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Brain-body physiology: Local, reflex, and central communication

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SUMMARY

Behavior is tightly synchronized with bodily physiology. Internal needs from the body drive behavior selection, while optimal behavior performance requires a coordinated physiological response. Internal state is dynamically represented by the nervous system to influence mood and emotion, and body-brain signals also direct responses to external sensory cues, enabling the organism to adapt and pursue its goals within an ever-changing environment. In this review, we examine the anatomy and function of the brain-body connection, manifested across local, reflex, and central regulation levels. We explore these hierarchical loops in the context of the immune system, specifically through the lens of immunoception, and discuss the impact of its dysregulation on human health.

As we deepen our understanding of organism physiology, it becomes apparent that we are missing an important piece of the puzzle. The organism does not act as a mere sum of its components—rather, new properties emerge when we observe the organism as an integrated entity. There is a remarkable synchronization at play—each organ tunes its function in rhythm with other physiological systems and contributes its unique inputs and needs, with the brain and nervous system orchestrating the entire symphony.

Brain-body communication is bidirectional. On the one hand, the central nervous system can respond to physiological demands by evoking the behaviors that may fulfill them. For instance, an organism might seek warmth when its body temperature drops or crave specific foods when nutrients are deficient. On the other hand, physiology must adapt to mental and

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DECLARATION OF INTERESTS

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behavioral needs, allowing the organism to effectively execute its goals, such as the increase in heart rate during a flight from a predator attack. Even the very belief that a meal is imminent triggers brain-body signals that prepare the digestive system for food intake, as Pavlov first described.[1]

The connections between mental and physiological states manifest in modern medicine in the epidemiological correlation between elevated stress levels and the emergence of disease[2,3] or in the improved physiological state in patients receiving a placebo pill. Interventions aimed at the brain-body connection, such as breathing practices, meditation and relaxation techniques, and exercise, are supported by an emerging body of correlative evidence for the benefit of treating a patient's emotional, psychological, and cognitive needs.[4] Nevertheless, we do not understand how these therapies work, leaving us with a significant challenge to uncover the underlying mechanisms of brain-body communication in health and disease.

The segregation between the brain and the body that has come to dominate modern medicine is motivated by the need to understand the causal mechanisms of physiological phenomena. It required dissecting the underpinning of each physiological system in isolation to gain a detailed understanding of its components. This contrasts with Eastern medical practices, which are governed by an integrated mind-body perception. However, modern science and medicine have reached a point in which emerging evidence in fields ranging from immunology, reproduction, cardiovascular disease, microbiology, and others highlights the relevance of interconnections between these systems. In seeking to reunite our understanding of the brain and body, science has provided evidence for interactions between the nervous system and other physiological systems at multiple levels of interaction. We will define these interactions as a set of hierarchical loops: local, reflexive, and central (Figure 1). This conceptual segregation, although artificial, will allow us to discuss each loop with its own set of parameters and specific regulation and to define how they synchronize in the overall scheme of brain-body integration. Finally, we will exemplify how these concepts apply to the interaction of the brain with one essential peripheral system, the immune system, and the concept of immunoception.

INPUTS TO THE NERVOUS SYSTEM

The nervous system constantly senses and evaluates the physiological condition of the body. The brain receives information in two primary forms: soluble molecules that reach circumventricular organs (CVOs) and other brain borders (see Box 1), and sensory neurons, which serve as direct information highways from the body (Figure 2). Sensory neurons include cranial nerves, with the vagus and glossopharyngeal nerves providing dominant innervation of organs in the abdomen and thorax, as well as spinal nerves from the dorsal root ganglia (DRGs).

The vagus nerve collectively innervates a variety of organs in the gut as well as the airways (lungs, trachea, and larynx), vasculature (heart, arteries), and other abdominal and thoracic sites. Vagal sensory neurons include first-order sensors that directly sense stimuli, as well as second-order neurons that receive inputs from upstream sentinel cells like enteroendocrine

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cells in the intestine, glomus cells in the vasculature, neuroepithelial bodies in the lung, taste cells in the larynx, and immune cells.[9] Some are chemosensory neurons, specialized to detect hypoxic or hypercapnic conditions, ingestion of nutrients or nausea-inducing toxins, inhalation of certain cough-inducing irritants, or infection by sickness-causing pathogens. Others are mechanosensory neurons that detect changes in blood pressure or blood volume, airway closure, and stretch of organs like the lungs, stomach, heart, esophagus, and intestine. Single-cell atlases of vagal sensory neurons[10–12] revealed incredible cell diversity, with dozens of distinct cell types, far more than the number of known vagal reflexes. Furthermore, genetic and anatomical mapping approaches revealed many vagal terminal morphologies with unknown sensory properties. Thus, there are additional capabilities of the vagus nerve that await characterization.

Vagal axons enter the brain bilaterally through the jugular foramina, and those from the largest vagal ganglion (the nodose ganglion) target the brainstem at the nucleus of the solitary tract (NTS), with some also projecting to the area postrema (AP). Vagal neurons of the jugular ganglion instead target the spinal trigeminal tract.[9] A topographic organization of visceral sensory input arises in the NTS from disordered representations in peripheral ganglia,[13] and is generally maintained in higher-order nuclei, such as the viscerosensory nuclei of the thalamus and insular cortex (IC).[14]

DRG neurons that innervate internal organs are even less well understood. DRG neurons are classically known to detect stimuli associated with sensations of touch, proprioception (movement and location of body muscles), nociception (pain and itch), and temperature and send axonal inputs to the dorsal horn of the spinal cord. Signals are then further transmitted through spinothalamic-cortical pathways, where they synapse with higher-order neurons. Single-cell transcriptomics identified 17 distinct types of mouse DRG neurons, most of which are conserved in humans.[15,16] Many neuron types respond to classical stimuli associated with touch, heat, cold, and itch, while the functions of others are not yet fully understood. In addition to their classical roles in somatosensation, some also innervate internal organs, including the bladder, colon, heart, and spleen.[17–20] Still, the diversity of somatosensory neuron types involved in visceral representations, as well as their functions, response properties, and signaling mechanisms, remain largely unknown.[17,18] Moreover, we are lacking functional studies to understand the division of labor between sensory pathways of cranial nerves, spinal nerves, and CVOs.

OUTPUTS OF THE NERVOUS SYSTEM

As sensory information is received by the brain, communication with the body occurs through major humoral and neuronal pathways. The endocrine system secretes hormones into the bloodstream, while the somatic nervous system controls voluntary muscle movement, and the autonomic nervous system regulates a variety of internal organ functions, which we focus on here. The autonomic nervous system is broadly divided into two main programs: the sympathetic and parasympathetic systems. The sympathetic nervous system is widely recognized for triggering the “fight or flight” response, a term coined by Walter B. Cannon in the early 20th century to describe a series of rapid and powerful physiological adjustments to prepare the body for facing or escaping urgent threats. By contrast, the

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parasympathetic nervous system is often associated with the “rest and digest” state, supporting essential bodily functions during more tranquil times. The autonomic nervous system not only adjusts physiological processes during emotional states and behaviors but is also integral in our daily lives for maintaining homeostasis, i.e., ensuring the constancy of organ physiology amid ever-changing internal and external conditions.

The sympathetic and parasympathetic nervous systems are often partners in the same dance, with opposing but coordinated motions that maintain a delicate physiological balance. The baroreceptor reflex exemplifies this coordination, ensuring real-time stabilization of the cardiovascular system. Baroreceptor sensory neurons alert the brain to changes in blood pressure through PIEZO-dependent detection of arterial distension, triggering responses that adjust heart rate and vascular resistance by engagement of parasympathetic outflow and simultaneous disengagement of sympathetic outflow.[21] These systems exhibit dynamic sensitivity, with central circuits adapting during physiological states such as exercise. Similar antagonistic functions of the sympathetic and parasympathetic systems have been described across physiological systems, from respiration to digestion. Understanding this yin-yang hallmark of brain-body communication in the context of the immune system and whether the systems truly have opposing roles has become an emerging area of research.[22]

Autonomic outflow involves a characteristic two-neuron relay, with preganglionic neurons in the central nervous system and postganglionic neurons typically in peripheral ganglia. The preganglionic neuron has a motor axon that targets peripheral ganglia in the body, and the postganglionic neuron relays descending motor commands directly to a target organ (Figure 2). Some sympathetic preganglionic neurons also target hormone-producing cells of the adrenal medulla. Sympathetic preganglionic neurons are situated in the thoracic and upper lumbar segments of the spinal cord, with sympathetic ganglia comprising either the sympathetic chain adjacent to the vertebrae or prevertebral sympathetic ganglia. Sympathetic preganglionic neurons release acetylcholine, which acts on nicotinic receptors to excite postganglionic neurons or adrenal chromaffin cells. The postganglionic neurons then typically release norepinephrine or, in rare cases, acetylcholine and other secreted molecules to regulate specific tissue functions. Adrenal chromaffin cells, on the other hand, directly secrete catecholamines such as epinephrine and norepinephrine into the bloodstream, thereby more broadly influencing organ function. Cellular responses to norepinephrine are notably dose-dependent and influenced by perfusion efficiency at receptor sites, meaning that nerves innervating specific targets can create higher local norepinephrine concentrations and trigger distinct reactions compared with systemic norepinephrine.[23]

Parasympathetic preganglionic neurons instead reside directly in the brainstem, in motor nuclei associated with cranial nerves (III, VII, IX, and X), or in sacral segments of the spinal cord. Postganglionic parasympathetic neurons are located near or within target organs; for example, postganglionic parasympathetic neurons in the gut are part of the enteric nervous system. Acetylcholine is the primary neurotransmitter used at both preganglionic and postganglionic synapses of the parasympathetic system. Peripheral neurons (parasympathetic and sympathetic) can sometimes co-release neuropeptides or nitric oxide together with amines.

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Recent studies using single-cell RNA sequencing have revealed a surprising diversity within the sympathetic and parasympathetic systems, challenging the old view of these systems as providing uniform “all-or-nothing” responses.[24–27] Cellular atlases have provided markers enabling the development of genetic tools for selective mapping and control of molecularly defined neurons, revealing that transcriptional diversity likely underlies functional diversity. For instance, transcriptomic analysis has revealed a diversity of vagal preganglionic neurons, with at least seven neuron subtypes within the dorsal motor nucleus of the vagus (DMV) and a smaller group within the nucleus ambiguous (nAmb).[24,25] These neuron subtypes exhibit distinct connectivity patterns within the body, and early studies suggest a functional division of labor. Different neuronal subtypes within the nAmb mediate the baroreceptor reflex, the dive reflex, and motor control over the esophagus.[25,28] Each neuron type potentially exerts differential and nuanced physiological control rather than a singular, all-or-nothing, rest and digest response. Together, these findings indicate that transcriptional diversity is a crucial organizational principle in parasympathetic preganglionic neurons, with each neuron type assuming a unique projection pattern and specific function.

Similar approaches are starting to shed light on the transcriptional diversity of the sympathetic nervous system, corroborating early histology and electrophysiology studies that observed differences in soma size, dendrite morphology, response property, and neuropeptide expression. Single-cell analyses identified 16 types of cholinergic preganglionic neurons that comprise the thoracolumbar and sacral outflows,[27] and five to seven subtypes in the superior cervical, stellate, and thoracic ganglia.[26,29] These studies reveal expression of numerous genes encoding neuropeptides and hormone receptors, suggesting more complex communication mechanisms and modulatory mechanisms beyond canonical aminergic transmission. Moreover, these rich datasets enable an unprecedented opportunity to study the intricate mechanisms of signal transduction and neuron modulation in the sympathetic nervous system and will potentially reveal new organizational features and functions. Genetic access to molecularly defined autonomic neurons will provide a road map to link transcriptional profiles, morphological features, projection patterns, response properties, and functions. Pharmacological tools that target specific neuronal populations may provide tailored control of physiology and new therapeutic opportunities for selective adjustment of autonomic tone. This neuronal diversity also highlights precise and complex mechanisms during neural development to ensure proper wiring and function, as well as exciting developmental and mechanistic questions that await further investigation.

NEURONAL REGULATION ACROSS HIERARCHIES: THE INTERCONNECTEDNESS OF LOCAL, REFLEXIVE, AND CENTRAL REGULATION

The intricate and interwoven architecture of the nervous system is characterized by a series of hierarchical controls of bodily physiology that, as described in the previous section, connect the peripheral to the central nervous system. This complex network is a continuum, fine-tuned by integrating local, reflexive, and central regulatory levels to coordinate the body’s interactions with its environment and promote homeostasis on both a short and long timescale.

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Local control

Peripheral sensory neurons are deeply embedded within tissues.[30] In addition to transmitting sensory information to the central nervous system, sensory neurons and/or their communication partners, like enteroendocrine cells in the gut, can in some cases have more local functions, releasing peptides that elicit direct physiological effects on peripheral tissues.[9,31] It should be noted, however, that the existence of local responses does not exclude the routing of relevant information through the brain.

These local effects of sensory neurons were demonstrated in the context of immunity. Peripheral sensory neurons innervate tissues inhabited by immune cells. These neurons can directly sense the presence of pathogens or changes in immune activity via cytokine receptors or pattern recognition receptors that detect pathogen-derived component.[32] In addition to transmitting this immune-related sensory information to the central nervous system, these sensory neurons can also locally modulate the immune response. They can secrete regulatory factors such as calcitonin gene-related peptide (CGRP), substance P (SP), and vasoactive intestinal peptide (VIP).[33] Accordingly, sensory neurons were implicated in suppressing inflammation, driving it, and mediating resistance to infections.[34,35–37] Local interactions between somatosensory neurons and immune cells are particularly evident in nociceptive mechanisms, where immune cells release inflammatory mediators that sensitize or activate sensory neurons, contributing to the onset and maintenance of pain and sickness behavior.[38,39] Mast cells, neutrophils, and macrophages contribute to this interaction by playing discrete roles in affecting neurons, mediating pain and itch.[40,41,42] These local mechanisms are evident and further complicated in clinical settings, where damage to nerves has been associated with improvement to psoriasis,[43] whereas a genetic mutation that results in the lack of somatosensory neurons is associated with more bacterial infections.[44] Yet, it is important to note that some of these effects can take place also at reflexive and central regulatory levels.

The connection between pain and inflammation serves an important adaptive role across all these levels. Pain sensitization leads to modified behavior to protect affected areas and avoid pressure on an inflamed spot. According to this line of reasoning, one can expect that pro-inflammatory cytokines will exacerbate pain while anti-inflammatory cytokines help alleviate it. However, the activity programs of sensory neurons are not as discrete, and variations in the activating pathogens (e.g., bacteria vs. virus), the affected tissue, the specific types of sensory neurons involved, and the prevailing condition of the tissue. All highlight a major gap in our understanding of the local interactions between pain and immunity.

Another conceptual gap that highlights the importance of further research in this direction is the understanding of why sensory neurons secrete immune mediators despite the presence of other tissue cells, such as epithelial subsets, which are capable of fulfilling this role. One possibility is that these local sensory neurons possess some level of integrative capacity that manifests in their differential effects on the local immune response.

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Reflexive control

Beyond the local sensory response, a pathway followed by a reflexive activity, known as the reflex arc, typically involves a sensory neuron that detects the stimulus and a motor neuron that carries out the response (Figure 3). However, reflexive activities can involve more complex pathways, including additional neuronal relays. This additional processing of information within the spinal cord or brainstem may lead to more nuanced responses based on other sensory stimuli or the physiological state of the tissue or organism.

Reflex circuits are heavily involved in regulating homeostasis, the delicate balance of maintaining physiological conditions within a narrow set point.[47] This set point encompasses constants like core body temperature, blood pressure, and systemic sugar levels, which can be largely regulated by physiological reflex arcs without the involvement of higher brain areas. These types of classical reflex arcs are reactive systems that provide direct negative feedback control by triggering stereotypical compensatory actions when physiological parameters deviate from their predefined set points.[47] More complex reflex arcs also allow for dynamic changes in physiological set points; for example, exercise dampens the baroreceptor reflex to allow heart rate and blood pressure to remain elevated as needed.

One example of a reflex response at the neuro-immune axis is the inflammatory reflex (Figure 3). It was initially observed that electrical stimulation of the vagus nerve dampens the systemic immune response to endotoxin shock[45] (the specific mediators that activate this response are still not fully elucidated). Vagal motor neurons were proposed to innervate spleen-projecting postganglionic neurons located in the celiac-superior mesenteric ganglia of the sympathetic prevertebral ganglia. Postganglionic neurons then release noradrenaline in the spleen, which signals to cholinergic T cells through β2-adrenergic receptors. T cell-derived acetylcholine subsequently acts via a nicotinic receptor (α7nAChR) on macrophages, suppressing the inflammatory cytokine response. This neuronal mechanism facilitates a rapid, system-wide response essential for survival.[48]

This is important because immune cells communicate via dispersed chemical signals, resulting in a slower, localized response. This is crucial for carefully regulating immune reactions. However, when a faster and more systemic response is required (e.g., sepsis), the nervous system can bridge the gap. These are hard-wired programs crucial for survial. For example, neurons in the caudal NTS respond indirectly to cytokines secreted during inflammation and work to suppress the inflammation.[49]

Another component of inflammation, sickness behavior, has also been shown to be mediated by neurons in the NTS and AP.[5,50] The AP is directly activated by certain cytokines, like GDF15, and mediates sickness-related behaviors such as nausea.[5,6] While these behaviors also involve higher brain structures and require complex processing by the brain, direct reflex loops between immune signals reaching the AP and autonomic responses have been demonstrated (Figure 3).

An intriguing variation of neuroimmune reflexes has been reported in studies involving electroacupuncture stimulation (ES). These studies found that stimulation of specific subsets

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of peripheral sensory neurons at acupuncture points can result in vagal-adrenal activation, which induces an anti-inflammatory effect (Figure 3).[51] Notably, one study demonstrated that this is intensity-dependent: high-intensity ES activates a different mechanism via the spinal-sympathetic axis, which may drive inflammation.[46] These findings highlight an important gap in this field, raising questions about potential sympathetic reflex loops. Additionally, they underscore our incomplete understanding of the interactions between the two components of the autonomic nervous system.

A promising application of the inflammatory reflex is the use of vagal nerve stimulation (VNS) for reducing inflammation in diseases such as inflammatory bowel disease (IBD), pancreatitis, kidney injury, and rheumatoid arthritis.[48,52] Notably, VNS has been effective in calming gut inflammation by acting directly on specific immune cells in the gut rather than through the spleen or T cells.[53] However, the broad activation of vagal sensory and motor neurons by VNS limits the generalization of this approach. More selective targeting of specific neuronal populations could improve efficacy while limiting side effects. Understanding which specific motor neurons interact with the immune system, along with the corresponding sensory pathways they receive information from, is crucial. This research prompts critical questions about the benefits of anti-inflammatory neural circuits and the broader implications for functions governed by similar reflexes. It also highlights the communication between these regulatory loops; while these networks initiate responses at the brainstem level, they result in a more complex set of behaviors regulated by central and interoceptive pathways.

Central regulation and immunoception

Local and reflexive levels of control provide fast and direct reactive regulation of bodily physiology through hard-wired action programs. Higher-order brain areas act more adaptively, synchronizing changes across physiological systems and timescales, adjusting bodily functions in real time during behavior, and proactively initiating central regulatory actions. They integrate information about the current state of different bodily systems and environmental conditions with evolutionarily selected programs, prior experience, and motivational state. This processing enables the brain to anticipate future states and adjust bodily functions to meet incoming needs or challenges.[47] To achieve such adjustments, higher-order brain areas exert top-down control of physiology, including temporary alterations of the homeostatic set points to accommodate expected states, as well as of motivational drives and behavior (Figure 1). Central circuits of the interoceptive nervous system are thus essential for adapting body physiology in dynamic environments (Figure 4).[47,54] Emerging theories propose that adaptive homeostasis is central to brain function and provide working models for interoception and bodily regulation (Box 2).

Interoceptive brain areas integrate visceral information ascending from vagal and spinal afferents, passing through the NTS, parabrachial nucleus (PBN), and interoceptive thalamic nuclei, and ultimately reaching the posterior IC (pIC), the anterior cingulate cortex (ACC), and the somatosensory cortices.[55,64] In parallel, bloodborne molecules are sensed by CVOs and other border regions (Box 1), which also ultimately relay information to cortical regions, including the IC and ACC. Cortical sites receiving interoceptive information are

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interconnected with visceromotor cortical regions, such as the anterior IC (aIC), ACC, ventromedial prefrontal, and orbitofrontal cortices, which are thought to mediate adaptive homeostatic control (Box 2).[59] At this level, a more complex multisensory integration is performed, as well as processing in the context of prior experience, motivational drives, emotion, and cognition. As a result, these brain areas are thought to compute interoceptive predictions, based on which coordinated autonomic, motivated behavioral, neuroendocrine, and immune commands are generated to ensure an optimal contextual adaptation of the organism's physiology. Coordinated visceromotor predictions are broadcast to subcortical structures that recruit the adaptive reactions, such as the hypothalamus, central amygdala (CeA), bed nucleus of the stria terminalis (BNST), periaqueductal gay (PAG), PBN, and autonomic motor nuclei, including the DMV and ventrolateral medulla (VLM) (Figure 4). Motor cortices, including M1, M2, and the supplemental motor area, also contribute through striatal muscle control and sympathetic modulation.[65,66]

While the described pathways outline a general axis for interoception and central regulation, the cortical and subcortical regions involved are highly interconnected. Most of these structures process interoceptive information and act as visceromotor centers, forming hierarchical control loops with multiple feedforward and feedback mechanisms between the different levels of control (Figures 1 and 4).[64,67] The NTS and PBN have direct bidirectional connections to hypothalamic nuclei, such as the paraventricular hypothalamic nucleus (PVN) and lateral hypothalamic area (LHA), the CeA, BNST, and PAG.[64,68–71] These projections are involved, for example, in modulating emotion states and motivated behaviors during inflammation and pain,[70,72,73] or in regulating systemic immune activity in response to pro-inflammatory signals.[71]

The maintenance of fluid balance serves as an excellent example to conceptualize how the brain coordinates reactive control with anticipatory regulation, driving adaptive changes upon processing of internal sensory information.[74] When the body detects changes in blood volume, a cascade of compensatory actions is recruited to restore fluid homeostasis through negative feedback loops. Following events such as severe dehydration, autonomic responses ensure substantial blood pressure and tissue irrigation by accelerating heart rate and inducing peripheral vasoconstriction, while hormonal adjustments preserve fluid volume. Different arms of the interoceptive nervous system collaborate to produce these complex responses, including baroreceptors in the cardiovascular system, hormones like angiotensin II, and osmolarity sensors in CVOs. Dehydration also activates specific neurons, promoting thirst perception and motivating water-seeking and drinking behaviors. These neurons indirectly relay information to the anterior regions of the cingulate cortex and the IC, important in thirst perception and driving these behaviors.[67,74–77] Importantly, anticipation of increased water need, such as during food consumption, or decreased water need immediately after drinking can adjust behavior and physiology. These changes occur prior to measurable changes in blood osmolarity, blood volume, or hormone levels, consistent with a role for central circuits in top-down physiological and behavioral control.[74,76,77] Pavlov's salivating dogs provide another classical example illustrating a similar anticipatory central circuit modulation of bodily processes.

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The IC has long been recognized as the primary visceral cortex, receiving strong sensory input from multiple bodily systems and actively regulating physiology.[14,65,78,79] Accumulating evidence supports the role of the IC in integrating internal and external sensory inputs with anticipatory contextual information, shaping interoceptive representations, and regulating physiology directly or indirectly through changes in motivation and behavior.[79] In humans, the experience of thermal pain intensity and affective touch activates the mid IC and pIC, while their contextual or cue-evoked anticipation activates the aIC.[80,81] Predictions of breathing changes also modulate aIC activity.[82] In rodents, similar "anticipatory" neurons in the IC respond to associative cues signaling the occurrence of sensory stimuli affecting the physiological state, such as food, water, or aversive foot-shock.[67,83,84] Anticipatory activity signaling the availability of food or water was found to depend strongly on the body's need state. This need-dependent saliency of relevant cues is relayed from the hypothalamus through the paraventricular thalamus and basolateral amygdala, projecting to the IC.[85] IC anticipatory activity contributes to guiding motivated behaviors that promote homeostasis and to adaptively control physiology, such as during emotion states. Indeed, IC neurons responsive to food or water cues are necessary for motivated behaviors exhibited during anticipation, like approaching food,[83] or increasing action vigor for receiving water during thirst.[67] Illustrating the recruitment of adaptive bodily changes in the context of emotions, neurons projecting from the pIC to the CeA are active in anxiogenic contexts and induce an increase in breathing rate while also promoting avoidance or anxiety-like behavior.[79] These and other studies suggest that neurons in the IC may encode anticipatory signals related to the internal state, integrating bodily need states, and regulate emotional and motivational states alongside bodily physiology to form a coordinated response.[84] Importantly, this evidence highlights how emotions serve as an adaptive central mechanism for direct and indirect adjustments of physiology in contexts that are salient for survival. In turn, bodily reactions during emotion responses influence the persistence of emotion memories.[84] This bidirectional interaction is increasingly seen as fundamental to maintaining physiological and emotional homeostasis.

The brain does not only anticipate needs and physiological states but synchronizes them across multiple systems and throughout time. The brain's unique ability to monitor time makes it a very effective synchronization mechanism. For example, our circadian rhythm synchronizes immune cell mobilization throughout the day. Also, bone growth and the movement of hematopoietic stem cells within the blood and bone marrow are timed to occur at night, synchronized by the release of growth hormone (GH) and managed by sympathetic innervation to the bone marrow.[86] In addition to circadian rhythms coordinating physiological processes over the course of a day, time perception is also part of our interoceptive processes as we anticipate how long a certain process will take and orchestrate our behavior and physiology accordingly. Wound healing has been shown to vary with time perception rather than actual time, suggesting that clock manipulation can affect physiological responses.[87] Similarly, in patients with type 2 diabetes, blood glucose levels seem more responsive to perceived time than actual time.[88] This indicates that the brain's internal clock, the suprachiasmatic nucleus (SCN) of the hypothalamus, can synchronize bodily functions with environmental cues or circadian rhythms scale to avoid internal conflicts. Interestingly, there are also peripheral circadian clocks that can maintain

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circadian oscillations in isolation from the SCN but nonetheless rely on central inputs for synchronization across the organism.[89]

The anticipatory capacity of the brain in the context of immune regulation is manifested by motivated behaviors, such as mating and feeding, which can potentially increase pathogen exposure. These behaviors involve the ventral tegmental area's (VTA) dopaminergic neurons, an area implicated in motivated behaviors. Indeed, a study has shown that anticipation of mating is sufficient to prime the immune system, specifically an increase in interleukin (IL)-2 levels, but inhibition of VTA activity eliminates this typical response.[90] Direct activation of the VTA with DREADDs was shown to enhance immune activity against bacteria and cancer.[91,92] It is important to note that the artificial manipulations of the VTA or other reward system components with chemogenetics or optogenetics are isolated from the physiological context, and more detailed analysis of the specific projections is required. Interestingly, positive expectations like hope that involve reward system activation have been associated with the placebo response and improved physiological responses. Nevertheless, the placebo is a more complex phenomenon that also involves conditioning processes.

Indeed, early 20th-century studies demonstrated that the immune system could undergo conditioning. Exposure to an immune-stimulating or suppressive agent coupled with a neutral stimulus (saccharine) can induce conditioned immune responses to the neutral stimulus alone.[93] Several brain areas, including the IC, were implicated in this conditioning.[94] Recently, it was shown that the IC stores an immunological representation in the brain.[95] Reactivation of neuronal ensembles in the IC that were active during inflammatory conditions resulted in a recall of the inflammatory state, even in the absence of a new immune challenge. These effects were suggested to be mediated by IC neurons connected to peripheral organs such as the colon and peritoneum through the DMV and rostral VLM, supporting the role of the autonomic nervous system in mediating these effects.[95]

These findings suggest that the brain can induce specific immunological reactions, which may have evolved as a mechanism for efficiently addressing environmental challenges that are likely to recur. This phenomenon could be likened to the body's anticipatory measure against future assaults similar to the original encounter. This "immunological memory" within the brain, specifically in the IC, can create a rapid and efficient defense mechanism before the body is challenged. For example, it can prime gut immune cells when preparing to drink from a water source that previously caused an infection. However, such "memory responses" can become maladaptive in autoimmune patients by triggering inflammatory episodes in response to specific stimuli. Recent studies on allergies revealed that avoidance behaviors induced when encountering an established allergen are a result of neuroimmune interactions.[96,97] These studies show that mast cells connected to allergen-specific IgE antibodies secrete mediators that activate the NTS, PBN, and CeA.[97] Also, in cases of IBD, imaging studies show altered activity in key brain areas involved in interoception, potentially inducing inflammatory flares in response to stressful triggers. Indeed, manipulation of key brain areas by deep brain stimulation (DBS) or reactivation of cytokine-activated NTS neurons has potent immunomodulatory and endocrine effects.[98] By understanding these

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underlying mechanisms, we can develop more effective and targeted therapeutic strategies that leverage the neuroimmune interface. Furthermore, these findings emphasize the brain's role as a synchronizer and regulator of bodily physiology, as these specific stimulations had local effects on the immune response.

Another aspect that highlights the anticipatory component of the neuroimmune connection is stress. The stress response predicts potential damage to the organism and influences the distribution and activity of leukocytes. Immune cells can be rapidly mobilized to the blood in response to acute stress, positioning the immune system for any potential challenge. Interestingly, different acute stressors involve distinct brain areas, which induce various effects on the immune system. For instance, motor circuits can prompt rapid neutrophil mobilization from bone marrow to tissues, mediated by neutrophil-attracting chemokines from skeletal muscle.[99] By contrast, the PVN governs the movement of monocytes and lymphocytes from secondary lymphoid organs back to the bone marrow through glucocorticoid signaling.[99] Similarly, neurons in the CeA and PVN that express corticotropin-releasing hormone (CRH) are connected to the splenic nerve and autonomically enhance humoral responses.[100] These stress-induced leukocyte shifts are also associated with altered disease susceptibilities. Yet, they represent an essential brain-immune connection to prepare the immune system for an upcoming challenge and are part of the ongoing process of immunoception.

Immunoception, the brain's representation of the immunological state of the organism, like other aspects of interoception, is bidirectional and dynamic. It is composed of local, reflex, and central components that feed into each other. The immune system, highly diverse and deeply embedded, constantly monitors the local environment. When detecting damage, it requires mobilization of the immune cells to target sites, facilitated by changes in behavior, metabolism, and local blood flow. These changes are orchestrated by cytokines and immune mediators required for communication between immune cells, but also with the sensory neurons embedded in these tissues. The nervous system can then alter the blood flow to the target site. For example, sympathetic fibers surrounding blood vessels can regulate vessel permeability, influencing immune cell extravasation.[23] Then, at the reflex level, areas in the brainstem can become sensitive to these cytokines, initiating corrective responses that can dial up or tune down the immune response.[7,49,101] However, this reflexive response may not be sufficient to support every need of the organism, including changes in metabolic programs and behaviors relevant to support them. For example, various inflammatory states must align with specific metabolic programs to trigger tissue-protective mechanisms.[102] Indeed, surviving viral inflammation relies on functioning glucose utilization pathways, while bacterial inflammation survival depends on alternative fuels and ketogenic processes, which require changes in feeding behavior.[103] Therefore, the immune system necessitates integration with the nervous system to coordinate the complex physiological and behavioral changes needed for the organism's survival. One intriguing example involves cachexia, which is evident in some forms of cancer. This severe wasting syndrome was shown to be mediated in part by the response to detection of circulating IL-6 by the AP. This leads to the activation of interconnected areas, including the NTS, PBN, PVN, CeA, BNST, and arcuate hypothalamic nucleus,[101] which collectively can induce the complex set of behavioral and metabolic changes evident in cachexia. Cachexia is functionally unclear

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because it is detrimental for survival, yet it may represent an adaptive process that goes awry of altering metabolic programs as a survival attempt.

These examples highlight that the interplay between the nervous system and the immune system occurs through multiple levels of interaction. Each level processes different inputs and integrates other available information, infusing the immune system with additional capabilities and improving the overall physiological response. These capabilities include continuous monitoring, predictive functions, and the integration of complex data—faculties that greatly extend the autonomous capacity of the immune system. However, it is also clear that we are just in the early stages of understanding these interactions. We are only beginning to uncover how the brain forms immune representations and which information is gathered by the brain to form these representations (cytokines, immune activity, changes in affected tissues, metabolic information, etc.). Nevertheless, such understanding will allow us to better grasp the brain's potential in modulating immune processes. Such understanding can lead to novel therapeutic strategies guided by the basic regulatory principles revealed by the nervous system.

CONCLUDING REMARKS

The nervous system pervades every organ and tissue in the body, providing an extraordinary capability for integrating information, eliciting rapid responses, and anticipating specific experiences. This intricate system enables the organism to operate cohesively. Despite our growing knowledge, we are still only at the threshold of understanding the complex mechanisms at play. Ongoing research promises to unveil new facets of physiology and may provide insights into conditions often regarded as psychosomatic. It is a common misconception to trivialize these conditions as being "all in your head," yet it is increasingly clear that the brain's activities resonate throughout the entire organism. What transpires within the neural confines has systemic repercussions, challenging us to broaden our perspective on health and disease.

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REFERENCES

1. Pavlov IP, and Thompson WH (1902). The Work of the Digestive Glands: Lectures by Professor J. P. Pawlow (Franklin Classics).
2. Maunder RG, and Levenstein S. (2008). The role of stress in the development and clinical course of inflammatory bowel disease: epidemiological evidence. Curr. Mol. Med. 8, 247–252. 10.2174/156652408784533832. [PubMed: 18537632]
3. Wright RJ (2011). Epidemiology of stress and asthma: from constricting communities and fragile families to epigenetics. Immunol. Allergy Clin. North Am. 31, 19–39. 10.1016/j.iac.2010.09.011. [PubMed: 21094921]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

4. Lagraauw HM, Kuiper J, and Bot I. (2015). Acute and chronic psychological stress as risk factors for cardiovascular disease: insights gained from epidemiological, clinical and experimental studies. Brain Behav. Immun. 50, 18–30. 10.1016/j.bbi.2015.08.007. [PubMed: 26256574]
5. Ilanges A, Shiao R, Shaked J, Luo JD, Yu X, and Friedman JM(2022). Brainstem ADCYAP1+ neurons control multiple aspects of sickness behaviour. Nature 609, 761–771. 10.1038/s41586-022-05161-7. [PubMed: 36071158]
6. Zhang C, Vincelette LK, Reimann F, and Liberles SD (2022). A brainstem circuit for nausea suppression. Cell Rep. 39, 110953. 10.1016/j.celrep.2022.110953.
7. Luan HH, Wang A, Hilliard BK, Carvalho F, Rosen CE, Ahasic AM, Herzog EL, Kang I, Pisani MA, Yu S, et al. (2019). GDF15 is an inflammation-induced central mediator of tissue tolerance. Cell 178, 1231–1244.e11. 10.1016/j.cell.2019.07.033. [PubMed: 31402172]
8. Strazielle N, and Ghersi-Egea JF (2000). Choroid plexus in the central nervous system: biology and physiopathology. J. Neuropathol. Exp. Neurol. 59, 561–574. 10.1093/jnen/59.7.561. [PubMed: 10901227]
9. Prescott SL, and Liberles SD (2022). Internal senses of the vagus nerve. Neuron 110, 579–599. 10.1016/j.neuron.2021.12.020. [PubMed: 35051375]
10. Kupari J, Häring M, Agirre E, Castelo-Branco G, and Ernfors P. (2019). An atlas of vagal sensory neurons and their molecular specialization. Cell Rep. 27, 2508–2523.e4. 10.1016/j.celrep.2019.04.096. [PubMed: 31116992]
11. Bai L, Mesgarzadeh S, Ramesh KS, Huey EL, Liu Y, Gray LA,Aitken TJ, Chen Y, Beutler LR, Ahn JS, et al. (2019). Genetic identification of vagal sensory neurons that control feeding. Cell 179, 1129–1143.e23. 10.1016/j.cell.2019.10.031. [PubMed: 31730854]
12. Prescott SL, Umans BD, Williams EK, Brust RD, and Liberles SD (2020). An airway protection program revealed by sweeping genetic control of vagal afferents. Cell 181, 574–589.e14. 10.1016/j.cell.2020.03.004. [PubMed: 32259485]
13. Ran C, Boettcher JC, Kaye JA, Gallori CE, and Liberles SD(2022). A brainstem map for visceral sensations. Nature 609, 320–326. 10.1038/s41586-022-05139-5. [PubMed: 36045291]
14. Cechetto DF, and Saper CB (1987). Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat. J. Comp. Neurol. 262, 27–45. 10.1002/cne.902620104. [PubMed: 2442207]
15. Wang K, Cai B, Song Y, Chen Y, and Zhang X. (2023). Somatosensory neuron types and their neural networks as revealed via single-cell transcriptomics. Trends Neurosci. 46, 654–666. 10.1016/j.tins.2023.05.005. [PubMed: 37268541]
16. Qi L, Iskols M, Shi D, Reddy P, Walker C, Lezgiyeva K, Voisin T, Pawlak M, Kuchroo VK, Chiu IM, et al. (2024). A mouse DRG genetic toolkit reveals morphological and physiological diversity of somatosensory neuron subtypes. Cell 187, 1508–1526.e16. 10.1016/j.cell.2024.02.006. [PubMed: 38442711]
17. Wolfson RL, Abdelaziz A, Rankin G, Kushner S, Qi L, Mazor O,Choi S, Sharma N, and Ginty DD (2023). DRG afferents that mediate physiologic and pathologic mechanosensation from the distal colon. Cell 186, 3368–3385.e18. 10.1016/j.cell.2023.07.007. [PubMed: 37541195]
18. Marshall KL, Saade D, Ghitani N, Coombs AM, Szczot M, Keller J, Ogata T, Daou I, Stowers LT, Bönnemann, C.G., et al. (2020). PIEZO2 in sensory neurons and urothelial cells coordinates urination. Nature 588, 290–295. 10.1038/s41586-020-2830-7. [PubMed: 33057202]
19. Mohanta SK, Yin C, Weber C, Godinho-Silva C, Veiga-Fernandes H, Xu QJ, Chang RB, and Habenicht AJR (2023). Cardiovascular brain circuits. Circ. Res. 132, 1546–1565. 10.1161/CIRCRESAHA.123.322791. [PubMed: 37228235]
20. Wu M, Song G, Li J, Song Z, Zhao B, Liang L, Li W, Hu H, Tu H, Li S, et al. (2024). Innervation of nociceptor neurons in the spleen promotes germinal center responses and humoral immunity. Cell 187, 2935–2951.e19. 10.1016/j.cell.2024.04.027. [PubMed: 38772371]
21. Zeng W-Z, Marshall KL, Min S, Daou I, Chapleau MW, Abboud FM, Liberles SD, and Patapoutian A. (2018). PIEZOs mediate neuronal sensing of blood pressure and the baroreceptor reflex. Science 362, 464–467. 10.1126/science.aau6324. [PubMed: 30361375]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

22. Udit S, Blake K, and Chiu IM (2022). Somatosensory and autonomicneuronal regulation of the immune response. Nat. Rev. Neurosci. 23, 157–171. 10.1038/s41583-021-00555-4. [PubMed: 34997214]

23. Schiller M, Azulay-Debby H, Boshnak N, Elyahu Y, Korin B, Ben-Shaanan TL, Koren T, Krot M, Hakim F, and Rolls A. (2021). Optogenetic activation of local colonic sympathetic innervations attenuates colitis by limiting immune cell extravasation. Immunity 54, 1022–1036.e8. 10.1016/j.immuni.2021.04.007. [PubMed: 33932356]

24. Tao J, Campbell JN, Tsai LT, Wu C, Liberles SD, and Lowell BB(2021). Highly selective brain-to-gut communication via genetically defined vagus neurons. Neuron 109, 2106–2115.e4. 10.1016/j.neuron.2021.05.004. [PubMed: 34077742]

25. Veerakumar A, Yung AR, Liu Y, and Krasnow MA (2022). Molecularly defined circuits for cardiovascular and cardiopulmonary control. Nature 606, 739–746. 10.1038/s41586-022-04760-8. [PubMed: 35650438]

26. Furlan A, La Manno G, Lübke M, Häring M, Abdo H, Hochgerner H, Kupari J, Usoskin D, Airaksinen MS, Oliver G, et al. (2016). Visceral motor neuron diversity delineates a cellular basis for nipple- and pilo-erection muscle control. Nat. Neurosci. 19, 1331–1340. 10.1038/nn.4376. [PubMed: 27571008]

27. Alkaslasi MR, Piccus ZE, Hareendran S, Silberberg H, Chen L,Zhang Y, Petros TJ, and Le Pichon CE (2021). Single nucleus RNA-sequencing defines unexpected diversity of cholinergic neuron types in the adult mouse spinal cord. Nat. Commun. 12, 2471. 10.1038/s41467-021-22691-2. [PubMed: 33931636]

28. Coverdell TC, Abraham-Fan R-J, Wu C, Abbott SBG, and Campbell JN (2022). Genetic encoding of an esophageal motor circuit. Cell Rep. 39, 110962. 10.1016/j.celrep.2022.110962.

29. Mapps AA, Thomsen MB, Boehm E, Zhao H, Hattar S, and Kuruvilla R. (2022). Diversity of satellite glia in sympathetic and sensory ganglia. Cell Rep. 38, 110328. 10.1016/j.celrep.2022.110328.

30. Blake KJ, Jiang XR, and Chiu IM (2019). Neuronal regulation of immunity in the skin and lungs. Trends Neurosci. 42, 537–551. 10.1016/j.tins.2019.05.005. [PubMed: 31213389]

31. Fromy B, Josset-Lamaugarny A, Aimond G, Pagnon-Minot A, Marics I, Tattersall GJ, Moqrich A, and Sigaudo-Roussel D. (2018). Disruption of TRPV3 impairs heat-evoked vasodilation and thermoregulation: A critical role of CGRP. J. Invest. Dermatol. 138, 688–696. 10.1016/j.jid.2017.10.006. [PubMed: 29054601]

32. Prado J, Westerink RHS, Popov-Celeketic J, Steen-Louws C, Pandit A, Versteeg S, van de Worp W, Kanters DHAJ, Reedquist KA, Koenderman L, et al. (2021). Cytokine receptor clustering in sensory neurons with an engineered cytokine fusion protein triggers unique pain resolution pathways. Proc. Natl. Acad. Sci. USA 118, e2009647118. 10.1073/pnas.2009647118.

33. Chiu IM, Heesters BA, Ghasemlou N, Von Hehn CA, Zhao F,Tran J, Wainger B, Strominger A, Muralidharan S, Horswill AR, et al. (2013). Bacteria activate sensory neurons that modulate pain and inflammation. Nature 501, 52–57. 10.1038/nature12479. [PubMed: 23965627]

34. Huang S, Ziegler CGK, Austin J, Mannoun N, Vukovic M, Ordovas-Montanes J, Shalek AK, and von Andrian UH (2021). Lymph nodes are innervated by a unique population of sensory neurons with immunomodulatory potential. Cell 184, 441–459.e25. 10.1016/j.cell.2020.11.028. [PubMed: 33333021]

35. Tamari M, Del Bel KL, Ver Heul AM, Zamidar L, Orimo K, Hoshi M, Trier AM, Yano H, Yang TL, Biggs CM, et al. (2024). Sensory neurons promote immune homeostasis in the lung. Cell 187, 44–61.e17. 10.1016/j.cell.2023.11.027. [PubMed: 38134932]

36. Talbot S, Abdulnour REE, Burkett PR, Lee S, Cronin SJF,Pascal MA, Laedermann C, Foster SL, Tran JV, Lai N, et al. (2015). Silencing nociceptor neurons reduces allergic airway inflammation. Neuron 87, 341–354. 10.1016/j.neuron.2015.06.007. [PubMed: 26119026]

37. Takahashi S, Ochiai S, Jin J, Takahashi N, Toshima S, Ishigame H, Kabashima K, Kubo M, Nakayama M, Shiroguchi K, et al. (2023). Sensory neuronal STAT3 is critical for IL-31 receptor expression and inflammatory itch. Cell Rep. 42, 113433. 10.1016/j.celrep.2023.113433.

38. Yang J-X, Wang H-F, Chen J-Z, Li H-Y, Hu J-C, Yu A-A, Wen J-J, Chen S-J, Lai W-D, Wang S, et al. (2022). Potential neuroimmune interaction in chronic pain: a review on immune

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

cells in peripheral and central sensitization. Front. Pain Res. (Lausanne) 3, 946846. 10.3389/fpain.2022.946846.

39. Pinho-Ribeiro FA, Verri WA, and Chiu IM (2017). Nociceptor sensory neuron–immune interactions in pain and inflammation. Trends Immunol. 38, 5–19. 10.1016/j.it.2016.10.001. [PubMed: 27793571]
40. Mai L, Liu Q, Huang F, He H, and Fan W. (2021). Involvement ofmast cells in the pathophysiology of pain. Front. Cell. Neurosci. 15, 665066. 10.3389/fncel.2021.665066.
41. Baral P, Umans BD, Li L, Wallrapp A, Bist M, Kirschbaum T, Wei Y, Zhou Y, Kuchroo VK, Burkett PR, et al. (2018). Nociceptor sensory neurons suppress neutrophil and gd T cell responses in bacterial lung infections and lethal pneumonia. Nat. Med. 24, 417–426. 10.1038/nm.4501. [PubMed: 29505031]
42. Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, Chen S, Trier AM, Xu AZ, Tripathi SV, et al. (2017). Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. Cell 171, 217–228.e13. 10.1016/j.cell.2017.08.006. [PubMed: 28890086]
43. Kodji X, Arkless KL, Kee Z, Cleary SJ, Aubdool AA, Evans E,Caton P, Pitchford SC, and Brain SD (2019). Sensory nerves mediate spontaneous behaviors in addition to inflammation in a murine model of psoriasis. FASEB J. 33, 1578–1594. 10.1096/fj.201800395RR. [PubMed: 30204499]
44. Imhof S, Kokotovic T, and Nagy V. (2020). PRDM12: new opportunity in pain research. Trends Mol. Med. 26, 895–897. 10.1016/j.molmed.2020.07.007. [PubMed: 32828702]
45. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, Wang H, Abumrad N, Eaton JW, and Tracey KJ (2000). Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 405, 458–462. 10.1038/35013070. [PubMed: 10839541]
46. Liu S, Wang Z, Su Y, Qi L, Yang W, Fu M, Jing X, Wang Y, andMa Q. (2021). A neuroanatomical basis for electroacupuncture to drive the vagal–adrenal axis. Nature 598, 641–645. 10.1038/s41586-021-04001-4. [PubMed: 34646018]
47. Petzschner FH, Garfinkel SN, Paulus MP, Koch C, and Khalsa SS (2021). Computational models of interoception and body regulation. Trends Neurosci. 44, 63–76. 10.1016/j.tins.2020.09.012. [PubMed: 33378658]
48. Kelly MJ, Breathnach C, Tracey KJ, and Donnelly SC (2022). Manipulation of the inflammatory reflex as a therapeutic strategy. Cell Rep. Med. 3, 100696. 10.1016/j.xcrm.2022.100696.
49. Jin H, Li M, Jeong E, Castro-Martinez F, and Zuker CS (2024). Abody–brain circuit that regulates body inflammatory responses. Nature 630, 695–703. 10.1038/s41586-024-07469-y. [PubMed: 38692285]
50. Zhang C, Kaye JA, Cai Z, Wang Y, Prescott SL, and Liberles SD(2021). Area postrema cell types that mediate nausea-associated behaviors. Neuron 109, 461–472.e5. 10.1016/j.neuron.2020.11.010. [PubMed: 33278342]
51. Lim H-D, Kim M-H, Lee C-Y, and Namgung U. (2016). Anti-inflammatory effects of acupuncture stimulation via the vagus nerve. PLoS One 11, e0151882. 10.1371/journal.pone.0151882.
52. Ghia JE, Blennerhassett P, Kumar-Ondiveeran H, Verdu EF, andCollins SM (2006). The vagus nerve: A tonic inhibitory influence associated with inflammatory bowel disease in a murine model. Gastroenterology 131, 1122–1130. 10.1053/j.gastro.2006.08.016. [PubMed: 17030182]
53. Matteoli G, Gomez-Pinilla PJ, Nemethova A, Di Giovangiulio M,Cailotto C, van Bree SH, Michel K, Tracey KJ, Schemann M, Boesmans W, et al. (2014). A distinct vagal anti-inflammatory pathway modulates intestinal muscularis resident macrophages independent of the spleen. Gut 63, 938–948. 10.1136/gutjnl-2013-304676. [PubMed: 23929694]
54. Paulus MP, Feinstein JS, and Khalsa SS (2019). An active inferenceapproach to interoceptive psychopathology. Annu. Rev. Clin. Psychol. 15, 97–122. 10.1146/annurev-clinpsy-050718-095617. [PubMed: 31067416]
55. Berntson GG, and Khalsa SS (2021). Neural circuits of interoception. Trends Neurosci. 44, 17–28. 10.1016/j.tins.2020.09.011. [PubMed: 33378653]
56. Hulme OJ, Morville T, and Gutkin B. (2019). Neurocomputational theories of homeostatic control. Phys. Life Rev. 31, 214–232. 10.1016/j.plrev.2019.07.005. [PubMed: 31395433]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

57. Owens AP, Allen M, Ondobaka S, and Friston KJ (2018). Interoceptive inference: from computational neuroscience to clinic. Neurosci. Biobehav. Rev. 90, 174–183. 10.1016/j.neubiorev.2018.04.017. [PubMed: 29694845]
58. Pezzulo G, Rigoli F, and Friston K. (2015). Active Inference, homeostatic regulation and adaptive behavioural control. Prog. Neurobiol. 134, 17–35. 10.1016/j.pneurobio.2015.09.001. [PubMed: 26365173]
59. Barrett LF, and Simmons WK (2015). Interoceptive predictions in thebrain. Nat. Rev. Neurosci. 16, 419–429. 10.1038/nrn3950. [PubMed: 26016744]
60. Seth AK, and Friston KJ (2016). Active interoceptive inference and the emotional brain. Philos. Trans. R. Soc. Lond. B Biol. Sci. 371, 20160007. 10.1098/rstb.2016.0007.
61. Parr T, Pezzulo G, and Friston K. (2022). Active Inference: the Free Energy Principle in Mind (MIT Press) 10.7551/mitpress/12441.001.0001.
62. Keller GB, and Mrsic-Flogel TD (2018). Predictive processing: A canonical cortical computation. Neuron 100, 424–435. 10.1016/j.neuron.2018.10.003. [PubMed: 30359606]
63. O'Toole SM, Oyibo HK, and Keller GB (2023). Molecularly targetable cell types in mouse visual cortex have distinguishable prediction error responses. Neuron 111, 2918–2928.e8. 10.1016/j.neuron.2023.08.015. [PubMed: 37708892]
64. Saper CB (2002). The central autonomic nervous system: consciousvisceral perception and autonomic pattern generation. Annu. Rev. Neurosci. 25, 433–469. 10.1146/annurev.neuro.25.032502.111311. [PubMed: 12052916]
65. Levinthal DJ, and Strick PL (2020). Multiple areas of the cerebral cortex influence the stomach. Proc. Natl. Acad. Sci. USA 117, 13078–13083. 10.1073/pnas.2002737117. [PubMed: 32434910]
66. Dum RP, Levinthal DJ, and Strick PL (2019). The mind–body problem: circuits that link the cerebral cortex to the adrenal medulla. Proc. Natl. Acad. Sci. USA 116, 26321–26328. 10.1073/pnas.1902297116. [PubMed: 31871146]
67. Deng H, Xiao X, Yang T, Ritola K, Hantman A, Li Y, Huang ZJ,and Li B. (2021). A genetically defined insula-brainstem circuit selectively controls motivational vigor. Cell 184, 6344–6360.e18. 10.1016/j.cell.2021.11.019. [PubMed: 34890577]
68. Pauli JL, Chen JY, Basiri ML, Park S, Carter ME, Sanz E,McKnight GS, Stuber GD, and Palmiter RD (2022). Molecular and anatomical characterization of parabrachial neurons and their axonal projections. eLife 11, e81868. 10.7554/eLife.81868.
69. Gasparini S, Howland JM, Thatcher AJ, and Geerling JC (2020). Central afferents to the nucleus of the solitary tract in rats and mice. J. Comp. Neurol. 528, 2708–2728. 10.1002/cne.24927. [PubMed: 32307700]
70. Palmiter RD (2018). The parabrachial nucleus: CGRP neurons functionas a General Alarm. Trends Neurosci. 41, 280–293. 10.1016/j.tins.2018.03.007. [PubMed: 29703377]
71. Jagot F, Gaston-Breton R, Choi AJ, Pascal M, Bourhy L, Dorado-Doncel R, Conzelmann KK, Lledo PM, Lepousez G, and Eberl G. (2023). The parabrachial nucleus elicits a vigorous corticosterone feedback response to the pro-inflammatory cytokine IL-1β. Neuron 111, 2367–2382.e6. 10.1016/j.neuron.2023.05.009. [PubMed: 37279750]
72. Zhao W, Zhang K, Dong WY, Tang HD, Sun JQ, Huang JY,Wan GL, Guan RR, Guo XT, Cheng PK, et al. (2024). A pharynx-to-brain axis controls pharyngeal inflammation–induced anxiety. Proc. Natl. Acad. Sci. USA 121, e2312136121. 10.1073/pnas.2312136121.
73. Phua SC, Tan YL, Kok AMY, Senol E, Chiam CJH, Lee CY,Peng Y, Lim ATJ, Mohammad H, Lim JX, et al. (2021). A distinct parabrachial–to–lateral hypothalamus circuit for motivational suppression of feeding by nociception. Sci. Adv. 7, eabe4323. 10.1126/sciadv.abe4323.
74. Gizowski C, and Bourque CW (2018). The neural basis of homeostaticand anticipatory thirst. Nat. Rev. Nephrol. 14, 11–25. 10.1038/nrneph.2017.149. [PubMed: 29129925]
75. Livneh Y, Sugden AU, Madara JC, Essner RA, Flores VI, Sugden LA, Resch JM, Lowell BB, and Andermann ML (2020). Estimation of current and future physiological states in insular cortex. Neuron 105, 1094–1111.e10. 10.1016/j.neuron.2019.12.027. [PubMed: 31955944]
76. Saker P, Farrell MJ, Adib FRM, Egan GF, McKinley MJ, andDenton DA (2014). Regional brain responses associated with drinking water during thirst and after its satiation. Proc. Natl. Acad. Sci. USA 111, 5379–5384. 10.1073/pnas.1403382111. [PubMed: 24706817]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

77. Becker CA, Flaisch T, Renner B, and Schupp HT (2017). From thirstto satiety: the anterior mid-cingulate cortex and right posterior insula indicate dynamic changes in incentive value. Front. Hum. Neurosci. 11, 234. 10.3389/fnhum.2017.00234. [PubMed: 28553214]

78. Yasui Y, Breder CD, Saper CB, and Cechetto DF (1991). Autonomic responses and efferent pathways from the insular cortex in the rat. J. Comp. Neurol. 303, 355–374. 10.1002/cne.903030303. [PubMed: 2007654]

79. Gehrlach DA, Dolensek N, Klein AS, Roy Chowdhury R, Matthys A, Junghänel M, Gaitanos TN, Podgornik A, Black TD, Reddy Vaka N, et al. (2019). Aversive state processing in the posterior insular cortex. Nat. Neurosci. 22, 1424–1437. 10.1038/s41593-019-0469-1. [PubMed: 31455886]

80. Lovero KL, Simmons AN, Aron JL, and Paulus MP (2009). Anteriorinsula cortex anticipates impending stimulus significance. Neuroimage 45, 976–983. 10.1016/j.neuroimage.2008.12.070. [PubMed: 19280711]

81. Geuter S, Boll S, Eippert F, and Büchel, C. (2017). Functional dissociation of stimulus intensity encoding and predictive coding of pain in the insula. eLife 6, e24770. 10.7554/eLife.24770.

82. Harrison OK, Köchli L, Marino S, Luechinger R, Hennel F, Brand K, Hess AJ, Frässle S, Iglesias S, Vinckier F, et al. (2021). Interoception of breathing and its relationship with anxiety. Neuron 109, 4080–4093.e8. 10.1016/j.neuron.2021.09.045. [PubMed: 34672986]

83. Kusumoto-Yoshida I, Liu H, Chen BT, Fontanini A, and Bonci A(2015). Central role for the insular cortex in mediating conditioned responses to anticipatory cues. Proc. Natl. Acad. Sci. USA 112, 1190–1195. 10.1073/pnas.1416573112. [PubMed: 25583486]

84. Klein AS, Dolensek N, Weiand C, and Gogolla N. (2021). Fear balance is maintained by bodily feedback to the insular cortex in mice. Science 374, 1010–1015. 10.1126/science.abj8817. [PubMed: 34793231]

85. Livneh Y, Ramesh RN, Burgess CR, Levandowski KM, Madara JC, Fenselau H, Goldey GJ, Diaz VE, Jikomes N, Resch JM, et al. (2017). Homeostatic circuits selectively gate food cue responses in insular cortex. Nature 546, 611–616. 10.1038/nature22375. [PubMed: 28614299]

86. Scheiermann C, Kunisaki Y, Lucas D, Chow A, Jang JE, Zhang D,Hashimoto D, Merad M, and Frenette PS (2012). Adrenergic nerves govern circadian leukocyte recruitment to tissues. Immunity 37, 290–301. 10.1016/j.immuni.2012.05.021. [PubMed: 22863835]

87. Aungle P, and Langer E. (2023). Physical healing as a function of perceived time. Sci. Rep. 13, 22432. 10.1038/s41598-023-50009-3. [PubMed: 38104155]

88. Park C, Pagnini F, Reece A, Phillips D, and Langer E. (2016). Blood sugar level follows perceived time rather than actual time in people with type 2 diabetes. Proc. Natl. Acad. Sci. USA 113, 8168–8170. 10.1073/pnas.1603444113. [PubMed: 27382161]

89. Tahara Y, Kuroda H, Saito K, Nakajima Y, Kubo Y, Ohnishi N, Seo Y, Otsuka M, Fuse Y, Ohura Y, et al. (2012). *In vivo* monitoring of peripheral circadian clocks in the mouse. Curr. Biol. 22, 1029–1034. 10.1016/j.cub.2012.04.009. [PubMed: 22578421]

90. Kayama T, Ikegaya Y, and Sasaki T. (2022). Phasic firing of dopaminergic neurons in the ventral tegmental area triggers peripheral immune responses. Sci. Rep. 12, 1447. 10.1038/s41598-022-05306-8. [PubMed: 35087155]

91. Ben-Shaanan TL, Azulay-Debby H, Dubovik T, Starosvetsky E, Korin B, Schiller M, Green NL, Admon Y, Hakim F, Shen-Orr SS, et al. (2016). Activation of the reward system boosts innate and adaptive immunity. Nat. Med. 22, 940–944. 10.1038/nm.4133. [PubMed: 27376577]

92. Ben-Shaanan TL, Schiller M, Azulay-Debby H, Korin B, Boshnak N, Koren T, Krot M, Shakya J, Rahat MA, Hakim F, et al. (2018). Modulation of anti-tumor immunity by the brain's reward system. Nat. Commun. 9, 2723. 10.1038/s41467-018-05283-5. [PubMed: 30006573]

93. Ader R, and Cohen N. (1975). Behaviorally conditioned immunosuppression. Psychosom. Med. 37, 333–340. 10.1097/00006842-197507000-00007. [PubMed: 1162023]

94. Giustino TF, and Maren S. (2015). The role of the medial prefrontal cortex in the conditioning and extinction of fear. Front. Behav. Neurosci. 9, 298. 10.3389/fnbeh.2015.00298. [PubMed: 26617500]

95. Koren T, Yifa R, Amer M, Krot M, Boshnak N, Ben-Shaanan TL, Azulay-Debby H, Zalayat I, Avishai E, Hajjo H, et al. (2021). Insular cortex neurons encode and retrieve specific immune responses. Cell 184, 5902–5915.e17. [PubMed: 34752731]

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96. Plum T, Binzberger R, Thiele R, Shang F, Postrach D, Fung C,Fortea M, Stakenborg N, Wang Z, Tappe-Theodor A, et al. (2023). Mast cells link immune sensing to antigen-avoidance behaviour. Nature 620, 634–642. 10.1038/s41586-023-06188-0. [PubMed: 37438525]

97. Florsheim EB, Bachtel ND, Cullen JL, Lima BGC, Godazgar M, Carvalho F, Chatain CP, Zimmer MR, Zhang C, Gautier G, et al. (2023). Immune sensing of food allergens promotes avoidance behaviour. Nature 620, 643–650. 10.1038/s41586-023-06362-4. [PubMed: 37437602]

98. Puk O, Jabłońska M, and Sokal P. (2023). Immunomodulatory and endocrine effects of deep brain stimulation and spinal cord stimulation – A systematic review. Biomed. Pharmacother. 168, 115732. 10.1016/j.biopha.2023.115732.

99. Poller WC, Downey J, Mooslechner AA, Khan N, Li L, Chan CT,McAlpine CS, Xu C, Kahles F, He S, et al. (2022). Brain motor and fear circuits regulate leukocytes during acute stress. Nature 607, 578–584. 10.1038/s41586-022-04890-z. [PubMed: 35636458]

100. Zhang X, Lei B, Yuan Y, Zhang L, Hu L, Jin S, Kang B, Liao X,Sun W, Xu F, et al. (2020). Brain control of humoral immune responses amenable to behavioural modulation. Nature 581, 204–208. 10.1038/s41586-020-2235-7. [PubMed: 32405000]

101. Sun Q, van de Lisdonk D, Ferrer M, Gegenhuber B, Wu M, Park Y,Tuveson DA, Tollkuhn J, Janowitz T, and Li B. (2024). Area postrema neurons mediate interleukin-6 function in cancer cachexia. Nat. Commun. 15, 4682. 10.1038/s41467-024-48971-1. [PubMed: 38824130]

102. Ganeshan K, and Chawla A. (2014). Metabolic regulation of immune responses. Annu. Rev. Immunol. 32, 609–634. 10.1146/annurev-immunol-032713-120236. [PubMed: 24655299]

103. Wang A, Huen SC, Luan HH, Baker K, Rinder H, Booth CJ, andMedzhitov R. (2018). Glucose metabolism mediates disease tolerance in cerebral malaria. Proc. Natl. Acad. Sci. USA. 115, 11042–11047. 10.1073/pnas.1806376115. [PubMed: 30291189]

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Box 1.

Circumventricular organs: Detecting hormones and cytokines in the brain

The brain is nearly impenetrable, guarded closely by the restrictive blood-brain barrier. Bloodborne cells and large macromolecules are intentionally excluded from the brain to safeguard it from infection and damage. Yet, there is valuable information in the blood stream in the form of hormones and cytokines that can provide insights into the internal physiological status. The brain has specialized structures called CVOs with fenestrated capillaries and a reduced blood-brain barrier, where the presence of bloodborne chemicals can be detected. The area postrema is one CVO that acts as a hotspot for neuroimmune interactions. Cytokines like growth differentiation factor 15 (GDF15) trigger area postrema (AP) responses, leading to sickness and nausea as well as autonomic and immunological changes. Cytokines can affect brain activity by directly interacting with neurons, glia, and/or ependymal cells. Another example is the adipocyte hormone leptin that can access neurons in the hypothalamus to control feeding behavior. Single-cell sequencing has revealed a diversity of sensory neurons across CVOs, and additional studies are needed to understand the biology of many of these brain-resident sensory neurons and their roles in body-brain communication.[5–7] The secretory CVOs are release sites for neurohormones that control body physiology and include the subcommissural organ (SCO), pituitary gland, median eminence, and pineal gland. The choroid plexus produces cerebrospinal fluid (CSF) but, notably, lacks neurons. It is crucial for neurohumoral modulation by regulating the exchange of molecules between the blood and CSF, secreting CSF, and transporting hormones, cytokines, and nutrients. It also serves as an immunological interface, producing signaling molecules that modulate immune responses within the central nervous system.[8]

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Box 2.

Theoretical frameworks for interoception and bodily regulation

Interoception stands as a key process through which the brain integrates and interprets signals from within the body to maintain homeostasis and promote adaptive changes in physiology. Two prominent theoretical frameworks that describe how the brain balances reactive and proactive bodily control are “homeostatic reinforcement learning” (HRL)[56] and “interoceptive active inference” (IAI).[57–60] Under certain assumptions, these frameworks converge in many aspects.[47,56,61] Both emphasize the brain’s predictive capabilities in actively controlling bodily processes to shift the current observed internal state toward a desired, predicted state. Central to these models is the concept that internal states optimal for survival in various contexts are re-experienced, becoming likely, predicted, and functioning as homeostatic (predefined) or adaptive set points.

HRL proposes that organisms aim to align their current physiological state with a desired set point, reducing homeostatic imbalances to maximize expected rewards in the long term. Behaviors that move the physiological state closer to this set point are reinforced. IAI suggests that the brain operates based on an internal model of the organism within the environment. It contextually infers the body’s internal state and generates predictions, which are then compared with actual sensory input, and errors are signaled when they do not match. A central function of the brain is minimizing these prediction errors, either by revising the internal model or by recruiting regulatory actions to reduce discrepancies. IAI assumes a hierarchical architecture where models exist at each level and predictions are transmitted via top-down connections, while prediction errors are relayed through bottom-up signals. In IAI, predictions at increasingly higher levels in the neural hierarchy guide increasingly complex responses.[47] Lower-level predictions address immediate reflexive needs by acting as set points, while higher-level predictions integrate interoceptive signals with more complex inputs, managing longer-term, goal-directed regulation and adapting set points accordingly.[60] This framework ensures stable internal models and efficient regulation across different timescales.[57,58,60]

The embodied predictive interoception coding (EPIC) model[59] proposes how IAI might be implemented in the brain of humans and primates. According to the model, visceromotor, agranular cortices at the apex of the interoceptive hierarchy, such as the aIC and ACC, generate higher-order interoceptive predictions, including both visceromotor and viscerosensory predictions. The viscerosensory predictions are then transmitted to the granular insular cortices, which serve as the primary interoceptive processing cortical centers. Here, prediction errors are calculated, and feedback is sent up the hierarchy to refine these predictions. Visceromotor predictions are conveyed to subcortical regions, including the amygdala, hypothalamus, VS, PAG, and other brainstem areas involved in homeostatic control. This communication helps to activate adaptive physiological responses aimed at aligning the internal state with the predicted state. Both prediction mechanisms work to minimize prediction errors, while active regulation is thought to play the main role in this process.

While some anatomical and functional studies support these theories,[62,63] there is still a lack of clear biological evidence for the implementation in the brain of the processes and architecture assumed by the theories. Further research is needed to better understand the brain mechanisms involved in adaptive control.

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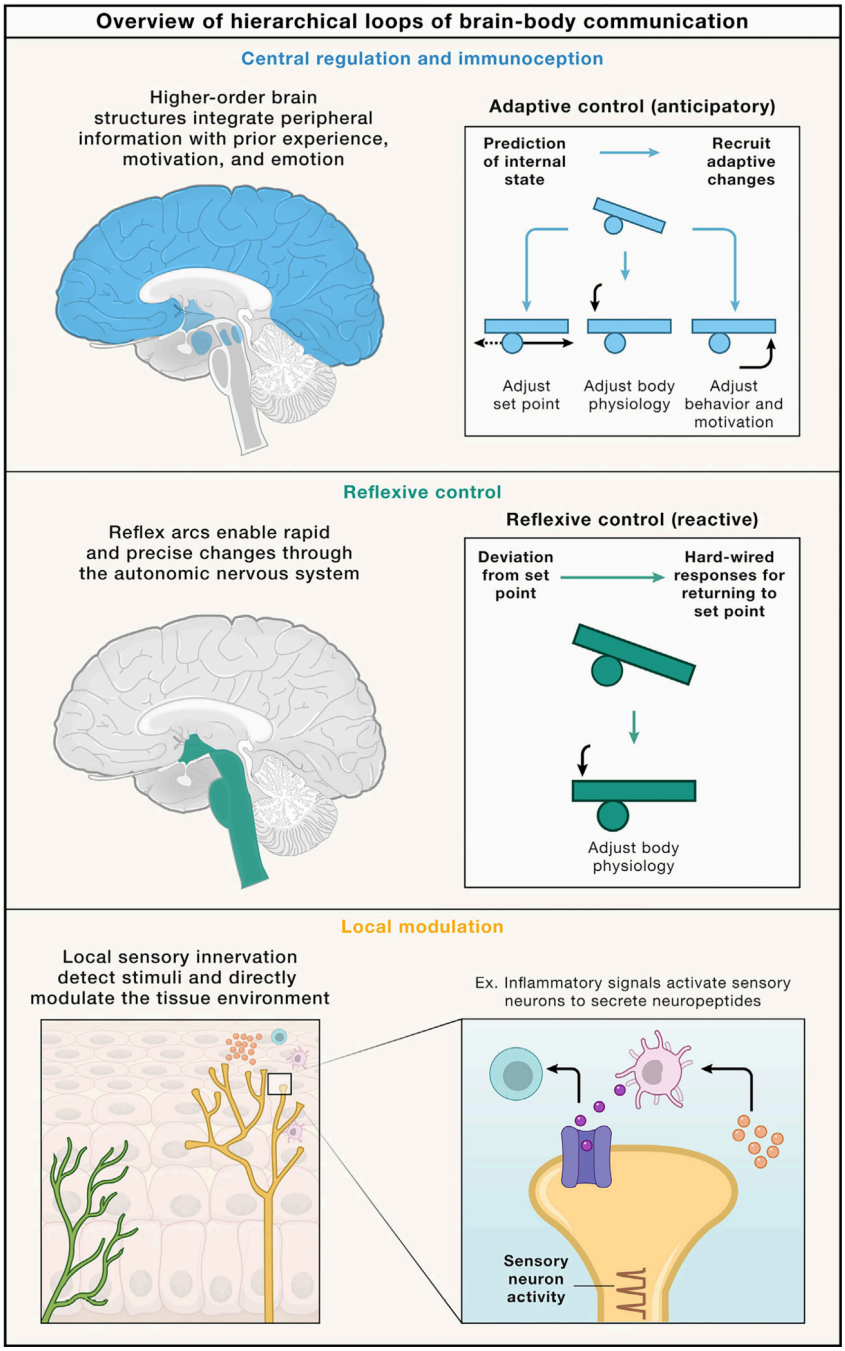

Figure 1. Overview of hierarchical loops of brain-body communication

The nervous system communicates with every physiological system in the body through multiple interconnected levels. These levels form control loops, with higher levels regulating lower ones to achieve adaptive bodily control. Top: central, adaptive regulation, and immunoception involve higher-order brain structures integrating interoceptive information with external sensory data, past experiences, motivational drives, and emotions to form a complex representation. This integration allows adaptive modulation of the internal physiological state, including of the immune system, across different contexts and

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timescales, enabling prospective and goal-directed regulation of physiology. This regulation includes adjusting the homeostatic set points and modulating body phyisiology directly and indirectly through adjustments in motivation and behavior. Adaptive control is guided by cortical regions (darker blue) such as the aIC, ACC, vmPFC, and OFC, while subcortical regions (lighter blue) like the CeA, BNST, hypothalamus, VS, PAG, and PBN implement the integrated adjustments in physiology, motivation, and behavior. Middle: reflexive control is a quick, reactive system that integrates at subcortical sites (green), such as the hypothalamus or the NTS and AP in the brainstem. Here, current bodily state information is compared to predefined homeostatic set points, and if a deviation is sensed, hard-wired responses regulate physiology to return to its set point, such as during inflammation. The autonomic nerves, including the sympathetic and parasympathetic branches, carry instructions from the brain and exert differential effects on inflammation. Bottom: local modulation occurs in a bidirectional manner between sensory neurons innervating peripheral sites and local cells, including immune cells. These interactions influence inflammation by modulating cytokine or neuropeptide secretion (right side). aIC, anterior insular cortex; ACC, anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; OFC, orbitofrontal cortex; CeA, central nucleus of the amygdala; BNST, bed nucleus of the stria terminalis; VS, ventral striatum; PAG, periaqueductal gray; PBN, parabrachial nucleus; NTS, nucleus of the solitary tract; AP, area postrema.

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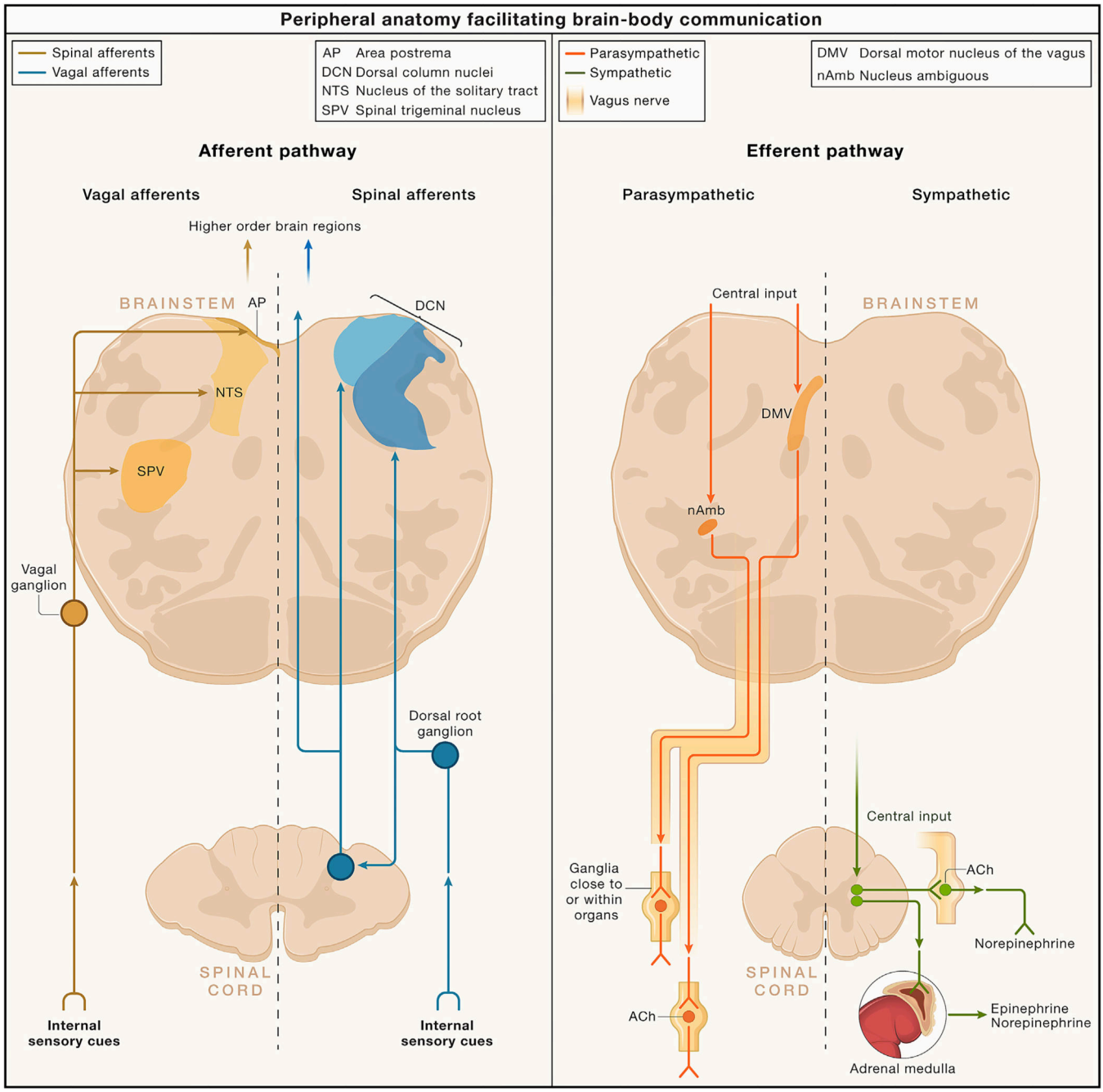

Figure 2. Peripheral anatomy facilitating brain-body communication

Left: Internal sensory information reaches the brain through major humoral and neuronal pathways (afferent pathways).

Right:The autonomic nervous system is broadly divided into two main programs: the sympathetic and parasympathetic systems (efferent pathways).

All these pathways are present bilaterally in the body and are illustrated according to human anatomy. Left panel illustrates the afferent pathways, composed of vagal (left) and spinal (right) afferents. Vagal afferents are pseudounipolar sensory neurons in the nodose or jugular ganglia (vagal ganglion in figure). These sensory neurons send a peripheral branch to

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innervate organs and a central branch to the brainstem. Nodose neurons synapse in the NTS and sometimes in the AP, while jugular neurons synapse in the SPV. This internal sensory information is then transmitted from these brainstem sites to higher-order neurons. Spinal afferents are pseudounipolar neurons in the dorsal root ganglia (DRGs). DRG neurons extend a peripheral branch to innervate organs and a central branch to the dorsal horn of the spinal cord, and occasionally to the DCN in the brainstem. This sensory information is subsequently relayed to higher-order neurons. Right panel illustrates the efferent pathways—parasympathetic and sympathetic nervous systems. Descending neuronal signals reach areas in the brainstem such as the DMV and the nAmb, where parasympathetic preganglionic neurons reside. These neurons send projections to the periphery through the motor arm of the vagus nerve. Parasympathetic preganglionic neurons synapse with postganglionic neurons located in ganglia close to or within target organs. The preganglionic neurons release ACh to communicate with postganglionic neurons, which in turn secrete acetylcholine or other molecules to regulate the function of target organs. Central output reaches sympathetic preganglionic neurons in the spinal cord. These preganglionic neurons send short axons to synapse on postganglionic neurons in the paravertebral or prevertebral sympathetic ganglia. A population of sympathetic preganglionic neurons project directly to the adrenal medulla. Communication between preganglionic and postganglionic neurons is mediated by acetylcholine. The postganglionic neurons extend axons to target organs and primarily release norepinephrine to modulate physiological functions. Adrenal chromaffin cells within the adrenal medulla secrete catecholamines such as epinephrine and norepinephrine into the circulation. NTS, nucleus of the solitary tract; AP, area postrema; SPV, spinal trigeminal nucleus; DCN, dorsal column nuclei; DMV, dorsal motor nucleus of the vagus; nAmb, nucleus ambiguus; ACh, acetylcholine.

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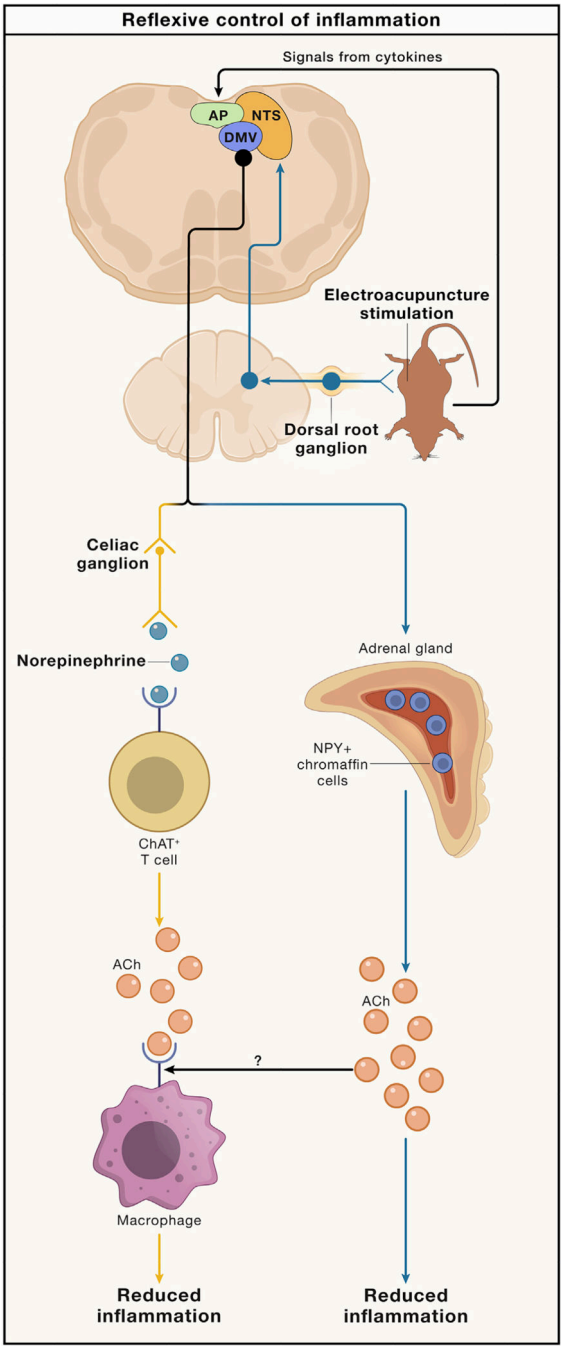

Figure 3. Reflexive control of inflammation

Reflex circuits play a critical role in maintaining homeostasis. During inflammation, these circuits can be engaged by peripheral signals such as cytokines. Brainstem areas including the NTS, AP, and DMV are activated by these signals to reduce inflammation or mediate behaviors. (The anti-inflammatory reflex, which ultimately reduces inflammation, consists of splenic projecting postganglionic neurons from the DMV that secrete NE, which acts on B2AR on T cells. These T cells then secrete ACh, which helps to reduce inflammation.[45] Similar circuits can be deliberately engaged to reduce inflammation by electrostimulation.

For example, stimulating the acupuncture point ST36 activates the DMV, which projects to the adrenal gland.[46] Here, neuropeptide Y (NPY)+ chromaffin cells secrete ACh, reducing inflammation. CG, celiac ganglion; NE, norepinephrine; B2AR, β2-adrenergic receptors.

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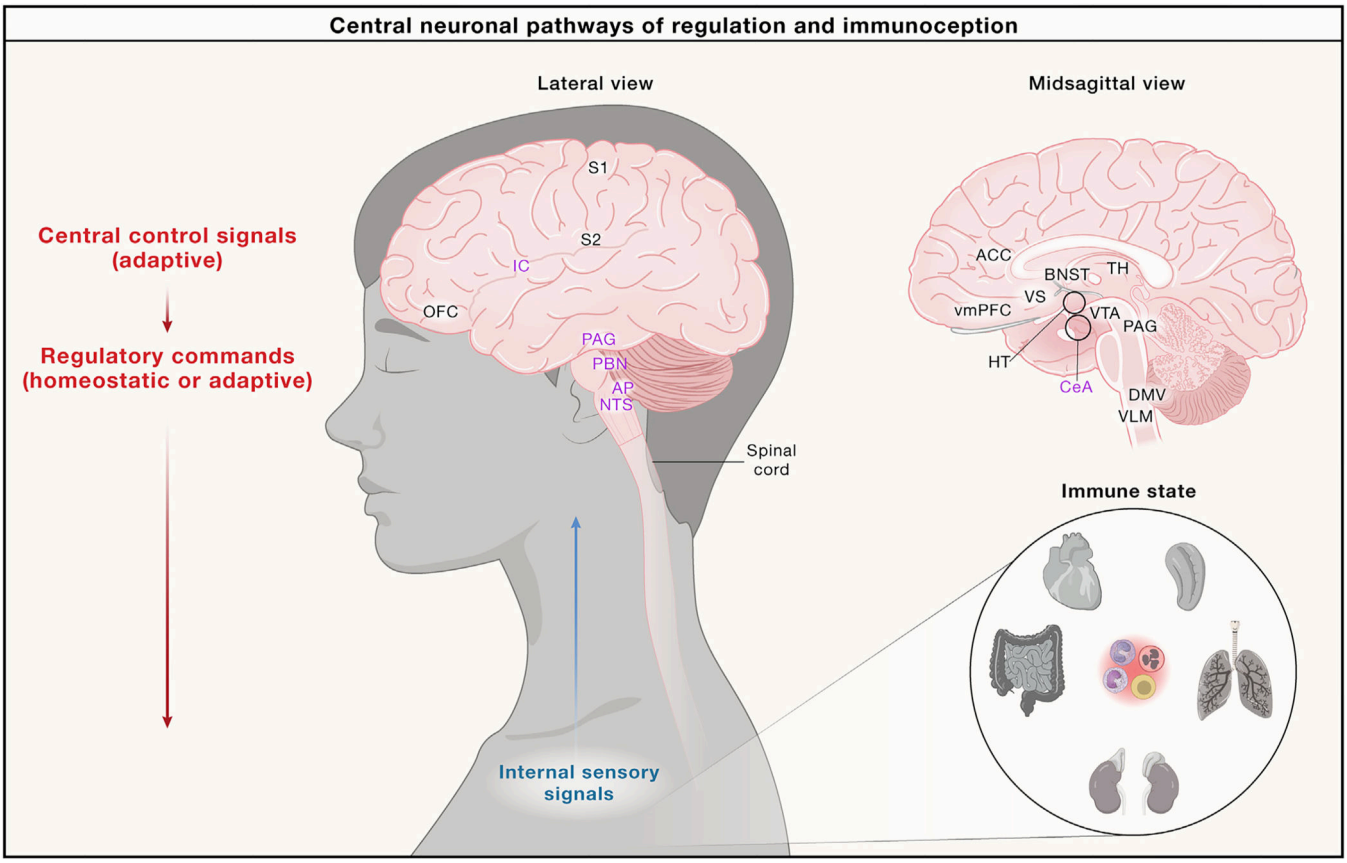

Figure 4. Central networks of bodily physiology and immunoception

Information from the periphery, including immune signals, is relayed to the brain through vagal and spinal afferents. These pathways converge in the NTS and PBN, ascend via the thalamus (e.g., ventromedial and ventroposterior lateral nuclei), and reach cortical areas such as the posterior IC, ACC, S1, and S2.[55] Humoral information detected by CVOs (e.g., IL-6) is also transmitted through neural pathways to higher brain regions. Visceromotor cortices, including the aIC, ACC, vmPFC, and OFC, mediate the contextual and adaptive regulation of physiology, initiating coordinated responses across physiological systems and behavior. These responses are recruited by interconnected subcortical structures, with the hypothalamus (e.g., PVN and LHA) playing a crucial role in sensing physiological needs and mediating homeostatic control by engaging autonomic, neuroendocrine, immune, and motivated behavioral responses as needed. The CeA and BNST are involved in processing emotions and stress and in recruiting the physiological responses associated with their expression. Additional regions contributing to adaptive physiological changes include the VS and VTA, which process reward and motivation, the PAG, which coordinates integrated behavioral-autonomic responses, and autonomic nuclei such as the DMV and VLM. Central bodily regulation among these and other brain regions involves numerous feedforward and feedback modulatory connections across different levels of the neural hierarchy to process and control the internal physiological state. Abbreviations in violet correspond to brain regions located deeper in the brain with respect to the views provided in the illustration. NTS, nucleus of the solitary tract; AP, area postrema; PBN, parabrachial nucleus;

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PAG, periaqueductal gray; TH, thalamus; IC, insular cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; OFC, orbitofrontal cortex; VLM, ventrolateral medulla; DMV, dorsal motor nucleus of the vagus; CeA, central nucleus of the amygdala; VTA, ventral tegmental area; HT, hypothalamus; PVN, paraventricular nucleus of the hypothalamus; LHA, lateral hypothalamic area; BNST, bed nucleus of the stria terminalis; VS, ventral striatum; ACC, anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex.