobiology. Cytokine receptors expression can be described by two main components, which captured 50.1% of the variance in a parallel analysis using the varimax rotation method. The heatmap (bottom right) presents Spearman correlations between PCA scores and structural brain alterations across psychiatric disorders, based on ENIGMA consortium neuroimaging meta-analyses (available as part of the ENIGMA toolbox at https://enigma-toolbox.readthedocs.io/en/latest/index.html)**.** Type I cytokine receptors (e.g., IL-6R, CSF1R) are most prominently expressed in the hippocampus, prefrontal cortex, and anterior cingulate - regions involved in mood and cognition - while Type II receptors (e.g., IFNGR1) are enriched in basal ganglia and entorhinal areas, supporting roles in motivation and psychomotor control. Bidirectional signalling is evident in TNF and IL-1 receptor families, balancing neuroinflammatory and neuroprotective responses. The co-expression of pro- and anti-inflammatory receptors in key circuits suggests a dynamic equilibrium that shapes neurobehavioural homeostasis.

Figure 3. Cytokine modulation of monoaminergic, GABAergic and glutamatergic neurotransmission. The diagrams summarize the multiple mechanisms through which

cytokines can regulate the synthesis, release, reuptake, and postsynaptic signalling of monoamines (dopamine, serotonin, noradrenaline), GABA and glutamate.

Figure 4. Neurobehavioral effects of immune challenges in humans. This schematic illustrates key brain regions in which structure, function, or neurochemistry have been shown to be modulated by immune challenges in human studies. Behavioral and cognitive domains are positioned adjacent to the brain regions most consistently implicated in those functions, providing an intuitive mapping of immune-related neurobehavioral effects. While many regions contribute to multiple domains, this layout emphasizes primary associations without implying strict one-to-one mappings. The figure synthesizes converging evidence from neuroimaging, pharmacological, and translational studies examining the impact of inflammation on human brain function.