Neuronal regulation of immunity: why, how and where?

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Abstract | Neuroimmunology is one of the fastest-growing fields in the life sciences, and for good reason; it fills the gap between two principal systems of the organism, the nervous system and the immune system. Although both systems affect each other through bidirectional interactions, we focus here on one direction — the effects of the nervous system on immunity. First, we ask why is it beneficial to allow the nervous system any control over immunity? We evaluate the potential benefits to the immune system that arise by taking advantage of some of the brain's unique features, such as its capacity to integrate and synchronize physiological functions, its predictive capacity and its speed of response. Second, we explore how the brain communicates with the peripheral immune system, with a focus on the endocrine, sympathetic, parasympathetic, sensory and meningeal lymphatic systems. Finally, we examine where in the brain this immune information is processed and regulated. We chart a partial map of brain regions that may be relevant for brain–immune system communication, our goal being to introduce a conceptual framework for formulating new hypotheses to study these interactions.

The nervous system and the immune system are both crucial for the organism's survival. Traditionally, these systems were thought to act independently, and the interactions between them were associated mainly with the emergence of brain disease, most notably multiple sclerosis, in which the immune system attacks the brain tissue[1,2]. However, increasing scientific evidence[3] and even our own life experiences argue for an active and beneficial dialogue between these two systems. One of the classic examples of such neuro-immune communication is the phenomenon known as sickness behaviour. Sickness behaviour can be triggered by a peripheral disease in the absence of direct central nervous system (CNS) disease[4–6]. Cytokines induced by peripheral inflammation affect complex activities controlled by the brain, such as sleep[7,8] and hunger[9,10]. These behavioural changes are crucial for survival, enabling the optimal allocation of physiological resources required for the recovery process. However, the collaboration between these two systems goes beyond just sickness behaviour and is not limited to pathological conditions. It is now clear that CNS resident and infiltrating immune cells routinely patrol the brain's immune compartment (both the parenchyma and tissues encompassing the brain's border) and play a central role in CNS function (BOX 1). For example, immune cells and cytokines were shown to affect cognitive processes such as learning and memory[11], social behaviour[12,13] and psychiatric (for example, depression[14,15]) and neurodegenerative (such as schizophrenia[16] and Alzheimer disease[17]) diseases. In recent years, this ability of the immune system to impact the CNS has become one of the most extensively studied aspects of neuroimmunology, in part because it has an enormous therapeutic potential for treating brain disorders through immune modulation. Nevertheless, here we will focus on the reverse interaction, namely how the brain and nervous system affect immunity, specifically peripheral immunity.

While our knowledge of how immunity affects neuronal activity has increased significantly over the past decade, our understanding of how the brain affects peripheral immunological activity is far more limited. This may seem surprising as the effects of mental and emotional states on our health are familiar to most of us from our daily lives. For example, we tend to get sick after stressful events[18,19], and depression is known to reduce the effectiveness of immune activity and is associated with increased mortality[20–22]. Positive mental states, notably those observed in the placebo effect, demonstrate that even a sugar pill can have a positive impact on a patient's disease if the patient expects that the pill will improve his or her condition[23]. Nevertheless, negative expectations can lead to negative outcomes if one anticipates side effects, a phenomenon known as the nocebo response[24]. Lessons about how the brain affects immunity can also be derived from the literature regarding stroke. Patients with stroke often experience systemic immunosuppression following this neurological event[25,26]. The mechanisms underlying such stroke-induced immunosuppression are largely

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Box 1 | **Neuro-immune communication within the brain**

It is now clear that the brain hosts a vibrant immune environment even under homeostatic conditions. The brain's immune compartment is composed of resident cells (microglia) located mainly in the parenchyma and infiltrating immune cells residing mainly in the meninges and choroid plexus. The blood vessels in the central nervous system (CNS) are separated from the tissue by the blood–brain barrier (BBB), which controls the transfer of peripheral compounds to the CNS. Yet, direct interactions between the blood and the CNS can occur in circumventricular organs (CVOs), which are highly permeable and fenestrated capillaries located in specific sites. In mammals, these are found in the median eminence and adjacent neurohypophysis, organum vasculosum, lamina terminalis, subfornical organ and the area postrema, and act as important hubs for neuroimmune interactions.

In this Review, we focused mainly on the effects of the nervous system on the peripheral immune response; however, neuronal activity can also affect the immune response within the brain (brain-resident immune cells or the infiltrating immune population from the periphery). The brain's borders, such as the choroid plexus, meninges, CVOs and the BBB, are innervated. Thus, brain activity can affect the secretion of chemotactic molecules in the meninges and choroid plexus, alter the permeability of the BBB and impact the activity of epithelial cells in the CVOs. For example, BBB permeability is disrupted in certain depressive disorders[225], and inhibition of synthesis of serotonin (a neurotransmitter thought to be deficit in depression[226,227]) reduced BBB permeability[228]. We showed that short sleep deprivation increases expression of CXCL13 in the meninges, altering B cell homing to the brain's borders[229]. It was also shown that severe stress affects leukocyte trafficking through the choroid plexus in a glucocorticoid-dependent manner[230]. Blocking the glucocorticoid receptor signalling facilitates the recruitment of GATA3-expressing and FOXP3-expressing T cells to the brain and attenuates post-traumatic behavioural deficits[230].

The complexity of the neuro-immune interactions within the brain is not limited to the immune cells themselves. The classic immune cells in the brain, the microglia, which participate in tissue maintenance, synaptic pruning and plasticity[231,232], are directly affected by neuronal activity. Microglia express receptors for many neurotransmitters (for example, noradrenaline[233], acetylcholine[234], serotonin[235] and glutamate[236]), and the activation of these receptors affects their function[237,238]. In addition to microglia, other cells, such as astrocytes[239,240], oligodendrocytes[241] and even neurons[242], respond to cytokines and immune-related receptors. For example, Toll-like receptors can regulate the differentiation[243] and activity[244] of neurons. Thus, the neuro-immune dialogue that occurs within the brain tissue has unique characteristics and has an evident impact on the brain's physiology and function.

unknown. Yet, emerging studies provide interesting mechanistic insights, and one such example was demonstrated in mice. It was shown that following stroke, the brain, via sympathetic innervations to the liver, alters the activity of invariant natural killer T (NKT) cells to suppress inflammatory responses[27]. This reaction may have evolved to protect the brain from an overwhelming immune response, which is expected following any form of tissue damage. However, such immunosuppression also attenuates antibacterial immunity, thereby increasing susceptibility to infection, to the extent that one third of patients with stroke experience pneumonia, a major cause of poststroke death[28]. Furthermore, a number of clinical observations indicate that lateralization of the stroke site affects the course of immune-mediated diseases. For example, patients with arthritis who experienced a stroke were shown to have enhanced antigen-specific T cell reactivity on the stroke-affected side of the body[29]. This effect was proposed to be mediated by changes in sympathetic activity[30]. Accordingly, manipulating neuronal activity in either the left or the right hemisphere of the rodent brain was shown to result in opposing immunological reactions[31–34], suggesting that the two hemispheres have distinct effects on the peripheral immune response. This can potentially be attributed to the lateralized organization of the brain and to the distinct anatomical connections of the two hemispheres with the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS)[35–38].

Evidence for the neuronal regulation of immunity ranges from epidemiological studies to mechanistic studies in experimental animals. Although these studies are beginning to establish the connections between the brain, psychological states and immunity, we still lack knowledge of fundamental aspects of the underlying mechanisms and their biological relevance. To gain a deeper understanding of the interactions between these two highly complex systems, we need to study them systematically within a defined conceptual framework. This will allow us to formulate specific testable hypotheses, which can introduce a physiological mechanistic perspective to psychosomatic conditions (BOX 2). In this Review, we offer such a conceptual framework by examining three basic questions regarding the interaction between the CNS and the immune system: why do these interactions occur? How are these signals mediated? And where in the brain are these responses controlled?

Why does the brain regulate immunity?

A key question that emerges when exploring the neuronal regulation of immune processes is why should the nervous system affect the activity of an independent and effective system, such as the immune system? Is there any evolutionary advantage for such neuro-immune regulation? Here we propose that due to the unique features of the nervous system, such as the type of inputs it receives, its mode of action and its anatomy, it can offer the immune system unique advantages that can increase the organism's fitness: (1) integration and synchronization, (2) prediction and (3) speed (FIG. 1).

Integration and synchronization

The brain is the central regulator of the organism, responsible for maintaining the organism's homeostasis. The immune system restores homeostasis following pathogenic attacks, development of malignant cells or tissue damage. Thus, it is to be expected that over the course of evolution, the brain would attain at least some control over the immune system, as it has over most other physiological systems. The brain constantly monitors the external and internal environments and integrates this information to generate a detailed depiction of the organism and its potential challenges. Thus, the brain can prepare the organism for an upcoming danger by altering behaviour and allocating physiological resources to cope with an upcoming threat. Accordingly, the brain can directly regulate the function of most physiological systems, including the cardiovascular system, the renal system, the digestive system, body temperature, blood flow, feeding and metabolism. The immune system itself is affected by many of these physiological parameters. Thus, synchronizing immunity with these physiological functions may be valuable for an effective immune response. For example, the immune system is a metabolically costly system. Immune activation in humans and other species increases the resting metabolism by around 30%, at a caloric cost of about 2,000 kJ per day[39–42].

Tissue tolerance
The mitigation of tissue damage following exposure to an adverse stimulus.

However, increasing caloric intake to support immune activity is not always beneficial. It was shown that shifting from glucose to ketone bodies and free fatty acid utilization is protective in bacterial sepsis[43,44], suggesting that fasting may be critical to surviving septic shock. Wang et al. demonstrated that fasting, a conduct often associated with infection[10] as part of sickness behaviour[4], is crucial for survival following bacterial infection. This behaviour induces ketone bodies that limit the production of reactive oxygen species during inflammation, thereby increasing tissue tolerance during bacterial infection[45]. Loss of appetite, which may facilitate fasting behaviour, is mediated by the hypothalamus[9,46]. Indeed, it was shown that following lipopolysaccharide (LPS) administration, there were changes in activity in the hypothalamus, specifically in the area responsible for feeding behaviour[47]. Thus, by generating an integrated representation of the organism's status, the brain can synchronize behaviour, metabolism and immune activity to increase the potential for survival.

One of the strongest synchronizing factors is the circadian rhythm, which is regulated by an inner clock located in the suprachiasmatic nucleus of the hyopthalamus[48]. This inner clock allows various physiological functions to be orchestrated according to the behavioural and functional demands imposed by the day–night cycle. Therefore, physiological functions, which may be opposing, interdependent, or compete for similar resources, are coordinated throughout the 24-hour cycle. The immune system was also shown to be synchronized by the circadian rhythm. For example, the number of circulating leukocytes oscillates between the tissue and blood in a manner proposed to facilitate the physical activity of the organism and its potential exposure to pathogens or tissue damage[49,50]. Generally, circulating leukocyte levels peak in the blood during the resting phase, while leukocyte recruitment to tissues occurs preferentially during the active phase of the organism. These changes are mediated by the expression of cell adhesion molecules and chemokines[49]. Accordingly, it was shown that infection in different circadian periods can significantly affect the outcome. For example, death rates in mice peaked when LPS was administered during the diurnal rest period (~80% lethality) versus the nocturnal activity period (~10% lethality)[51]. Moreover, human studies show that vaccinations in the morning induce an enhanced antibody response compared with vaccinations in the afternoon[52]. Immune processes during the homeostatic states are also regulated by circadian signals. For example, the routine egress of haematopoietic stem cells from the bone marrow to the blood demonstrates circadian oscillations[53]. In part, the responsiveness of these stem cells to chemokines, mediated via suppressor of cytokine signalling (SOCS), is regulated by growth hormone[54], which is specifically released during sleep. In general, sleep is a central physiological state induced by the brain and synchronizes various processes, including reduction of heart rate and changes in metabolism. According to the systems consolidation theory[55], one of the major processes coordinated during sleep is consolidation and stabilization of memories in the brain[56,57]. It was proposed that the immune memory response is also enhanced by sleep[58,59] and that sleep promotes the spatial redistribution of immune cells throughout the body[58,60]. From the findings taken together, different forms of brain-orchestrated synchronization activity link immunity with other physiological systems. Such synchronization enables optimization of the conditions under which these physiological processes are executed, prevents interference between processes that compete for the same physiological resources and coordinates the organism's internal state with that of the external environment.

Prediction

One of the brain's most important roles is to perceive and assess threats before they physically affect the organism. This predictive capacity enables our body to prepare for upcoming challenges, ranging from cellular changes to behavioural ones. Perhaps the most well-known example is the classical Pavlovian conditioning paradigm, in which a physiological function (for example, increased salivation) is induced by a predictive cue (for example, a bell), even in the absence of food. This capacity of the brain to plan ahead may also benefit the immune response, as preparing the immune system in advance for an upcoming challenge could induce a more effective and swifter response. Indeed, Pavlovian conditioning of the immune system was demonstrated in numerous settings. This phenomenon, known as immune conditioning, was first demonstrated in Russia in the 1920s and was rediscovered by Ader and Cohen in the 1970s[61]. Ader and Cohen demonstrated that repeated coadministration of a naive conditioned stimulus (for example, saccharin) with an immunomodulating agent (for example, cyclosporine A)

Box 2 | **A physiological perspective of the mind–body connection**

In the seventeenth century, René Descartes separated the notion of mind, which holds abstract thoughts and emotions, from that of the physical body. However, the concept that these two entities are not really separate and that emotions affect physical health dates as far back as the second-century physician Galen and the medieval physician and philosopher, Moses Maimonides. Plato, in his famous dialogue *Charmides*, argued that medical treatment alone is insufficient to produce recovery without a certain psychological interaction with the healer[245]. Schools of East Asian medicine interpret the human body and its disorders, including emotional and psychosomatic disorders, using a holistic approach. Even for Western medicine, over most of its history, medical practice had a limited pharmacological arsenal and consisted mainly of emotional and cognitive manipulations. Moreover, the placebo effect, which has muddled clinical trials for the past 50 years, repeatedly reminds us that one's thoughts and emotions affect physiology. Nevertheless, this aspect of physiology remains largely unexplored in modern medicine.

One of the limitations in studying these connections in modern clinical settings is that we are still confined by our subjective measurements and insufficient understanding of the underlying mechanisms. However, we can now 'translate' this philosophical mind–body question into a physiological one. By taking a reductionist approach, instead of asking how emotions affect immune activity, we can investigate how different brain areas associated with specific emotions and behavioural manifestations affect immunity[246]. The analysis of the causal effects of specific neuronal targets on immunity became especially accessible with the emergence of new tools in neuroscience. These new technological developments, such as genetic manipulations, optogenetics and chemogenetics (designer receptors exclusively activated by designer drugs (DREADDs))[247,248], enable unprecedented specificity of neuronal manipulations. These tools help us to establish causal relationships between specific brain activity and ensuing changes in immune functions, supporting a physiological basis for what may otherwise be considered complex and largely uncharacterized psychosomatic processes.

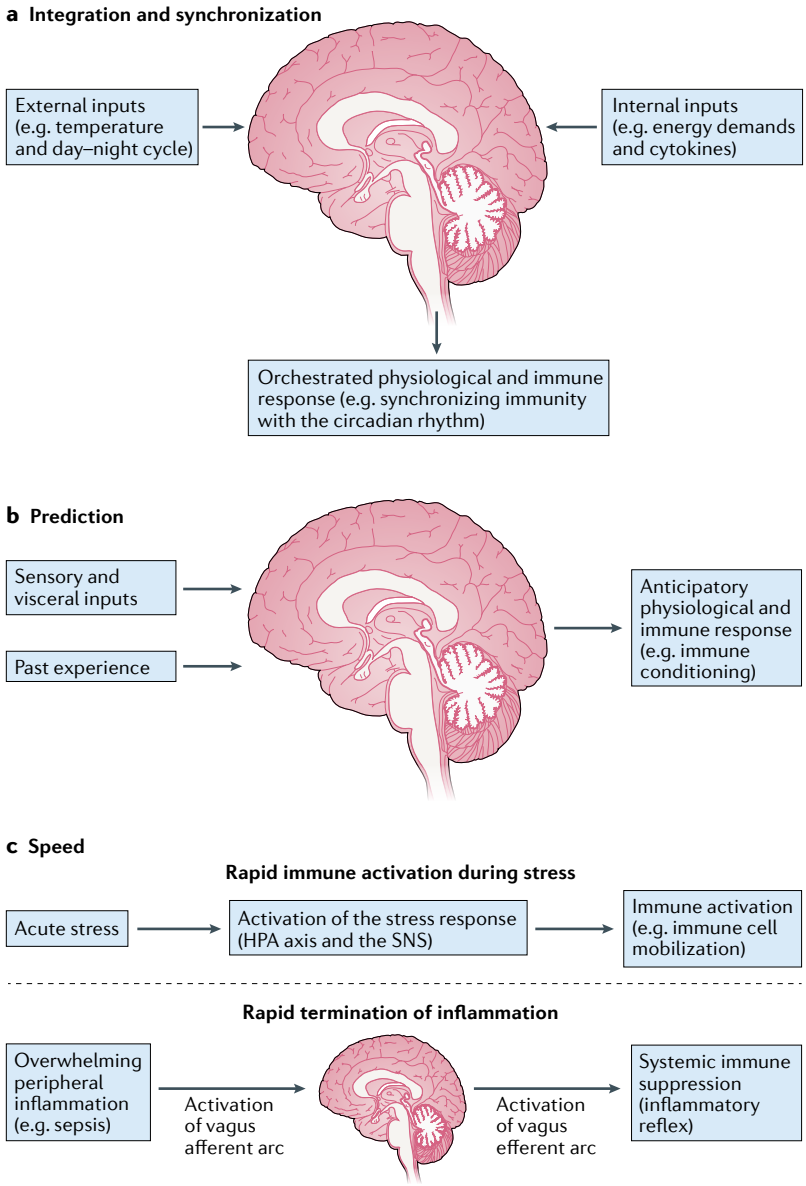


Fig. 1 | **Why? Why is it beneficial to allow the nervous system any control over immunity?** Presented are some unique properties of the brain, which offer a functional benefit for the immune system. **a** | The brain's ability to integrate and synchronize different phsyiological and behavioural processes. The immune response is only one part of the organism's response to a challenge. Thus, immune activity has to be synchronized with other physiological processes to optimize the effectiveness of the response. The brain receives external inputs (for example, the external temperature and the day–night cycle) and internal inputs (for example, the body's energy demands and cytokines secreted in the body). These inputs are integrated by the brain, which in turn can orchestrate and adapt the entire physiological response, including the immune response, circadian rhythm, sleep, metabolism, food intake, blood pressure and temperature. Such synchronized response can also optimize the physiological conditions for a more effective immune response. **b** | The brain's ability to generate predictions and anticipate challenges. The immune system responds to signals only after it encounters them, while the brain acts as a prediction machine, anticipating upcoming events. Adding predictive value to the immune system can allow it to mount a protective response, even before the exposure to the challenge. The brain receives sensory and visceral inputs, which can be evaluated in light of past experiences, thus producing anticipatory physiological and immune responses. A classic example for such prediction is immune conditioning, whereby a naive stimulus (sucrose) is coupled with an immunosuppressant drug. After the coupling process, the sucrose alone can elicit immunosuppression. **c** | The brain's ability to execute fast and systemic responses, speed. The nervous system reacts within milliseconds, while the immune system reacts on a timescale of minutes to days. There are cases in which a swift and systemic immune response is necessary. For example, during the acute stress response when the body is preparing for an upcoming threat, there may be a need for a rapid immune activation. The stress response activates the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), both of which are known to affect immune activity. For example, the SNS was shown to induce immune cell mobilization. A different example is the brain's capacity to terminate the immune response when it becomes overwhelming and can cause damage as in the case of sepsis. During a peripheral infection, the release of cytokines activates the vagus afferent arc, and the vagus efferent arc suppresses the immune system (a process termed the 'inflammatory reflex').

leads to coupling of the two stimuli, so administration of the conditioned stimulus alone (saccharine) can induce immunosuppression[61]. Immune conditioning has been demonstrated in lupus[62], allergy[63] and arthritis[64], and was applied for therapeutic effect, enabling reduction in the dosage of pharmacological agents without reducing efficiency[65,66]. Although the specific neuronal pathways involved are as yet unidentified, it was shown that the brain's insular cortex, amygdala and ventromedial nucleus of the hypothalamus are important in regulating different aspects of the conditioning response[67,68]. Thus, immune conditioning represents the brain's ability to anticipate an upcoming challenge and prepare the organism and its immune system.

Prediction can also be utilized in behaviours such as eating and mating, which are inherently associated with potential exposure to pathogens. Priming the immune response in expectation of these activities can be important for survival. Indeed, we recently showed that direct triggering of the brain's reward system, which is endogenously activated in anticipation of positive experiences (such as mating and feeding), boosts the antibacterial and antitumour immune response[69,70]. In a broader perspective, Cole et al. proposed that as different socio-environmental conditions expose the organism to distinct immune challenges, the immune profile should be correlated with one's lifestyle. Thus, for example, social isolation, social threat, and low or unstable social status are associated with differential gene expression in leukocytes[71]. Diverse types of social adversity positively correlated with the expression of pro-inflammatory genes and negatively correlated with the expression of genes involved in innate antiviral responses and antibody synthesis. These effects were proposed to be mediated mainly by neuroendocrine pathways[72].

Vagus nerve
The longest cranial nerve connecting the brainstem to the periphery via afferent and efferent projections. The vagus nerve delivers sensory information to the brain and regulates parasympathetic activity.

Another aspect of this predictive capacity was demonstrated in several recent studies describing an anticipatory immune response at the level of peripheral sensory neurons. This response is different from the predictive response mediated by the brain, as peripheral sensory neurons can directly sense pathogens and danger signals. The predictive effect is manifested by the capacity of these sensory neurons to detect the presence of pathogens even before they cause damage or activate the immune system. For example, bacteria can directly activate nociceptors, which in turn affect the local immune response[73]. Cutaneous TRPV1$^+$ neurons directly sense noxious stimuli, inflammatory cytokines and even pathogen-associated molecules. Their activation is sufficient to elicit a local IL-17-producing T cell-associated inflammatory immune response and to augment host defence against bacteria[74]. This effect, defined as an 'anticipatory immune response', was shown to promote elimination of the pathogen[75–78].

Another important site in which the predicative capacity of the brain may be especially relevant is the gastrointestinal tract. The immune system in the gastrointestinal tract constantly encounters new antigens. Thus, there is an ongoing need for rapid decision-making to evaluate the nature of the encountered antigen. In such a case, the predictive capacity of the brain may become relevant in assessing the environment or the context in which the antigen was consumed, to help estimate its safety. Indeed, the effects of neuronal modulation on immune processes was also demonstrated in the case of the gut–brain axis[79–88]. For example, the immune response in the gut to parasitic worms is regulated by type 2 innate lymphoid cells (ILC2s). ILC2s can be activated by the neuropeptide neuromedin U (NMU)[89,90], which is produced by neurons in the mucosal area that sense the presence of the invader. NMU treatment in vivo induces an immediate protective type 2 response, while ablation of the NMU receptor on ILC2s leads to a delayed and impaired type 2 response and poor control of the worm infection[90]. While neuro-immune interactions enhance protection of the host from infection by some pathogens, other pathogens can exploit the same pathways to facilitate their own survival[91].

Thus, the nervous system gathers information from sources that are not available to the immune system (for example, visual, auditory, metabolic and mechanical stimuli). These stimuli, integrated with information acquired in past experiences, allow the brain to quickly identify potential threats even before they are recognized by the immune system. This enables the organism to initiate an immediate and more effective immune response to an upcoming challenge.

Speed

One of the most prominent differences between the nervous system and the immune system is their speed of reaction. The nervous system can react within milliseconds, whereas immunological responses often require from several minutes up to weeks to develop. While this slower timescale of immune reaction is sufficient for many of its needs (and potentially even advantageous as it provides more opportunities for regulation), in some cases, a more rapid response may be beneficial. For example, during a stressful event, an immediate mobilization of immune cells can speed up the reaction to an upcoming challenge. Indeed, neuronal signals, especially via the SNS, induce immune cell mobilization[92–95]. Cytokines such as IL-6 and tumour necrosis factor (TNF), which characterize the early stages of an immune response, are induced in response to stress and SNS activation[96,97]. Furthermore, a rapid immune response is not only relevant for the initiation of an immune reaction but may be especially significant for its termination. An overactive immune response can become an immediate danger for the organism, as demonstrated in sepsis, which can lead to death within hours. Neuronal inputs were shown to provide an effective and timely termination signal initiated by the vagus nerve, the stimulation of which can attenuate immune activity systemically (known as the inflammatory reflex)[98] and enhance postsepsis survival[99].

Taken together, we propose that there are unique advantages offered by neuronal regulation of immunity. The nervous system can optimize the conditions under which the immune system operates by synchronizing its activity with other physiological functions. Moreover, the brain has a broad perspective of the challenges facing the organism, and can prioritize and allocate resources on the basis of these needs. For example, this could entail prioritizing the physiological and energetic resources needed to escape an immediate threat (for example, a lion) over fighting a bacterial infection. The immune system effectively detects pathogens and signs of damage, but it can respond to the challenge only following its encounter. The predictive capacity of the brain offers the immune system an opportunity to prepare for an upcoming challenge and eliminate it in a more timely and effective manner. This aspect of a timely response is also manifested by the capacity of the brain to deliver direct and rapid messages to the immune system to initiate, modulate or quickly terminate an overwhelming immune reaction across the entire organism.

How does the CNS regulate immunity?

The capacity of the nervous system to regulate immunity requires an infrastructure that enables signal propagation between these two systems. Here we discuss the major pathways that allow the CNS to regulate the activity of the peripheral immune system: (1) the endocrine pathway; (2) the neuronal efferent pathway composed of the sympathetic and parasympathetic arms; (3) sensory peripheral pathways; and (4) meningeal lymphatics. Each of these pathways can transmit unique information between the nervous system and the immune system, and uses distinct tools to deliver its messages (FIG. 2).

Endocrine pathways

The endocrine system is one of the most potent tools available to the brain, allowing it to regulate a myriad of physiological processes. Hormones, the release of which is regulated by the brain, are delivered via the bloodstream to target tissues. This pathway is an effective and rapid means of simultaneously delivering information to different organs and synchronizing physiological processes. The central regulator of the endocrine system

is the hypothalamus. This brain region communicates extensively with other areas of the brain and controls major physiological processes such as hunger, thirst, body temperature, circadian rhythm and sleep. Two main endocrine pathways are regulated by the hypothalamus; the hypothalamic–neurohypophyseal system and the hypothalamic–hypophyseal portal system. These pathways differ in the nature of the physiological processes they regulate and the number of relay stations they use.

The hypothalamic–neurohypophyseal system produces hormones in the hypothalamus synthesized by neurosecretory cells. The hormones are then stored in the posterior pituitary and are secreted directly into the bloodstream. This system is responsible for the secretion of oxytocin (which regulates behaviour during social interactions, including social bonding, or maternal care)[100,101] and arginine-vasopressin (AVP; released in response to hyperosmolality, increasing the reabsorption of water in the kidney)[102]. Both of these hormones have been linked to immune activity. Oxytocin was shown to suppress pro-inflammatory cytokines[103,104] and to promote wound healing[105] (which may be especially important in the postpartum period). AVP was shown to have anti-inflammatory effects during sepsis[106]. Inflammatory cytokines were shown to activate AVP-producing neurons[107], indicating that this endocrine pathway can also respond to changes in immune system activity.

The hypothalamic–hypophyseal portal system secretes hypothalamic hormones (for example, corticotropin-releasing hormone (CRH)), which reach the anterior pituitary and stimulate the release of the relevant pituitary hormone (for example, adrenocorticotropic hormone (ACTH)). The pituitary hormone is then released into the bloodstream, through which it ultimately reaches its target organ (for example, adrenal gland), where it induces the release of the final effector hormone (for example, cortisol). Various physiological processes are regulated via this pathway, consisting of five main axes: (1) the hypothalamic–pituitary–adrenal axis, which mainly regulates the stress response; (2) the hypothalamic–pituitary–thyroid axis, which is responsible for the release of thyroid hormones, which participate in regulation of metabolism; (3) the hypothalamic–pituitary–gonadal axis, which is responsible for secreting sex hormones to regulate reproduction; (4) the hypothalamic–pituitary–somatotropic axis, which is responsible for secretion of growth hormone and insulin-like growth factor 1 (IGF1); and (5) the hypothalamic–pituitary–prolactin axis, which secretes prolactin, which is best known for inducing the production of milk in females.

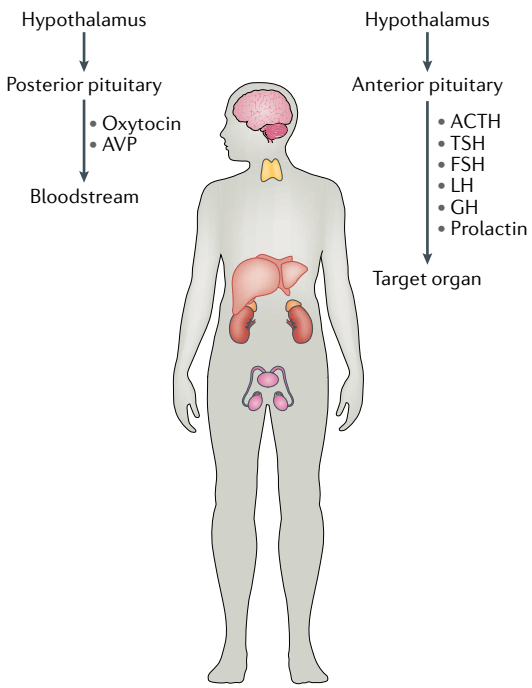
All of these endocrine pathways coordinate fundamental physiological and developmental events, which require adaptation of immune activity. Thus, it is not surprising that these hormones also affect the immune response. For example, in the hypothalamic–pituitary–gonadal axis, which regulates sexual development, gonadotropin-releasing hormone and sex steroids such as testosterone participate in the programming of the immune system[108]. This connection may be especially important in adapting immunity to the many physiological and behavioural changes that accompany sexual maturation, and the differences in energy consumption and nutritional requirements between males and females. Generally, testosterone has an immunosuppressive effect, while oestrogen has an immunoenhancing one[109]. Accordingly, females exhibit increased antibody production[110,111] and are less susceptible to viral infections, but, on the other hand, they are more prone to autoimmune disease[112,113]. Moreover, pregnancy presents the female immune system with unique challenges (for example, the need to tolerate an abundance of non-self-antigens derived from the fetus). Accordingly, oestrogen was shown to affect the immune response during pregnancy[114]. Another example is the hypothalamic–pituitary–thyroid axis, which generally enhances metabolic activity and has been associated with immune activation[115]. Thyroid hormones induce lymphocyte proliferation[116]. Accordingly, thyroidectomy (the removal of the thyroid gland) suppresses the immune response[117], and patients with hypothyroidism are significantly more susceptible to infection[118,119]. Thus, endocrine signals enable the synchronization of complex physiological processes and immune activity.

Neuronal efferent pathways

The peripheral nervous system comprises a network of neuronal pathways that can deliver timely and direct information to peripheral tissues. The autonomic nervous system (ANS) includes the PSNS and the SNS and is known mainly for its control of functions that are not under conscious control (for example, blood pressure, heart rate and gastrointestinal motility). The SNS and PSNS have some opposing effects on various physiological processes characterized by the 'fight or flight' response regulated by the SNS and the 'rest and digest' programme of the PSNS. The main neurotransmitter of the SNS is noradrenaline (recognized by α-adrenergic and β-adrenergic receptors), and the main PSNS neurotransmitter is acetylcholine (ACh; which is recognized by nicotinic and muscarinic ACh receptors). Both systems can affect immune activity, although immune organs such as the spleen, bone marrow, lymph nodes and thymus are innervated mainly by the SNS[120]. Functional receptors for neurotransmitters and neuropeptides secreted by the ANS are expressed by immune cells[120–122]. It is important to note that different neuronal factors can also be secreted by the immune cells themselves[123], indicating an even more complex relationship between the nervous system and immunity.

Sympathetic nervous system. Traditionally, SNS activity is associated with the stress response and is responsible for the increase in blood adrenaline and noradrenaline levels. However, this is only one aspect of the SNS, which is functionally and anatomically divided into two main arms: the systemic arm and the local arm. The systemic arm of the SNS is responsible for the increase in blood noradrenaline and adrenaline levels. Sympathetic fibres from the CNS reach the adrenal gland (specifically the adrenal medulla), leading to secretion of adrenaline and noradrenaline by the adrenal chromaffin cells. These neurotransmitters are secreted directly into the bloodstream and are thereby delivered to the entire organism. In contrast to this systemic response, the local arm of

a Endocrine pathway

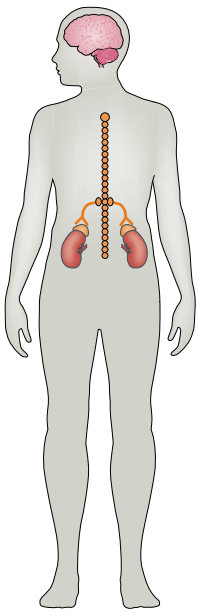


Fast, systemic inputs from the brain orchestrating complex physiological processes

Immune-related example:
HPG axis hormones affect T cell response

b Sympathetic nervous system pathway

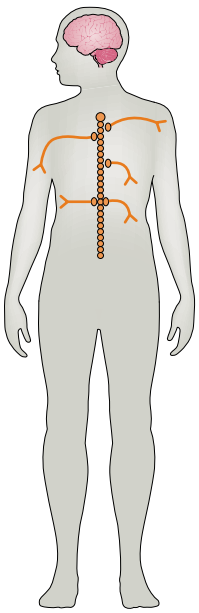
Systemic sympathetic pathway



Fast, systemic inputs from the brain mediated by adrenaline and noradrenaline released by the adrenal gland to the blood

Immune-related example:
Noradrenaline and adrenaline induce immune cell mobilization to the bloodstream

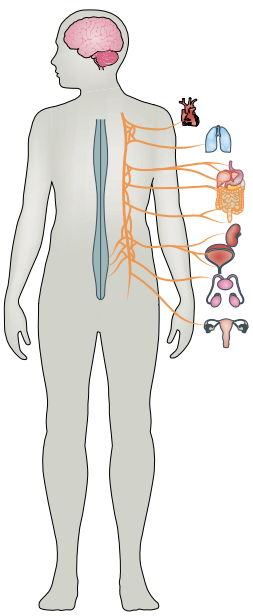
Local sympathetic pathway



Fast, localized signals from the brain mediated via a network of innervations to immune organs and target sites. Secretes noradrenaline and neuropeptides

Immune-related example:
SNS innervations to the liver suppress iNKT activity in the liver

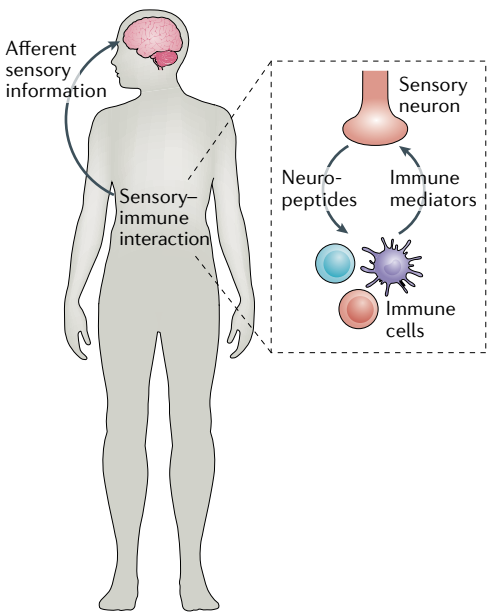
c Parasympathetic nervous system pathway



Fast and localized signals from the brain to specific target sites. Limited innervation of immune organs. Secretion of mainly ACh.

Immune-related example:
Vagus nerve activation suppresses pro-inflammatory cytokine release (the inflammatory reflex).

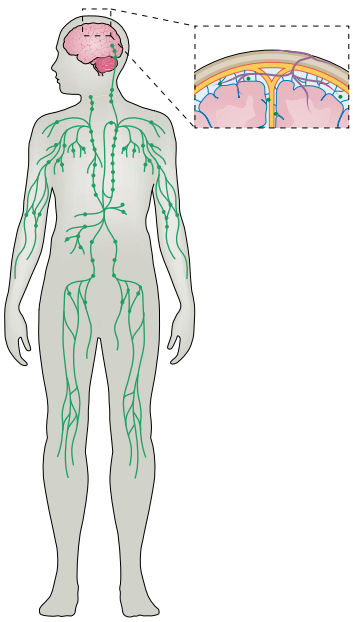
d Sensory pathway



Direct detection of potential threats in peripheral tissues. Transfers information from the periphery to the brain, and can also locally interact with the immune system via neuropeptide secretion.

Immune-related example:
Nociceptor sensory neurons inhibit neutrophil recruitment to infection site via CGRP secretion

e Meningeal lymphatic pathway



Delivers specific immune-related information regarding the brain's condition

Immune-related example:
Changes in the meningeal lymphatic function in mice affected CNS disease, neuroinflammation and cognitive task performance

◀ Fig. 2 | **How? How does the brain communicate with the peripheral immune system?** We depict here the main pathways that connect the brain with peripheral immunity. **a** | The endocrine pathway, composed of the hypothalamic–neurohypophyseal system (secreting mainly oxytocin and arginine-vasopressin (AVP)) and the hypothalamic–hypophyseal portal system (secreting mainly adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and growth hormone (GH)). **b** | The sympathetic nervous system (SNS) pathway, composed of the systemic and local sympathetic pathways. The systemic pathway is mediated mainly by the adrenal gland, resulting in the systemic secretion of adrenaline and noradrenaline. The local sympathetic pathway constitutes local sympathetic innervation, reaching all parts of the body, including every immune organ. **c** | The parasympathetic nervous system comprises cholinergic innervation, which reaches all parts of the body and secretes mainly acetylcholine (ACh). **d** | The sensory neurons can detect potential threats in the peripheral tissues. The sensory neurons may directly affect the immune cells in the peripheral tissue (via neuropeptide secretion) or send the relevant information from the periphery to the brain. **e** | The meningeal lymphatic system delivers immune cells and immune-related signals relating to the brain to the periphery. For each pathway a single representative example of immune effects is provided. CGRP, calcitonin gene-related peptide; CNS, central nervous system; HPG, hypothalamic–pituitary–gonadal; iNKT cell, invariant natural killer T cell.

the SNS provides targeted innervation to almost every tissue in the body. The sympathetic fibres at one tissue can be activated independently of fibres at another site[124], locally releasing noradrenaline. Thus, tissue-specific control can be achieved via these descending neuronal innervations. In addition to noradrenaline, these neurons are characterized by the presence of varicosities that store neuropeptides (such as neuropeptide Y and vasoactive intestinal peptide (VIP)), which can be released along with noradrenaline[125,126]. These neuropeptides participate in diverse physiological processes, including regulation of metabolism, vascular and immune function[127–131]. Nevertheless, it is unclear how the secretion of these neuropeptides is regulated, and their effects on the immune system are not fully understood.

The effects of the SNS on the immune system have been studied extensively, mainly in light of the relationship between the SNS and stress (BOX 3). Immune cells express both α-adrenergic and β-adrenergic receptors (adrenoceptors), and receptor expression levels vary with cell state, maturation or activation[95,132]. The adrenergic receptors were shown to functionally impact the activity of immune cells, specifically their migration[133], cellular activation[134] and cytokine production[135]. Reported effects of the SNS on the immune system are somewhat contradictory[136], with some studies indicating that SNS activity is mainly immunosuppressive and others demonstrating the stimulatory effects of the SNS on the immune response. For example, activation of the β-adrenergic receptor was shown to induce $CD4^+$ T cell proliferation and cytokine production[137,138], while inhibiting TNF production by macrophages in response to LPS[139]. Thus, adrenergic signals have distinct immunological impacts that can be attributed to the duration of exposure to the noradrenergic signal, its intensity (concentration), interaction with other factors such as neuropeptides or the functional roles of the adrenergic receptors on different immune subsets and in various immunological contexts. Another set of factors that may contribute to the diversity of SNS effects on the immune system are the differential effects of the systemic arm versus the local arm of the SNS. While the systemic arm can alter adrenaline and noradrenaline levels across the entire organism, the local arm enables the transduction of specific and direct signals to different sites. For example, sympathetic neurons affect tissue-specialized macrophages by switching their gene-expression profiles, and modulate changes in brown adipose tissue content, thermogenesis and regulation of weight loss in obese mice[140]. Sympathetic innervations to the bone marrow affect the immunosuppressive profile of myeloid-derived suppressor cells in tumour-bearing mice[70]. Innervations of the microenvironment in which tumours develop can also affect tumour growth[141]. In rodent breast cancer models, growth and progression were accelerated following stimulation of sympathetic nerves in tumours[142]. Moreover, sympathetic denervation was shown to suppress tumour growth and to downregulate the expression of immune checkpoint molecules (programmed cell death protein 1 (PD1) and programmed death ligand 1 (PDL1)[142].

Parasympathetic nervous system. Similar to the SNS, the PSNS plays a role in regulating several important functions in the body and was shown to directly regulate immunity. A crucial component of the PSNS is the vagus nerve, which controls heart rate and promotes intestinal motility and digestion, bronchodilation and pupil dilation. One of the most extensively studied examples of the connection between the brain and the peripheral immune system is the inflammatory reflex, which is induced by the vagus nerve. The inflammatory reflex is composed of an afferent arc and an efferent arc. The afferent arc of the vagus nerve is stimulated by cytokines at the inflammatory site, while the efferent arc of the vagus nerve secretes ACh in the periphery, which inhibits inflammation[143]. The secretion of ACh in the peripheral immune organs was shown to inhibit the immune response during sepsis and suppress cytokine release via the α7 nicotinic ACh receptor expressed by immune cells[144,145]. Some of the vagal effects are mediated via sympathetic nerves[99], further highlighting the complexity of neuronal control over peripheral immune responses. The understanding of this regulatory network may have major medical implications; for example, vagus nerve stimulation could be applied for treatment of autoimmune conditions, an approach already clinically tested for treating rheumatoid arthritis[146].

Taken together, the peripheral nervous system can modulate immunity both locally and systemically. The PSNS and the SNS are generally considered to induce opposing effects (fight or flight versus rest and digest). Parallel effects are also often observed at the level of the immune system. For example, in the context of breast cancer, a retrospective analysis of breast cancer specimens from 29 patients revealed that increased sympathetic nerve density and decreased parasympathetic nerve density in tumours were associated with poor clinical outcomes and correlated with higher expression of inhibitory immune checkpoint molecules[142].

The sensory nervous system

The sensory nervous system provides an additional pathway of neuronal communication between the brain and the periphery. Sensory neurons are categorized into

Box 3 | **Stress and immunity**

Stress is an important physiological adaptive response that prepares the organism for an upcoming challenge. However, stress has been commonly associated with adverse effects on health in general and specifically on immunity.

The effects of stress on immunity can be broadly divided into those of acute versus chronic stress, which appear to be different in their physiological and immunological impact. Studies suggest that acute stress induces leukocyte mobilization to the blood[92], enhances leukocyte infiltration into the site of inflammation[92,249] and affects the proliferative response of immune cells[250]. In humans, acute stress triggered by different paradigms such as parachute jumping[93], a difficult arithmetic examination[251] or confrontational role-play[252] increased the activity and abundance of natural killer cells and $CD8^+$ T cells. Conversely, chronic stress mostly has an immunosuppressive effect[253,254] in animals and humans[255]. Epidemiological and genomic studies demonstrate alterations in immune cell gene expression during stressful life events[72]. For example, increased exposure to stressful life situations is correlated with elevated expression of pro-inflammatory genes and a decrease in the expression of genes encoding type I interferons (involved in innate antiviral responses and antibody synthesis)[71,72,256,257]. Conversely, people practising cognitive–behavioural relaxation methods[258] or meditation[259] were able to reverse these patterns. However, chronic stress also increases proliferation of haematopoietic stem cells in the bone marrow, leading to the accumulation of pro-inflammatory leukocytes[260]. Moreover, chronic stress is a risk factor for the development and progression of many immune-related diseases[261]. It was proposed that by altering cytokine secretion (for example, T helper 1 cell-type cytokines/T helper 2 cell-type cytokines), long-term stress dysregulates the balance in the immune response, thereby exacerbating autoimmune conditions[262]. In the context of cancer research, chronic stress restructures lymphatic networks within and around tumours, promoting the escape of cancer cells[263]. Pharmacological manipulations of stress-related pathways such as adrenergic signalling are undergoing testing in clinical trials for treating women with breast cancer[264,265].

The effects of stress on immunity are thought to be mediated via two main pathways. The first is the hypothalamic–pituitary–adrenal axis, which results in glucocorticoid secretion. Glucocorticoids inhibit the immune response, and are administered routinely as potent immunosuppressive drugs[266]. The second is the neuronal pathway, mainly the sympathetic nervous system, which induces noradrenaline and adrenaline secretion. The effect of the sympathetic nervous system on immunity can be mediated either directly by noradrenaline receptors (α-adrenergic and β-adrenergic receptors) expressed on immune cells or indirectly via cells residing in the tissue (for example, endothelial cells and epithelial cells) that can also respond to sympathetic signals[267–269].

In spite of the clear evidence for the connection between stress and immunity, evidence in the field is often contradictory[270]. This is in part because stress is a very complex phenomenon that is likely to have different neuronal manifestations. Stress accompanies different types of emotional states, and thus the brain activity associated with different types of stress is distinct and may have different effects on the immune system. In addition, the timing of the stress response is also critical for the outcome. For example, it was demonstrated in mice that exposure to glucocorticoids specifically during the perinatal period reprogrammes the neuroendocrine stress pathway. This results in reduced glucocorticoid levels in adults, leading to attenuated antitumour and antibacterial $CD8^+$ T cell responses[271]. Thus, 'stress' — as a general term — cannot describe the complexity of the phenomenon nor its outcome. The field of neuroscience is undergoing a conceptual reframing of the stress response by characterizing the specific pathways involved in different aspects and types of stress[272]. This emerging understanding will also enable research in neuroimmunology to dissect the various implications of stress on immunity. From the findings taken together, although stress was mostly associated with its maladaptive effects, it is an essential physiological response that plays a central role in synchronizing the immune response with other physiological functions in anticipation of an upcoming challenge.

several heterogeneous populations, each responding to different aspects of tactile sensation (for example, thermal, mechanical and chemical)[147]. Although these sets of neurons are predominantly known for their role in conveying information to the brain, they can also locally release neuropeptides. In the context of neuro-immune interactions, the subpopulation of sensory C fibres, also known as peptidergic neurons, are the most extensively studied to date. These neurons secrete the neuropeptide substance P, calcitonin gene-related peptide (CGRP) and glutamate as their primary neurotransmitters[148,149]. They respond to a large variety of noxious stimuli, specifically heat[150], chemicals[151], inflammation-related factors[152,153] and bacterially derived molecules[73,77,154]. Sensory fibres were studied for their ability to communicate with cells of the immune system, especially in barrier tissues such as the skin[77,155], lung[156] and gut[157,158], where these neuronal innervations are particularly abundant, and reside in close proximity to immune cells. Immunohistochemical analysis of rat skin samples demonstrated that these peptidergic nerve endings are located close to lymphatic capillaries in the dermis and the subcutaneous layer[159]. Exposure to noxious stimuli triggers substance P and CGRP secretion, which was shown to have a functional impact on lymphatic drainage[160–162]. Studies also identified the direct effects of these sensory innervations on immune cell activity, demonstrating a protective role against endotoxaemia[163] and sepsis[164]. Selective genetic ablation of $TRPV1^+$ sensory neurons revealed their capacity to inhibit the recruitment of neutrophils to the site of infection via CGRP secretion[77]. This strategy was also applied to demonstrate the immunosuppressive role of sensory innervations in the lungs through their inhibition of neutrophil recruitment[156]. Moreover, activation of skin sensory neurons using optogenetics was shown to induce an IL-17 response[74]. Thus, the sensory nervous system can have a systemic effect on immunity by sending the sensory inputs to the brain, which in turn can regulate the peripheral immune response, and a local effect, by secreting neuropeptides directly in the tissue[165].

Meningeal lymphatic vessels

A different way in which the brain can affect immune activity is by introducing brain-specific antigens to the peripheral immune system. All tissues are monitored by resident or patrolling immune cells that collect information regarding the state of the tissue and potential invaders. These cells then travel to the lymph nodes via the lymphatic vessels, where they present antigens, inducing a relevant immune response. Recent studies have characterized the meningeal lymphatic vessels in the dura mater of the brain[166]. These vessels deliver antigens and immune cells from the brain to the lymph nodes and express lymphatic endothelial markers (for example, VEGFR3, CCL21 and PROX1)[167]. The lymphatic system surrounds the brain and drains excess fluid, proteins and immune cells from the tissue, which then reach peripheral lymph nodes[168]. Ablation of this meningeal lymphatic system in a mouse model of multiple sclerosis leads to diminished CNS disease and reduces the inflammatory response of T cells[169]. In a transgenic mouse model of Alzheimer disease, disruption of meningeal lymphatic vessels was shown to promote amyloid-β deposition in the meninges and aggravate parenchymal amyloid-β accumulation[170]. Thus, by transporting immune cells and antigens from the brain to the periphery, the meningeal lymphatic system can affect the peripheral and central immune response.

In summary, there are multiple lines of communication between the brain, the peripheral nervous system and the immune system. However, it is important to note that

these cues can affect not only the activity of immune cells but could potentially alter the function of other cell types, including epithelial, stromal and endothelial cells, as part of their capacity to initiate an integrated response. Some of these pathways, such as the endocrine and the systemic arm of the SNS, can induce rapid and extensive dissemination of information to the peripheral immune system. Other pathways, such as the local arm of the SNS and the PSNS, are characterized by their ability to deliver signals that are temporally and spatially localized. The effects of the sensory nervous system may be both local and systemic: the local signals are mediated by sensory neurons, which secrete neuropeptides in the tissue in which they are embedded; the systemic signals are sensory messages that are delivered to the brain, which can then induce a systemic response via any of the available descending pathways. The meningeal lymphatic drainage represents a somewhat different type of communication mode that can affect immune responses via specific signals that represent the state and needs of the brain itself.

Where in the brain?

The existence of distinct anatomical and functional communication routes between the nervous system and the immune system highlights the capacity of the nervous system to modulate immunity. Part of this communication, such as the local secretion of neuropeptides by sensory neurons, does not require the brain's direct involvement in the process. However, most of the neuro-immune interactions discussed in this Review depend on the brain and its unique capabilities.

To understand the brain's potential to regulate immunity, we must first identify brain centres relevant for such regulation and characterize how their activity affects immunity. Some insight into the areas that are potentially involved in the brain–immune system communication can be obtained from functional magnetic resonance imaging (fMRI) studies in humans. These studies demonstrate the activation of specific brain areas in response to peripheral acute and chronic inflammatory responses. A recent meta-analysis of 24 such studies revealed effects in the amygdala, hippocampus, hypothalamus, striatum, insula, midbrain, brainstem and prefrontal and temporal cortices during peripheral inflammation[171]. These effects on brain activity indicate that the brain is sensitive to changes in the peripheral immune system, but such fMRI studies cannot determine a causal effect between brain activity and immunity. Other, more mechanistic insights into brain areas relevant for immunoregulation emerge from immune analysis of patients with specific brain injuries and experimental studies in animals, in which we can monitor the immune changes following targeted lesions and manipulation of a specific brain region.

To generate a more comprehensive perspective of brain areas that are potentially involved in immune regulation, we catalogued these areas on the basis of their relevance to the concepts discussed in this Review: regulation of descending pathways from the brain, areas involved in integration and synchronization of physiological processes, and areas involved in prediction. Speed, which we indicated before to be another important advantage offered by the brain, is an intrinsic characteristic of the nervous system; thus, we do not expect it to be represented in a specific brain region. In a broader context, such a cataloguing approach can also be applied to identify brain areas involved in specific mental and emotional processes to understand how their activity can impact immunity (BOX 2).

In this section, we review the infrastructure needed to generate a conceptual map linking different forms of brain activity to the regulation of immunological processes (FIG. 3). Nevertheless, we must emphasize that such an approach requires oversimplification of the brain's complexity and by no means represents an exhaustive view of all the relevant brain areas or the complexity of neuro-immune interactions.

Brain regions involved in regulation of descending pathways

Brain areas involved in the regulation of descending neuronal and endocrine pathways, which send signals to the periphery and affect immune activity, are especially relevant to our discussion. Many of these regulatory centres are located in the brainstem. The brainstem is an evolutionarily conserved brain structure containing nuclei responsible for different physiological aspects of peripheral control by the brain. Here, we discuss mainly the areas involved in autonomic and endocrine regulation.

Autonomic regulation. Regulation of the ANS, although distributed throughout the brain, is associated with the activity of key areas; for example, the dorsal motor vagal nucleus, which regulates the PSNS[172], or the rostral ventrolateral medulla[173], locus coeruleus (LC)[174], A5 (REFS[175,176]) and the rostral raphe pallidus[177,178], which regulate sympathetic activity. Manipulation of these regions was previously associated with immune alterations. Optogenetic activation of C1 neurons in the rostral ventrolateral medulla, which innervates sympathetic and parasympathetic preganglionic neurons, was shown to protect mice from ischaemia–reperfusion injury by modulating T cell responses[179]. Chemical ablation of neurons in the LC and the A5 cell group in the brainstem of rats was accompanied by a decrease in cytokine production (IL-1β, IL-6 and TNF) by LPS-stimulated splenocytes[180]. In addition, ablation of LC neurons in rats suppressed the development of clinical signs of experimental allergic encephalomyelitis[181]. However, studies in a mouse model of Alzheimer disease showed that ablation of LC neurons resulted in increased neuroinflammation and neurodegeneration[182]. The LC also participates in the stress response[183,184], and it is activated by CRH. CRH administered into the LC in awake rats was shown to decrease blood and spleen T cell mitogenic responses to the phytohaemagglutinin concanavalin A[185]. Thus, activity of brain areas associated with ANS regulation appears to functionally impact peripheral immunity and can provide valuable insights into neuro-immune communication. However, it is important to bear in mind that any effects of these brain regions on the immune system might involve indirect communication via other CNS circuits, and may vary depending on the immune and psychological context.

Endocrine regulation. As previously mentioned, endocrine regulation is associated mainly with the hypothalamus and the pituitary gland. Modulation of hypothalamic neuronal activity was shown to affect immunity. Lesions to the paraventricular nucleus and the lateral hypothalamus affect the number of immune cells in the circulation[186,187]. Moreover, lateral hypothalamic lesions affect peripheral blood natural killer (NK) cell cytotoxicity[188], further supporting the relevance of this region for modulating immune activity.

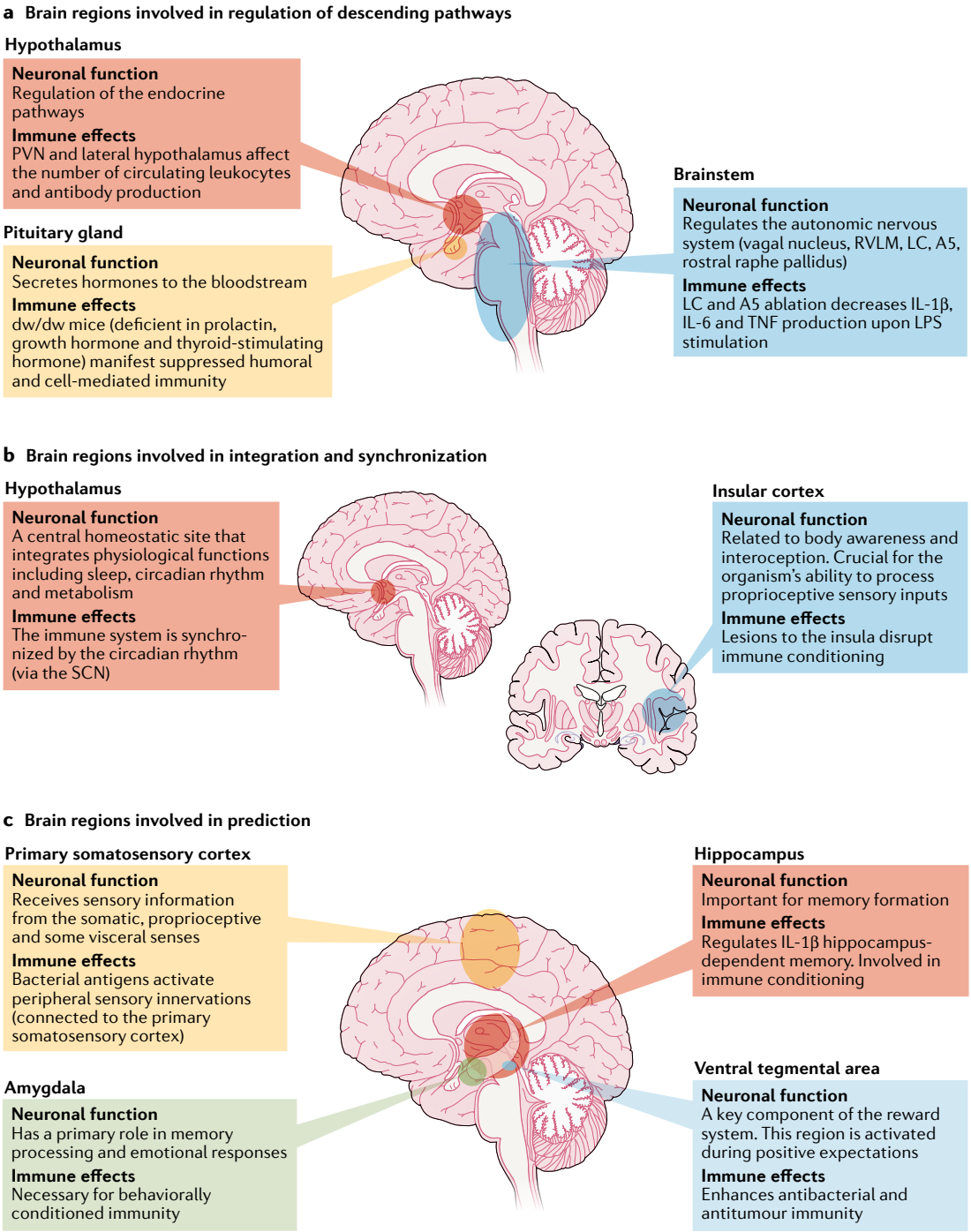


Fig. 3 | **Where? Where in the brain is immune information processed and regulated?** A schematic depiction of some representative brain regions relevant for brain–immune system communication organized based on their relevance to the key neuro-immune functions suggested in this Review. **a** | Brain regions involved in regulation of descending pathways: the hypothalamus, the pituitary gland and the brainstem. **b** | Brain regions involved in synchronization: the hypothalamus and the insular cortex. **c** | Brain regions involved in prediction: the primary somatosensory cortex, the amygdala, the hippocampus and the ventral tegmental area. For each brain area a single example of immune effects is provided in the associated boxes. LC, locus coeruleus; LPS, lipopolysaccharide; PVN, paraventricular nucleus; RVLM, rostral ventrolateral medulla; SCN, suprachiasmatic nucleus; TNF, tumour necrosis factor.

Neurons in the hypothalamus respond during peripheral inflammation[189,190], and some areas of the hypothalamus can directly sample the blood and release hormones to the circulation at specific sites called 'circumventricular organs'[191], which are characterized by dedicated fenestrations of the blood–brain barrier. It should be noted that the hypothalamus is composed of multiple neuronal nuclei, which are responsible for distinct physiological functions and are interconnected via reciprocal innervations. Thus, as we discuss in the next section, we expect other hypothalamic nuclei to have distinct impacts on the immune response. The hypothalamus is anatomically and functionally related to the pituitary gland. As indicated before, hormones secreted by the pituitary gland were shown to regulate the immune system[192–197]. For example, dw/dw mice (which are deficient in prolactin, growth hormone and thyroid-stimulating hormone) manifest suppressed humoral and cell-mediated immunity[197]. In general, the hypothalamus–pituitary complex is essential for the effective activity of the immune system.

Brain regions involved in integration and synchronization

Different brain processes are relevant for the integration and synchronization of the immune system with other physiological functions; these include the hypothalamus as a regulator of homeostasis, the insula, which acts as an interoceptive site, and other areas involved in processing pain, fear and stress. Here we focus on the hypothalamus and the insula.

As indicated before, the hypothalamus is a central homoeostatic site that integrates essential physiological functions. It receives inputs regarding the organism's metabolic state, satiety, thirst, temperature, circadian rhythm, sleep and other processes. Thus, the activity of the various hypothalamic nuclei can generate an orchestrated immune response, synchronized with the organism's physiological and behavioural functions. To integrate inputs from the periphery as well as inputs from other brain regions, the hypothalamus receives projections from numerous brain areas, including the brainstem, the hippocampus, the amygdala and cortical areas. Notably, one of the major sites that projects to the hypothalamus is the insular cortex. The insula is involved in body awareness. It receives sensory inputs regarding the positioning of the body (proprioception) and mediates processing of the internal state of the body (interoception). Therefore, insular activity is crucial for the organism's ability to detect proprioceptive sensory inputs representing the condition of the entire body and to execute corrective responses to maintain homeostasis[198,199]. The insular cortex receives multiple layers of information from the body (for example, inputs regarding tissue damage, metabolism and temperature)[199]. It integrates these inputs with other sensory and cognitive signals (for example, potential threats in the environment and past experiences) to trigger an orchestrated, corrective response that potentially includes immune activity. Indeed, immune challenges were shown to impact insular activity[200,201]. For example, a positron emission tomography study in humans showed that endotoxin administration is associated with increased metabolism in the insula[202]. Moreover, lesions to the insula were shown to disrupt immune conditioning[68,203].

Brain regions involved in prediction

There are different aspects of the brain's predictive capacity. These include different forms of memory and representation of relevant information, areas involved in regulation of behaviours that can expose the individual to potential immune challenges and areas involved in the processing of danger signals.

Prediction depends on previous experience, and thus builds on the memory capacity of the brain[204]. The most extensively studied aspect of memory in the context of immunity is immune conditioning. The specific brain areas involved in immune conditioning were studied in lesioning experiments induced by microinjection of toxin to a target area in the brain. It was shown that lesioning of the insular cortex and the amygdala disrupts the acquisition and evocation of immune conditioning[68]. These brain regions send projections to the nucleus of the solitary tract and other centres that regulate the ANS, indicating a possible route for brain–immune system communication. The dorsal hippocampus, which is known for its role in memory, was shown to be involved in heroin-associated contextual conditioning[205]. Heroin and other opioids negatively alter host immunity[206,207]. Accordingly, following repeated context–heroin pairings, exposure to the heroin-paired cue alone was sufficient to evoke heroin-conditioned suppression of LPS-induced peripheral immune response[208]. This form of association learning was shown to be mediated via IL-1β[209], and IL-1R1 antagonist disrupted the conditioned immune suppression[205].

Prediction can also stem from the anticipation of behaviours that typically expose the individual to pathogens, such as eating or mating. Eating introduces pathogens via food consumption, while mating and socializing expose the individual to bacteria and viruses carried by other individuals. Thus, brain areas involved in anticipation of these behaviours may induce some form of immune priming. We showed that activation of the reward system, specifically the ventral tegmental area, which is involved in positive expectations[210–212], primes antibacterial immunity[69]. Moreover, rewarding experiences are prone to repetition and hence to re-exposure to the same pathogens. Accordingly, exposure to a specific bacterium following reward system activation resulted in the formation of a stronger delayed-type hypersensitivity response[69], suggesting that pathogens encountered following reward system activation can induce stronger immune memory.

Brain areas that encode the novelty of an experience and predict a potential danger may also be relevant for immune activation. Behaviourally, the capacity to predict a potential threat embedded in new experiences is evident in the form of neophobia. For example, rodents presented with highly palatable solutions of saccharin will consume small amounts on the first exposure; on subsequent exposures, the animal learns the new stimulus is harmless and drinks more. On the basis of lesion and early neuronal activation studies (for example, involving FOS)[213], several areas were implicated in

neophobia, including the basolateral region of the amygdala, the medial amygdala, the insular cortex and the gustatory region of the thalamus. For example, lesioning of the basolateral amygdala attenuated the neophobic reaction to a novel saccharin solution[214]. Although novel experiences can indicate a potential danger that is also relevant for immune regulation, these areas were not specifically investigated in the context of immune activity. Analogously, one can expect that areas encoding negative odours and taste will also have a predictive value for regulating the immune response.

Another important mechanism for prediction of an upcoming danger is pain. The danger theory formulated by Matzinger[215] suggests that the immune system distinguishes between stimuli that can cause damage and stimuli that are benign. Following the same reasoning, pain provides information regarding the impact imposed by a given threat. Indeed, pain-sensing neurons were shown to affect immunity[73,216]. For example, in a mouse model of psoriasis, a subset of TRPV1$^+$ pain sensory neurons were shown to regulate the IL-23–IL-17 pathway and have an important role in cutaneous immunity[217]. However, these studies focused mainly on peripheral pain processing, and we have far less understanding of how the central processing of pain impacts the immune response. Multiple pathways in the CNS are involved in pain processing. The brain areas most commonly activated by noxious stimuli are the primary somatosensory cortex, the secondary somatosensory cortex, the anterior cingulate cortex, the insula, the prefrontal cortex, the thalamus and the cerebellum[218]. These regions receive nociceptive input from the periphery via specialized pathways in the spinal cord, the medulla and the periaqueductal grey[219,220]. The periaqueductal grey, one of the primary control centres for pain modulation, was previously implicated in immunomodulation. Stimulation of this region suppresses peripheral NK cell and T cell functions[221–224], providing additional evidence that areas involved in central processing of pain can affect immunity. Thus, pain, similarly to other cognitive, emotional and homeostatic processes that are integrated by the brain, may also serve as a CNS-integrated guiding cue for the immune system.

In conclusion, in this section we attempted to provide a selected example of the brain areas that are potentially relevant for brain–immune system communication. We focused on areas involved in prediction, integration and synchronization of central and peripheral inputs, and regulation of the brain's output to the periphery. This non-exhaustive list is only one possible approach to generate a framework to study neuro-immune interactions. Moreover, it is important to keep in mind that in spite of our artificial cataloguing, different brain areas are interconnected and interdependent. Thus, the same brain area may be involved in different functions, and their outputs may vary under different internal and external conditions.

Summary

For many decades the nervous and immune systems were studied independently, but it is now recognized that these systems communicate and that these intricate connections impact physiological adaptations in both health and disease. The brain integrates different types of inputs reflecting the internal state of the organism, the external environment and memories acquired in past experiences. The brain uses this integrated view of the organism and its surroundings to execute a synchronized and orchestrated physiological response, in which the immune system plays a central role. There are multiple pathways that enable the brain to convey its messages to the periphery and regulate immune reactions. It can regulate the secretion of hormones carried by the blood to the entire organism or deliver localized messages to specific tissues, which are innervated by sensory, sympathetic and parasympathetic neurons. Concomitantly, immune cells and other cell types express the relevant receptors required to respond to these signals. These neuro-immune interactions have the capacity to rapidly shape immunological processes in a context-dependent manner. Nevertheless, there are major gaps in our understanding of these complex interactions at every level, starting from the nature of the signals perceived by the brain, their processing by the brain, the kind of outputs delivered by the brain and how they vary depending on the specific context. Moreover, the relative contribution of the nervous system to immunoregulation is unclear. Namely, does the nervous system merely modulate ongoing immune reactions or is there a top-down control of the immune processes.

One strategy to fill these and other gaps in our knowledge, and to make sense of a very complex system, is to generate maps. For example, these would include maps of brain areas that modulate immune processes and the effects of these areas on immune activity under different physiological and psychological conditions. Moreover, although we discussed some of the communication pathways between the brain and the periphery, it is important to understand that our knowledge of these pathways is still limited. For example, we have limited information regarding the SNS and PSNS inputs to specific organs, the factors these nerves secrete at different target sites and how are they regulated. Thus, maps of the pathways connecting the two systems will be especially useful.

We also lack a proper characterization of the peripheral cells that can respond to these signals. It is clear that immune cells and other cells in the periphery express an arsenal of receptors for factors produced by neural tissue. However, these are mainly scattered pieces of evidence that lack the coherent perspective of the expression profiles and how they vary in different physiological and pathological conditions. Thus, we need to generate a comprehensive map of the receptor's expression profiles on immune cells in naive and disease states (for example, autoimmune diseases, cancer, viral infection and bacterial infection). Many of the tools required to address these questions (for example, single-cell RNA sequencing) and the computational capacity to process the huge resulting datasets are becoming available. Thus, we are encountering a unique opportunity to uncover a new frontier in physiology, one that will hopefully allow us to harness the brain's therapeutic capacity.

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