Symposium

The Neural Correlates of Sickness

Hunter Lanovoi,[1,2] Liu Yang,[3] Andrea Serino,[4] Tomás J. Ryan,[5] Ioana Carcea,[1,2]* and Jessica A. Osterhout[6]*

[1]Department of Pharmacology, Physiology, and Neuroscience, Rutgers New Jersey Medical School, Newark, New Jersey 07103, [2]The State University of New Jersey, Newark, New Jersey 07101-1709, [3]The Picower Institute for Learning and Memory and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, [4]MySpace Lab, Department of Clinical Neurosciences, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne 1011, Switzerland, [5]School of Biochemistry and Immunology and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2 D02 PN40, Ireland, and [6]Department of Neurobiology, The University of Utah School of Medicine, Salt Lake City, Utah 84112-9458

The brain protects animals during infection by detecting immune activity, coordinating behavioral and physiological defenses, anticipating potential infectious threats, and limiting excessive inflammation. Collectively termed sickness, these centrally organized responses include changes in body temperature, activity, energy balance, appetite, fluid intake, social behavior, neuroendocrine function, and autonomic output. Rather than constituting a single uniform state, sickness is generated by distributed and partially dissociable neural pathways that translate immune signals into responses appropriate to the nature and stage of an infection. Work presented at a symposium at the 2026 Society for Neuroscience meeting highlights how humoral and cranial sensory pathways detect ongoing immune responses; how social cues, expectations, and prior experience prepare the organism for anticipated threats; and how endocrine and autonomic circuits constrain inflammation and promote recovery. Together, these findings establish the brain as an active regulator of immunity across the full course of illness.

Key words: **brain-body communication; immune memory; inflammation; neuroimmune communication; sickness behavior**

Introduction

Infection triggers a coordinated set of behavioral, physiological, endocrine, and autonomic adaptations collectively known as sickness. Although often experienced as a collection of seemingly negative symptoms, including fatigue, anorexia, altered body temperature, reduced social interaction, and malaise, these responses are generally adaptive (Hart, 1988). By conserving energy, limiting exposure to additional threats, and supporting immune function, sickness helps animals survive infection. Sickness was historically viewed as a consequence of circulating inflammatory mediators acting diffusely on the brain (Dantzer and Kelley, 2007). Recent work instead reveals a distributed and highly organized neural system that detects immune activity and generates separable components of the sickness response (Saper et al., 2012; Dantzer, 2023). Cranial sensory neurons, neurovascular interfaces, and circumventricular organs (CVOs) provide complementary routes for immunoception, the brain's interoceptive sensing of immune state (Dantzer et al., 2008; Rolls, 2023). Downstream brainstem, hypothalamic, limbic, and cortical circuits regulate specific behavioral and physiological outputs. These pathways are shaped not only by ongoing inflammation but also by social information, expectations, and memories of prior immune states. At later stages of illness, neural, endocrine, and autonomic feedback mechanisms constrain inflammation and may coordinate the transition from sickness to recovery.

Here we review recent advances in understanding how the nervous system detects experienced and anticipated immune threats, transforms this information into coordinated but partly dissociable sickness responses, and limits these responses as the threat resolves. Together, these studies position the brain not as a passive recipient of inflammatory signals but as an active, even predictive, regulator of immunity and host defense across the full course of illness.

Neural Mechanisms for Sickness in Response to Systemic Inflammation

Although the blood–brain barrier limits the entry of pathogens and many circulating immune molecules into the brain, the nervous system rapidly detects peripheral inflammation through several complementary pathways. Cranial sensory neurons innervating internal organs, primarily vagal and glossopharyngeal visceral afferents, sense inflammatory molecules and transduce them into neural signals that are then conveyed to the brain. In parallel, circulating immune mediators act on brain endothelial cells and specialized neurovascular interfaces, including the CVOs, where vascular, glial, and neuronal cells translate humoral signals into neural activity. These pathways converge within distributed brain networks that coordinate distinct behavioral, autonomic, and physiological components of sickness (Fig. 1).

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*I.C. and J.A.O. contributed equally to this work.

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Correspondence should be addressed to Ioana Carcea at ioana.carcea@rutgers.edu or Jessica A. Osterhout at j.osterhout@neuro.utah.edu.

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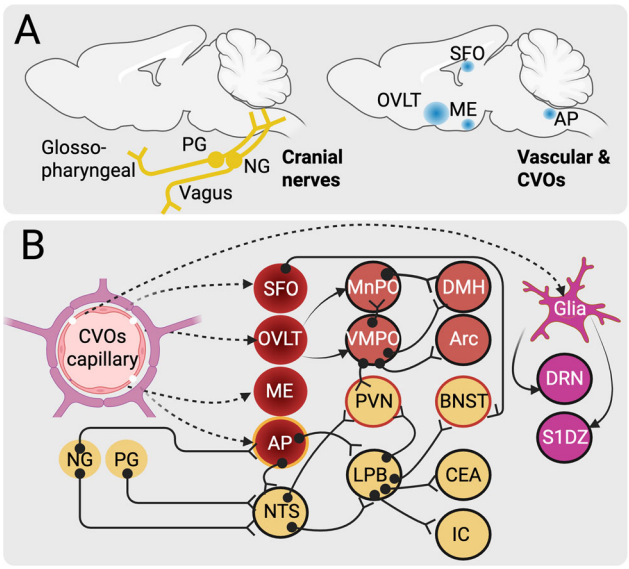


Figure 1. Distributed neural pathways for sensing systemic inflammation and generating sickness. ***A***, Peripheral inflammation is communicated to the brain through complementary neural and humoral routes. Vagal and glossopharyngeal sensory neurons, whose cell bodies reside in the nodose and petrosal ganglia, respectively, detect inflammatory signals in peripheral tissues and relay this information to the brainstem. In parallel, circulating immune signals are detected at brain endothelial cells and CVOs, including the SFO, OVLT, ME, and AP. ***B***, Cranial sensory afferents terminate primarily in the NTS and AP, which engage downstream hypothalamic, parabrachial, amygdalar, and cortical circuits. Fenestrated CVO vasculature exposes resident vascular, glial, and neuronal cells to circulating signals, linking the SFO, OVLT, ME, and AP to circuits controlling body temperature, feeding, neuroendocrine function, visceral malaise, and affective behavior. Cytokines and other immune mediators can also act on receptor-defined neurons and glia outside classical CVO-associated regions, including the DRN and S1DZ. Yellow structures indicate pathways emphasized in cranial sensory signaling, red structures indicate vascular and CVO-associated pathways, and magenta structures indicate additional cytokine-sensitive neural and glial populations. Multicolored structures represent sites at which these pathways converge. Dotted arrows indicate communication from the circulation, and solid black lines summarize anatomical or functional connections discussed in the text; the schematic does not imply that all connections are direct or monosynaptic. AP, area postrema; Arc, arcuate nucleus; BNST, bed nucleus of the stria terminalis; CEA, central amygdala; CVO, circumventricular organ; DMH, dorsomedial hypothalamus; DRN, dorsal raphe nucleus; IC, insular cortex; LPB, lateral parabrachial nucleus; ME, median eminence; MnPO, median preoptic area; NG, nodose ganglion; NTS, nucleus of the solitary tract; OVLT, organum vasculosum of the lamina terminalis; PG, petrosal ganglion; PVN, paraventricular nucleus of the hypothalamus; S1DZ, dysgranular zone of the primary somatosensory cortex; SFO, subfornical organ; VMPO, ventromedial preoptic area.

Cranial nerve pathway

Visceral sensory fibers of the vagus and glossopharyngeal cranial nerves have been extensively implicated in signaling sickness to the brain. Vagal fibers innervate thoracic and upper abdominal organs, and their cell bodies reside in the nodose ganglia. Vagal sensory afferents express toll-like receptors (TLRs) and can respond directly to bacterial products such as lipopolysaccharide (LPS; Jia et al., 2021). Additionally, they express receptors for cytokines and prostaglandins. A recent study has shown that sensory vagal neurons exhibit distinct response profiles to a range of pro- and anti-inflammatory cytokines (Huerta et al., 2025). Intriguingly, vagal fibers innervating the gut can be hijacked by microbial factors to modulate sickness symptoms and alter the balance between host survival and pathogen transmission (Rao et al., 2017).

Electrical stimulation of the vagus nerve can evoke sickness-like symptoms, including vomiting and weight loss, in the absence of peripheral inflammation (Snyder et al., 2023). The terminals of visceral vagal fibers terminate in the nucleus of the solitary tract (NTS) and the area postrema (AP) in the brainstem, where they activate several cell types, including ADCYAP1$^+$ neurons (Ilanges et al., 2022). These neurons play an essential role in sickness symptoms. Inflammation-triggered anorexia and hypolocomotion decrease following suppression of NTS/AP ADCYAP1$^+$ neurons (Ilanges et al., 2022). Conversely, chemogenetic activation of NTS/AP ADCYAP1$^+$ neurons was sufficient to induce these symptoms. Surprisingly, although ADCYAP1$^+$ neurons were not necessary for LPS-induced changes in core body temperature, their activation was sufficient to replicate thermal changes associated with sickness (Ilanges et al., 2022). Together, these results indicate that NTS/AP circuits receiving visceral sensory input are critical for the expression of several sickness symptoms.

The NTS is a major hub for sickness responses. NTS neurons project to the paraventricular nucleus of the hypothalamus (PVN) to regulate glucocorticoid hormones, as discussed later in this review. Additionally, NTS and AP neurons project to the external lateral parabrachial nucleus (LPB), where calcitonin gene-related peptide neurons (LPB-CGRP$^+$) respond to systemic LPS administration and NTS stimulation (Carter et al., 2013; Chen et al., 2018). Projections from LPB-CGRP$^+$ neurons to the central amygdala (CEA) and the bed nucleus of the stria terminalis (BNST) further propagate neuronal responses to inflammatory signals (Carter et al., 2013; Bowen et al., 2023). Within the CEA, systemic inflammation activates PKCδ$^+$ neurons, a GABAergic subtype implicated in integrating anorexigenic signals, and, in an unpublished preprint, oxytocin receptor-expressing neurons that may contribute to decreased locomotion, its unclear whether these are overlapping populations (Cai et al., 2014; Lanovoi et al., 2022). Findings from an unpublished abstract from the Society for Neuroscience meeting suggest that interindividual differences in CEA activation are associated with the magnitude of sickness behaviors, including decreased social novelty seeking and decreased locomotion (Lanovoi et al., 2023).

A recent preprint implicates the vagal pathway in severe forms of systemic inflammation, including sepsis (Bourhy et al., 2024). Evidence in animal models suggests that the activation of CEA neurons during sepsis leads to long-lasting behavioral consequences, such as increased anxiety (Bourhy et al., 2022). These findings may point toward interventions that mitigate the increased risk of psychiatric disorders following sepsis (Calsavara et al., 2018; Li et al., 2024; Wetterberg et al., 2026).

Visceral sensory fibers of the glossopharyngeal nerve innervate the neck and head regions, and their cell bodies reside in the petrosal ganglia, adjacent to the nodose and jugular ganglia. During influenza infection, prostaglandins produced within the oropharyngeal cavity activate GABRA1$^+$ glossopharyngeal neurons expressing the prostaglandin receptor EP3 (Bin et al., 2023). Both deletion of EP3 receptors from GABRA1$^+$ neurons and ablation of petrosal GABRA1$^+$ neurons reduce influenza-induced sickness symptoms, including anorexia, hypolocomotion, and changes in core body temperature (Bin et al., 2023). Unlike nodose neurons implicated in sickness, petrosal GABRA1$^+$ neurons project to the lateral part of the NTS but do not innervate the AP (Bin et al., 2023), indicating that, in addition to shared sickness symptoms, distinct cranial nerve–brainstem pathways may mediate responses specific to the location of inflammation.

In addition to vagal and glossopharyngeal visceral afferents, craniofacial nociceptive afferents of the trigeminal nerve detect cytokines and prostaglandins and mediate sickness-like

symptoms during migraine (Burstein et al., 2015). The cell bodies of trigeminal sensory fibers reside in the trigeminal ganglia and send central processes to the trigeminocervical complex (Brennan and Pietrobon, 2018). Ascending trigeminal pathways reach the thalamus and subsequently the somatosensory and insular cortices, contributing to pain perception, as well as brainstem and limbic regions including the NTS, LPB, and CEA, which are implicated in associated symptoms such as lethargy, anorexia, and social withdrawal (Noseda and Burstein, 2013). Importantly, migraine occurs in the absence of systemic inflammation and is not typically associated with fever or other prolonged changes in core body temperature, suggesting that recruitment of the NTS and related downstream regions is not sufficient to generate the full sickness syndrome.

Visceral sensory fibers of cranial nerves represent the best understood neural pathway for transmitting systemic inflammatory signals from the periphery to the brain to induce sickness symptoms. By comparison, the potential contribution of spinal sensory pathways to sickness is much less well understood. A subset of dorsal root ganglia (DRG) neurons innervates internal organs such as the digestive tract (including the distal colon) and the urogenital tract and can detect inflammatory cytokines such as IL-1β (Binshtok et al., 2008). Colon-innervating DRG neurons express pathogen-sensing pattern-recognition receptors (Hockley et al., 2019) and mount a conserved transcriptional response to intestinal inflammation (Forster et al., 2025). DRG responses to inflammation are best characterized in the context of pain: cytokines and prostaglandins lower nociceptor firing thresholds and produce hyperalgesia (Patapoutian et al., 2009; Jain et al., 2024). Despite the lack of direct evidence, DRG neurons have the potential to contribute to sickness. For example, both DRG and vagal neurons, from mice and humans, exhibit comparable calcium responses to the *Mycobacterium tuberculosis* glycolipid sulfolipid-1 in vitro (Ruhl et al., 2020). However, in the absence of DRG-specific manipulation, the role of DRGs in disease symptoms remains undetermined. Similarly, lung TRPV1$^+$ neurons detect LPS through TLR4 to drive hypothermia, PVN activation and release of corticotropin-releasing hormone (CRH) during pneumonia. Deleting TLR4 in all TRPV1+ neurons attenuates sickness, and deletion restricted to vagal sensory neurons reproduces this effect, but no DRG-restricted manipulation was tested (Granton et al., 2024). In both cases, DRG neurons exhibit molecular responses similar to those of vagal populations already implicated in these behaviors, but a direct DRG contribution remains untested. It will be important to determine how DRG-borne inflammatory signals ascend through the spinal cord and converge with cranial sensory pathways in the brainstem and forebrain and how sickness-responsive brain structures transform this convergent input into coordinated sickness responses.

Vascular and circumventricular sensing of systemic inflammation

The brain detects infection through both direct sensing of microbial products and indirect sensing of host-derived immune signals. Although the blood–brain barrier restricts most bacterially derived molecules, small peptidoglycan fragments known as muropeptides can reach the brain and activate the pattern-recognition receptor NOD2 in hypothalamic inhibitory neurons, thereby influencing feeding and body temperature (Gabanyi et al., 2022). In contrast, larger bacterial products such as LPS show minimal penetration across an intact blood–brain barrier and are therefore unlikely to act directly on parenchymal cells under most conditions (Banks and Robinson, 2010). During infection, activation of the innate immune system produces cytokines, chemokines, prostaglandins, and other circulating signals. The brain detects these signals through specialized blood–brain interfaces, including brain endothelial cells, the choroid plexus, and CVOs. CVOs, including the organum vasculosum of the lamina terminalis (OVLT), subfornical organ (SFO), median eminence (ME), and AP, contain fenestrated capillaries that provide greater exposure to circulating molecules than vessels protected by the conventional blood–brain barrier. Specialized astrocytic, ependymal, and tanycyte-like barriers nevertheless restrict entry into the cerebrospinal fluid and neighboring neural tissue (Miyata, 2022). This architecture allows vascular, glial, immune, and neuronal cells within CVOs to sample circulating signals and translate them into local paracrine and neural responses.

Circulating cytokines bind receptors on brain endothelial cells and stimulate local production of prostaglandins, cytokines, chemokines, and other immune mediators (Ek et al., 2001; Engblom et al., 2003; Nilsberth et al., 2009). Prostaglandin E2 (PGE2) is the best-established example of this neurovascular transduction. Circulating cytokines induce cyclooxygenase-2 (COX-2) and microsomal prostaglandin E synthase-1 in brain endothelial cells, producing PGE2 on the parenchymal side of the vasculature (Ek et al., 2001; Engblom et al., 2003; Engstrom et al., 2012). Selective disruption of endothelial PGE2 synthesis strongly attenuates fever without preventing inflammation-induced hypoactivity, demonstrating symptom-specific control rather than initiation of sickness as a whole (Engblom et al., 2003; Engstrom et al., 2012). Systemic LPS also induces delayed cytokine transcription in microglia, which may amplify or prolong inflammatory signaling (Quan et al., 1998).

The OVLT lies adjacent to the median and ventromedial preoptic regions, placing it in close proximity to neural circuits that control body temperature and other homeostatic responses. Following systemic LPS administration, concentrations of PGE2, IL-1β, and other inflammatory mediators increase over ~2–4 h (Osterhout et al., 2022; Wang et al., 2026). Locally produced PGE2 inhibits thermoregulatory neurons in the median preoptic area (MnPO) via expression of the EP3 receptor (Machado et al., 2020; Upton et al., 2021) and activates inhibitory neurons in the ventromedial preoptic area (VMPO) expressing the EP2 receptor, together shifting thermoregulatory circuitry toward fever (Lazarus et al., 2007; Osterhout et al., 2022; Machado et al., 2025). LPS-responsive VMPO neurons also respond directly to IL-1β and selected chemokines, coordinating fever, warmth-seeking behavior, and appetite suppression (Osterhout et al., 2022). Their connections with the thermoregulatory MnPO neurons and the appetite-controlling neurons in the arcuate nucleus link inflammatory sensing near the OVLT to neural systems that control body temperature and feeding.

The ME, located immediately ventral to the arcuate nucleus, is traditionally classified as a secretory CVO because it allows hypothalamic neuroendocrine signals to enter the portal circulation. However, the fenestrated vessels there also expose the mediobasal hypothalamus to circulating metabolic and inflammatory signals. Tanycytes lining the ME contact both these vessels and neighboring hypothalamic neurons, forming an actively regulated interface between the circulation and circuits controlling feeding and endocrine function. During systemic inflammation, IL-1β activates NF-κB signaling in tanycytes, inducing COX-2 expression and PGE2 production (Böttcher et al., 2020). Disrupting tanycytic NF-κB signaling attenuates IL-1β–induced anorexia

without altering fever or hypolocomotion, implicating the ME-tanycyte interface in selective control of sickness-induced appetite suppression (Böttcher et al., 2020).

The AP is positioned in the caudal brainstem and detects circulating toxins, hormones, and stress-associated signals, converting them into nausea-associated, aversive, metabolic, and autonomic responses (Miller and Leslie, 1994). AP neurons expressing the glucagon-like peptide 1 receptor contribute to conditioned avoidance of stimuli associated with LPS, lithium chloride, and GLP-1 receptor agonists (Miller and Leslie, 1994; Zhang et al., 2021). A second AP pathway detects growth differentiation factor 15 (GDF15), a circulating hormone and cellular stress signal that is elevated during infection, inflammation, tissue injury, several chronic diseases, and pregnancy (Emmerson et al., 2017; Zhang et al., 2023). Its receptor, GFRAL, is highly restricted to the AP and the neighboring NTS (Emmerson et al., 2017; Hsu et al., 2017). GDF15-GFRAL signaling suppresses food intake, promotes weight loss, and produces aversive, nausea-like responses (Hsu et al., 2017; Sabatini et al., 2021). During pregnancy, elevated fetoplacental GDF15 and maternal sensitivity to this signal contribute to nausea and vomiting, including hyperemesis gravidarum (Fejzo et al., 2024). Thus, the AP contains molecularly distinct pathways that link circulating signals to food avoidance and metabolic adaptation.

Systemic inflammation also activates neurons in the SFO (Ilanges et al., 2022; Zhang et al., 2024). The SFO is a major sensory node for fluid homeostasis and contains distinct neuronal populations that promote or suppress thirst and drinking (Oka et al., 2015). Thirst-promoting SFO neurons engage downstream circuits in the OVLT and MnPO to motivate water consumption (Leib et al., 2017). Because reduced drinking is a prominent component of sickness, inflammation-induced activity in the SFO could contribute to sickness-associated hypodipsia by altering these established thirst circuits, although this possibility has not been tested directly. Manipulating SFO activity does not alter fever, hypolocomotion, or anorexia but instead modulates inflammation-associated anxiety behavior (Zhang et al., 2024). Inhibition of SFO neurons exacerbates anxiety-like behavior following LPS administration, whereas their activation alleviates it (Zhang et al., 2024). Thus, distinct SFO populations or output pathways may regulate separable components of sickness, including fluid intake and affective behavior.

Other brain-border compartments also contribute to immunoception. At the choroid plexus, fenestrated stromal vessels expose resident immune and stromal cells to circulating inflammatory signals, while epithelial tight junctions regulate access to the cerebrospinal fluid. Systemic LPS rapidly induces cytokine and acute-phase responses within the choroid plexus (Marques et al., 2008; Shimada and Hasegawa-Ishii, 2021). During CNS inflammation, choroid plexus epithelial cells also coordinate the recruitment, survival, and differentiation of myeloid cells and subsequent barrier repair (Xu et al., 2024). Perivascular macrophages surrounding parenchymal vessels likewise respond to circulating inflammatory signals and regulate prostaglandin-dependent neuroendocrine responses (Serrats et al., 2010). Together, these compartments extend immune sensing beyond the CVOs and provide additional routes through which inflammation can influence the brain.

Beyond perivascular compartments, cytokine receptors are expressed by selected neuronal populations throughout the brain (Lee et al., 2025). A recent study identified IL-1 receptor type 1-expressing (IL-1R1) neurons in the dorsal raphe nucleus (DRN), many of which are serotonergic, as a critical target of IL-1β during systemic inflammation (Yang et al., 2026). Activating IL-1R1-expressing DRN neurons is sufficient to induce social withdrawal, whereas inhibiting these neurons or deleting IL-1R1 within the DRN attenuates social withdrawal during sickness (Yang et al., 2026). These manipulations do not affect locomotor activity, indicating that social withdrawal and hypolocomotion are mediated through different pathways. Thus, cytokines can engage symptom-specific neuronal circuits outside the classical CVO-associated regions.

Whereas systemic inflammation leads to social withdrawal in neurotypical subjects, it temporarily increases sociability in autistic children and in autism mouse models (Grzadzinski et al., 2018; Reed et al., 2020). Direct action of cytokine IL-17a decreases neuronal activity in the primary somatosensory cortex dysgranular zone (S1DZ), correcting sociability deficits in the maternal immune activation mouse model for autism spectrum disorders (Reed et al., 2020). S1DZ receptors for IL-17a are necessary for LPS-induced systemic inflammation to rescue sociability deficits. These data indicate that the effects of systemic inflammation can translate to opposite outcomes depending on developmental trajectories, baseline inflammatory status, or both.

Together, these findings identify CVOs and other neurovascular interfaces as major sites of immunoception. Endothelial cells, tanycytes, glia, and other perivascular cells detect circulating immune signals and recruit distinct circuits controlling fever, appetite, visceral malaise, and affective responses. These pathways can act together to generate coordinated sickness or independently to produce symptom-specific responses, establishing immune-to-brain communication as a distributed and modular sensory system that initiates and shapes sickness behavior.

Crosstalk between sickness pathways

Cranial and humoral sensory pathways intersect at multiple levels of the immune-to-brain axis (Fig. 1). In peripheral tissues, cytokines and prostaglandins produced during infection can activate visceral sensory neurons, converting local immune activity into rapid neural signals. A major site of central convergence is the dorsal vagal complex, where cranial sensory afferents terminate in the NTS, and the adjacent AP detects circulating inflammatory signals (Ilanges et al., 2022). This convergence continues within downstream brain circuits. Regions receiving input from the NTS-AP network can themselves remain directly sensitive to circulating or locally produced immune mediators. For example, recent work from an unpublished abstract presented at the 2023 Society for Neuroscience meeting shows that EP2-expressing neurons in the CEA respond to systemic LPS, suggesting that prostaglandin signaling can modulate a forebrain structure also recruited by ascending vagal pathways (Lanovoi et al., 2023). Pathway convergence may allow the brain to accelerate and amplify responses to systemic inflammation.

Neural Mechanisms That Anticipate Immune Challenge

The adaptive immune system responds more efficiently to previously encountered pathogens through prior exposure. The nervous system also uses experience and predictive cues to prepare the organism for potential immune challenges. Social signals, positive expectations, and learned associations with prior inflammation can alter immune activity and recruit behavioral or physiological responses prior to, or even in the absence of, direct pathogen detection. These effects do not uniformly produce

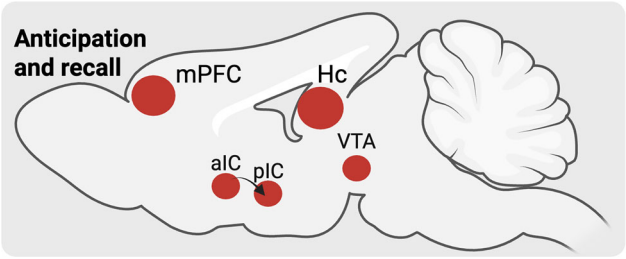


Figure 2. Brain regions implicated in the anticipation and recall of immune challenge. Social cues, positive expectations, conditioned associations, and memories of previous inflammatory states recruit partly distinct forebrain systems that can alter immune and sickness responses before direct pathogen detection. The mPFC and anterior IC participate in anticipatory responses to socially perceived infectious threats. VTA reward circuitry links positive expectations to modulation of innate and adaptive immunity. Communication between the anterior and posterior IC supports conditioned taste aversion and retrieval of conditioned immune responses, whereas hippocampal ensembles encode contextual memories associated with previous sickness and can reinstate metabolic and peripheral immune adaptations during recall. aIC, anterior insular cortex; Hc, hippocampus; mPFC, medial prefrontal cortex; pIC, posterior insular cortex; VTA, ventral tegmental area.

inflammation but can mobilize host defense, retrieve features of previously experienced immune states, or initiate anticipatory metabolic and behavioral adaptations. In this section, we discuss the neural mechanisms and central brain regions through which prediction and memory shape responses to potential infection (Fig. 2).

Social cues for sickness

Social species use vicarious experiences to efficiently prepare for responding to a challenge (Smith et al., 2016; Carcea et al., 2021). A similar mechanism primes the body to respond to others' infectious states. For example, mouse dams exposed to LPS-treated pups have increased synthesis of prostaglandins, cytokines, and chemokines in the brain and periphery (Castany et al., 2024). It remains to be determined if this immune priming induces sickness symptoms or enhances immune defense against subsequent exposure to real pathogens. Remarkably, vicarious immune activation does not require direct physical contact (Castany et al., 2024), raising the question of what sensory cues alert the immune system to the infectious threat.

Humans also show the ability to mount an inflammatory response to social infectious threats. When healthy human participants experience virtual reality avatars that appear to be sick, they exhibit enhanced defensive responses on approach to infection threats at long distances (Trabanelli et al., 2025), reminiscent of social avoidance developed during self-experienced sickness. Additionally, exposure to infectious, but not neutral or fearful, avatars induced changes in the frequency and activation state of innate lymphoid cells to a similar extent as receiving an influenza vaccine (Trabanelli et al., 2025) . Exposure to infectious avatars recruits, in an anticipatory way, brain structures in frontoparietal regions mapping one's peripersonal space, as well as areas of the salience network. Among these, the medial prefrontal cortex, the anterior cingulate cortex, and the anterior insula stand out as responding more strongly to distal than to near infectious avatars and to neutral or fearful avatars (Trabanelli et al., 2025). Thus, although the salience network is activated by other proximal threats, even distal infectious threats can recruit this network, indicating an anticipatory response to infections (Trabanelli et al., 2025). Remarkably, communication between these brain structures and activity of the hypothalamo–pituitary–adrenal (HPA) axis, as assessed by increased functional connectivity and hormonal measurements, predicted changes in innate immune responses. Interestingly, neuroinflammatory factors negatively correlated with activation of the infralimbic region of the prefrontal cortex, suggesting a self-regulation mechanism of inflammation to prevent overreaction to virtual infections.

Positive expectations in sickness

Anticipating a healing outcome from a medication is often sufficient to improve disease symptoms (Benedetti et al., 2011). The neural basis of this placebo effect relies, in part, on the activity of the brain reward system (de la Fuente-Fernández et al., 2001). Chemogenetic activation of dopamine neurons in the ventral tegmental area (VTA), a major source of dopaminergic input to the ventral striatum and the prefrontal cortex, is sufficient to boost innate and adaptive immune responses to *E. coli* infections (Ben-Shaanan et al., 2016). Following stimulation of VTA dopamine neurons, splenic B cells, macrophages, and monocytes have increased expression of TLRs and other markers that prepare immune cells for infection, without a clear pro- or anti-inflammatory response (Ben-Shaanan et al., 2016). This state of preparedness translated into increased phagocytosis of pathogens following *E. coli* infections (Ben-Shaanan et al., 2016). Stimulation of VTA dopamine neurons also boosted delayed and long-lasting adaptive immune responses to infection. The immune effects of chemogenetically activating a key component of the brain reward system are dependent on the integrity of the sympathetic nervous system, which has been shown to exert immunomodulatory effects (Elenkov et al., 2000; Ben-Shaanan et al., 2016). In a randomized, double-blind clinical trial, human participants were trained to upregulate VTA activity via functional magnetic resonance imaging neurofeedback. Upregulation of VTA activity, but not nucleus accumbens or control site activity, was associated with increased antibody production in response to hepatitis B vaccination (Lubianiker et al., 2026). These findings provide promising evidence that reward-system activity can modulate immune responses and suggest a potential path to brain-based interventions, although whether physiological reward-system activation causally enhances immunity in humans remains to be established.

Sickness memory

Experience can shape future immune and sickness responses by linking external cues to internal inflammatory states. In conditioned immune responses, a sensory cue, often a novel taste, is paired with an immune-modulating stimulus such as LPS (Cohen et al., 1994; Janz et al., 1996; Pavlov, 2010). Subsequent presentation of the conditioned cue alone evokes both avoidance of the associated taste and anticipatory changes in immune activity (Janz et al., 1996; Kayyal et al., 2025). Recent work identified a bidirectional circuit between the anterior and posterior insular cortex (IC) that mediates this response. Activity in the anterior-to-posterior insular projection is required for conditioned taste aversion, whereas communication in both directions regulates the anticipatory immune response (Kayyal et al., 2025). These findings suggest that the anterior insula conveys information about the identity and valence of the conditioned sensory cue to the posterior insular regions that represent the associated internal immune state.

A related form of experience-dependent immune-behavioral coupling occurs following allergic sensitization. In mice previously sensitized to a food antigen, subsequent ingestion of that allergen activates the NTS, parabrachial nucleus, and CEA and

drives antigen-specific avoidance (Florsheim et al., 2023). This immune-orientated form of sensitization requires allergen-specific IgE, mast cells, cysteinyl leukotrienes, and GDF15 and emerges before overt intestinal inflammation. In this case, adaptive immune memory in the periphery identifies the previously encountered antigen and recruits aversive neural circuits to prevent further exposure. Thus, prior immune experience can shape future behavior not only through conditioned sensory associations or centrally stored inflammatory representations but also through antigen-specific immune recognition.

Whereas allergen-specific avoidance depends on adaptive immune recognition, the neural activity patterns in the IC can also represent inflammatory states independently of an explicit conditioned cue. Neuronal ensembles activated during colitis or peritonitis can later be reactivated experimentally to reproduce similar inflammation in the peripheral gut tissue (Koren et al., 2021). Conversely, inhibiting these ensembles attenuates aspects of the inflammatory response. It remains unclear whether these ensembles are formed through experience-dependent plasticity and function as engrams or instead represent preexisting, innately organized populations that are preferentially recruited by particular inflammatory states. Either possibility would provide a mechanism through which the IC can reproduce specific peripheral immune responses. Thus, insular activity does not encode inflammation as a nonspecific state but can represent information about the location and character of an immune response.

Multimodal episodic or contextual memories have been shown to retrieve physiological adaptations associated with sickness (Stewart and Ryan, 2025). A recent preprint study combined contextual immune conditioning with engram labeling technology and whole-body metabolic recordings. Engram labeling enables the tagging and manipulation of neuronal ensembles allocated to specific memories (Josselyn and Tonegawa, 2020). Mice that were trained to associate a spatial context with LPS treatment subsequently displayed an acute reduction in whole-body metabolism when returned to the sickness-conditioned context (Douglas et al., 2025). Recall of the sickness-associated context reactivated engrams allocated to the sickness memory in the hippocampus and interconnected sickness-responsive regions, including the CEA and hypothalamus (Douglas et al., 2025). Within the hippocampal dentate gyrus, optogenetic reactivation of contextual engram cells associated with sickness was sufficient to reduce metabolism, whereas their inhibition attenuated the naturally recalled sickness memory response (Douglas et al., 2025). Additionally, both context-triggered recall and artificial engram reactivation increased hepatic expression of positive acute-phase response genes and reduced expression of negative acute-phase response genes, indicating that sickness memories can coordinate anticipatory metabolic and immune responses (Douglas et al., 2025). Together, these findings show that the brain stores both associations that predict inflammation and representations of the inflammatory state itself, allowing prior experience to shape future sickness and immune responses.

Neural Pathways Limiting Inflammation to Drive Recovery from Sickness

Innate inflammatory responses are essential for fighting infections and are rapidly amplified to provide effective protection. However, excessive inflammation poses great risks for the body, as it can eventually lead to tissue damage, organ failure, and death. Even in the absence of a "cytokine storm" in the periphery, excessive sickness symptoms are dangerous. Several protective processes have evolved to prevent harm to "self" during inflammation: (1) negative feedback mechanisms that limit inflammation, (2) anti-inflammatory and tissue repair mechanisms that resolve inflammation, and (3) restoration of behavioral and physiological setpoints to recover from sickness. Some of these processes have been described in the periphery: secretion of anti-inflammatory cytokines such as IL-10; specialized proresolving mediators such as lipoxins and resolvins; macrophage transitions from inflammatory to proresolving and repair-associated states; and restoration of tissue homeostasis. Remarkably, brain mechanisms embedded within the sickness neural network play key roles in coordinating several aspects of these processes (Fig. 3).

The cranial nerve pathway plays an important role in keeping inflammation under control by engaging the HPA axis for negative feedback and the autonomic nervous system for resolution and repair. In response to peripheral immune activation, catecholaminergic neurons in the NTS (A2) that project to the PVN stimulate neurons producing CRH to engage the HPA axis and induce the release of adrenal glucocorticoids, thus limiting inflammatory responses (Hosoi et al., 2000; Bonaz et al., 2016; Herman, 2018). The importance of this negative feedback pathway is highlighted by the fact that PVN also receives inputs from LPS-responsive VMPO located near the OVLT (Osterhout et al., 2022), and both PGE2 and IL-1β can excite parvocellular

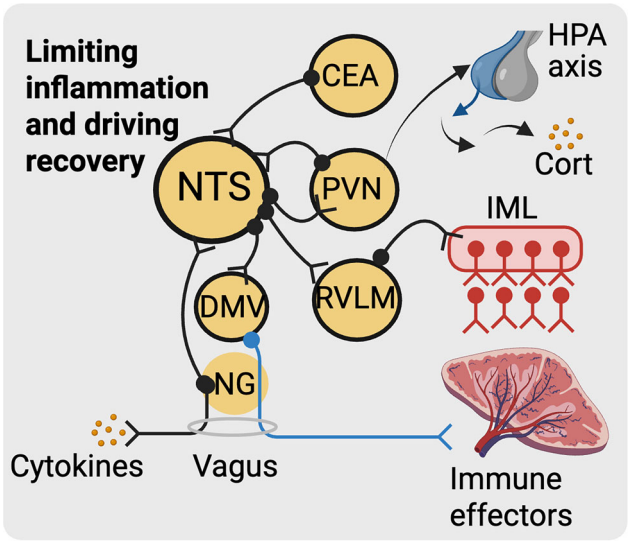


Figure 3. Brain–body pathways to limit inflammation and promote recovery from sickness. Peripheral cytokines activate vagal sensory neurons in the nodose ganglion, which relay immune information to the NTS. The NTS engages several efferent pathways capable of constraining peripheral inflammation. Catecholaminergic NTS inputs recruit CRH-expressing neurons in the PVN and activate the HPA axis, resulting in adrenal glucocorticoid release. NTS projections to the DMV engage parasympathetic vagal output, whereas projections through sympathetic premotor regions, including the RVLM and spinal IML, regulate sympathetic output to peripheral immune tissues. Forebrain structures such as the CEA and PVN provide additional descending control over these brainstem and autonomic circuits. Blue lines indicate parasympathetic vagal output, red structures indicate sympathetic output, and black lines summarize central connections discussed in the text. These simplified pathways may regulate cytokine production, immune-cell activity, resolution, and tissue repair through organ- and context-dependent mechanisms; not all illustrated connections are necessarily direct or monosynaptic. CEA, central amygdala; Cort, circulating adrenal glucocorticoids; DMV, dorsal motor nucleus of the vagus; HPA, hypothalamo–pituitary–adrenal; IML, intermediolateral cell column of the spinal cord; NG, nodose ganglion; NTS, nucleus of the solitary tract; PVN, paraventricular nucleus of the hypothalamus; RVLM, rostral ventrolateral medulla.

PVN neurons, in part by reducing inhibitory input (Ferri and Ferguson, 2003; Zhang et al., 2011).

Autonomic circuits can constrain inflammation and stimulate resolution and repair through organ- and context-specific sympathetic and parasympathetic mechanisms. Immune cells express nicotinic and adrenergic receptors, and therefore both cholinergic and adrenergic signaling can regulate cytokine production and immune differentiation (Wang et al., 2003). A seminal paper at the beginning of the millennium showed that acetylcholine suppresses proinflammatory cytokine production (TNF, IL-1β, IL-6) but does not affect production of anti-inflammatory cytokines such as IL-10 and that electrical stimulation of the distal end of the transected vagus nerve replicates suppression of serum and liver TNF levels (Borovikova et al., 2000). However, the anatomical basis of this anti-inflammatory pathway remains contested. Vagus nerve stimulation suppresses TNF through a splenic nerve-dependent pathway, consistent with a vagal–sympathetic relay, whereas other findings indicate that the endogenous anti-inflammatory reflex is mediated primarily by splanchnic sympathetic nerves rather than the vagus (Rosas-Ballina et al., 2008; Martelli et al., 2014). More recent work has also identified direct projections from neurons in the caudal dorsal medial nucleus of the vagus (DMV) to the spleen (Kobori et al., 2023). Several structures within the sickness network connect to the DMV to regulate parasympathetic output and to premotor sympathetic structures such as the rostral ventrolateral medulla (RVLM) and raphe pallidus (RPa). For example, NTS neurons project to cholinergic DMV neurons to regulate vagal parasympathetic output and peripheral acetylcholine release (Travagli et al., 2006) and to the caudal ventrolateral medulla to modulate RVLM activity and peripheral noradrenaline release (Moreira et al., 2005). DBH^+ neurons, a catecholaminergic subtype within the NTS, receive monosynaptic input from functionally distinct $TRPA1^+$ and $CALCA^+$ nodose neurons that preferentially respond to anti- and proinflammatory signals, respectively (Jin et al., 2024). $TRPA1^+$ vagal neurons respond to IL-10 and engage NTS circuits that reinforce anti-inflammatory signaling and suppress proinflammatory cytokines, whereas $CALCA^+$ vagal neurons respond to proinflammatory cytokines and engage a negative-feedback response that decreases peripheral proinflammatory cytokines (Jin et al., 2024). Together, these findings indicate that distinct vagal–NTS pathways may differentially limit inflammation and promote resolution and recovery.

Other brain structures within the sickness network project to the NTS, DMV, and sympathetic premotor regions and have the potential to suppress inflammation and support recovery from sickness symptoms. The medial nucleus of the CEA, which receives local inhibitory input from the LPS-responsive capsular and lateral CEA, projects to the DMV to control spleen maturation of immune cells during neuropathic pain (Zhu et al., 2024). PVN neurons can project directly to the sympathetic intermediolateral cell column to regulate peripheral noradrenaline release and project to the NTS and DMV, potentially modulating parasympathetic output as well. Consequently, stimuli that activate neuronal populations in these brain structures, such as fear-induced activation of the CEA, have the potential to affect the pace of recovery from sickness. The understanding of multiple brain–body mechanisms for neuroimmune regulation opens the door to several potential therapeutic approaches to treating acute and chronic inflammation, such as vagus nerve stimulation, electroacupuncture, and behavioral therapy (Liu et al., 2021; Kelly et al., 2022; Lubianiker et al., 2026). Neural circuits likely do not merely suppress excessive inflammation; they may continuously compare ongoing immune signals with the organism's physiological state to determine when individual components of sickness can be safely terminated. Whether fever, anorexia, fatigue, and social withdrawal recover through a common neural program or through independently regulated modules remains an important open question.

Conclusions

Sickness is not a uniform response imposed on the brain by peripheral inflammation. Instead, the nervous system detects immune activity through distributed humoral and neural pathways and transforms this information into coordinated, yet partly dissociable, behavioral, and physiological responses. Although these responses are generally thought to support host defense, their adaptive value depends on the nature of the infection and the physiological needs of the host (Sparling et al., 2026). For example, fasting metabolism promotes tissue tolerance during bacterial inflammation but is detrimental during viral inflammation, in which glucose utilization is protective (Wang et al., 2016). CVOs, neurovascular interfaces, cranial sensory pathways, and downstream forebrain circuits together form a system for immunoception that can tailor fever, anorexia, fatigue, aversion, and social behavior to the nature and magnitude of an immune challenge.

These same circuits are also shaped by context and experience. Social cues, expectations, and cognitive memories of prior inflammation can alter immune activity and recruit sickness-related responses before direct pathogen detection, while autonomic and endocrine pathways constrain inflammation and may help determine when individual components of sickness resolve. A major challenge will be understanding how these pathways interact over the course of illness and whether sickness is terminated by a common recovery program or by the independent resolution of symptom-specific modules. Defining these mechanisms may reveal new ways to modulate debilitating sickness symptoms without compromising protective immunity. Looking ahead, targeting the neuroimmune processes that generate sickness symptoms may offer new therapeutic strategies for neurological and neuropsychiatric disorders in which neuroinflammation contributes to disease pathophysiology, including multiple sclerosis, stroke, Parkinson's disease, Alzheimer's disease, autism spectrum disorder, and anorexia nervosa.

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