Review

The neuroimmune connectome in health and disease

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The nervous and immune systems have complementary roles in the adaptation of organisms to environmental changes. However, the mechanisms that mediate cross-talk between the nervous and immune systems, called neuroimmune interactions, are poorly understood. In this Review, we summarize advances in the understanding of neuroimmune communication, with a principal focus on the central nervous system (CNS): its response to immune signals and the immunological consequences of CNS activity. We highlight these themes primarily as they relate to neurological diseases, the control of immunity, and the regulation of complex behaviours. We also consider the importance and challenges linked to the study of the neuroimmune connectome, which is defined as the totality of neuroimmune interactions in the body, because this provides a conceptual framework to identify mechanisms of disease pathogenesis and therapeutic approaches. Finally, we discuss how the latest techniques can advance our understanding of the neuroimmune connectome, and highlight the outstanding questions in the field.

Adaptation to environmental changes is essential for survival, and requires the coordinated activity of the nervous and immune systems. However, early studies[1,2] suggested that immune activity was limited in the CNS[3], and that the nervous and immune systems operated independently. These ideas have since been abandoned, and we now know that neuroimmune interactions involving classic immune pathways[4] and neural circuits[5–9] participate in development and homeostasis, and when dysregulated, drive tissue pathology.

It is therefore important to understand the fundamental elements of neuroimmune interactions. We define neuroimmune interactions as a specialized case of cell–cell communication involving a cell of the nervous system and an immune cell, which could be either tissue-resident or recruited from circulation. This communication should modify the activity of at least one of the cells involved. By this definition, microglia–neuron and microglia–astrocyte interactions contain the fundamental elements of neuroimmune communication. By contrast, although the innervation of muscle by brain projection neurons or peripheral neurons may trigger cytokine production, it does not meet the definition of a neuroimmune interaction because it does not involve an immune cell.

This operational definition enables us to redefine the neuroimmune connectome, which was originally described as "a detailed map of connections, interactions, and interdependencies between different immune cell–derived molecules…and neural circuits"[10], as a detailed map of all the interactions between cells of the nervous and immune systems throughout the body. With this framework in place, we discuss the functions and regulation of the neuroimmune connectome, and the tools to investigate it, alongside open questions in the field.

Neurodegeneration

Prior to recent advances studying the anatomical sites of neuroimmune cross-talk, an understanding of the importance of neuroimmune interactions was born out of research on neurological diseases[11]. For example, histopathological studies of multiple sclerosis (MS) dating back to the nineteenth century began to show how the CNS responds to the peripheral infiltration of immune cells[12]. Indeed, CNS-resident cells undergo profound changes in response to inflammation and neurodegeneration[13,14]. Furthermore, we now know that the CNS is seeded early in development by immune cells[15], which have important roles in development, homeostasis and pathology[16]. Thus, the neuroimmune connectome has emerged as a complex involving multiple activation states and interactions between neurons, glia and immune cells.

T cells and neurodegeneration

The role of microglia and other CNS-resident immune cells in neurodegeneration has been extensively discussed elsewhere[16]. However, there is increasing interest in the role in neurodegenerative diseases of neuroimmune interactions involving CNS-recruited peripheral immune cells, such as T cells, which are classically considered to be a feature of autoimmune diseases such as MS[14,17] (Fig. 1). Patients with Alzheimer's disease display increased T cell reactivity to amyloid-β[18]. Indeed, clonally expanded cytotoxic $CD8^+$ T cells are detected in the cerebrospinal fluid (CSF) of patients with Alzheimer's disease[19]. Moreover, in an experimental tauopathy model, microglia trigger $CD8^+$ T cell-dependent neurotoxicity[20]. Similarly, $CD8^+$ T cells react with α-synuclein in Parkinson's disease[21,22]. Interestingly, $CD8^+$ T cells reactive with β-synuclein promote grey matter neurodegeneration in patients with MS and animal models[22], indicating

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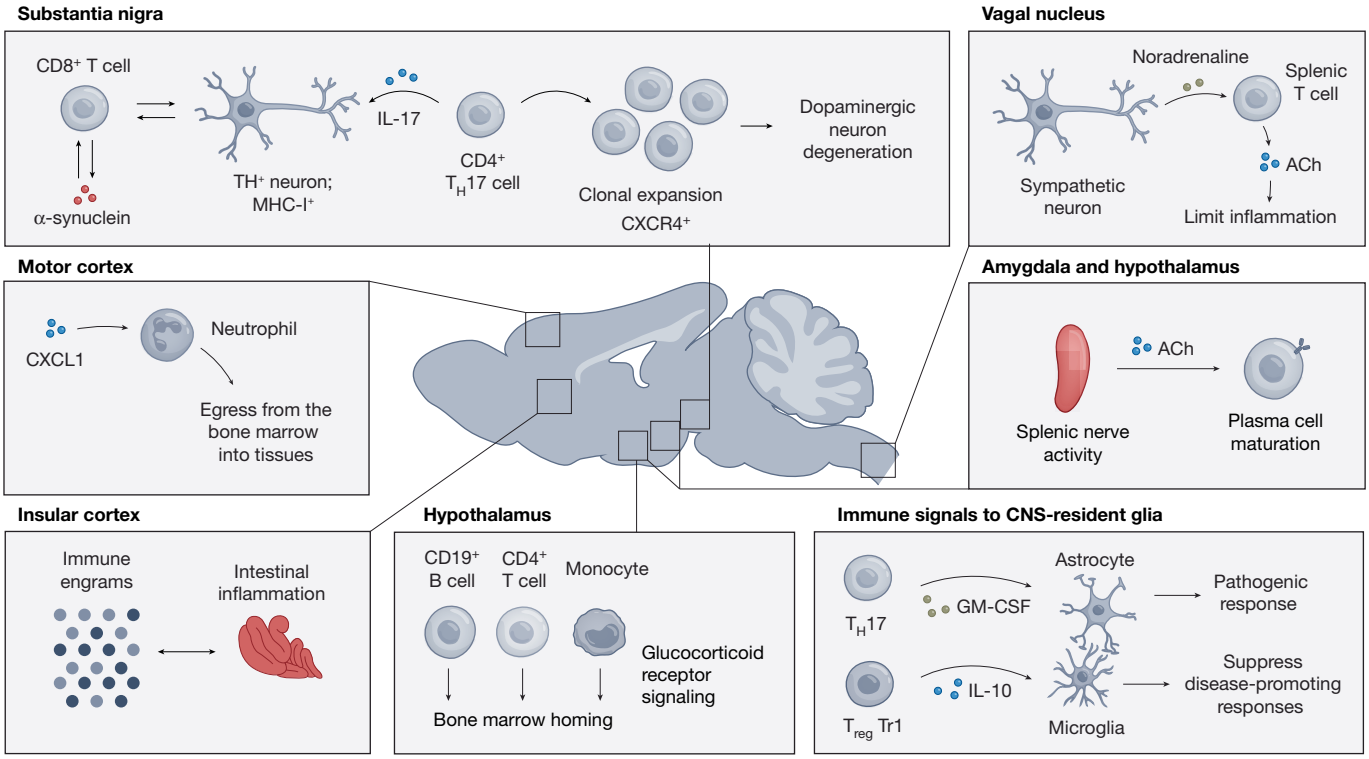

Fig. 1 | Neuroimmune interactions in inflammation and neurodegeneration. Selected neuroimmune interactions and their effects on tissue pathology. ACh, acetylcholine; TH, tyrosine hydroxylase; Tr1, type 1 regulatory T cell.

that dysregulated T cell responses promote neurodegeneration in multiple neurological diseases. Furthermore, T cells limit the regenerative potential of neuronal stem cells and neurons in mice and humans in the context of ageing[23,24]. Given the now-classical reports of neuronal major histocompatibility complex I (MHC-I) expression in learning-dependent plasticity[25] in mice, these findings indicate that the stimulus-dependent regulation of MHC-I, co-stimulatory molecules and cytokine expression in neurons[26] may modulate $CD8^+$ T cell-driven pathological neuroimmune interactions in neurodegenerative disorders, and even in ageing[27,28].

$CD4^+$ T cells have also been implicated in neurodegeneration, for example in Lewy body dementia-associated neurodegeneration in mice and humans[29]. $CD4^+$ T helper cells producing interleukin-17 (IL-17; T_H17 cells) adjoin tyrosine hydroxylase-positive dopaminergic neurons in the substantia nigra, a brain region that degenerates in Lewy body dementia and Parkinson's disease. These T_H17 cells display signs of clonal expansion, express C-X-C motif chemokine receptor 4 (CXCR4) and are associated with dopaminergic neuron degeneration. Interestingly, $CXCR4^+$ T_H17 cells have also been described to contribute to MS pathogenesis[30,31]. Thus, T_H17 cells and the death of dopaminergic neurons could be linked to pathogenesis in both Parkinson's disease and MS, and potentially in other disorders as well.

Immune cell control of neurodegeneration

CNS-reactive T cells can also promote tissue repair, as reported in models of optic nerve injury[32]. Based on these and other findings, it was proposed that 'interoceptive T cells' develop in the thymus with the ability to perceive, interpret and act on tissue cues to promote homeostasis and repair[33]. Thus, specific neuroimmune interactions driven by T cells could be therapeutically induced to promote tissue repair. Indeed, the controlled activation of CNS-reactive T cells is beneficial in certain contexts. For example, regulatory T cell (T_{reg} cell) ablation decreased pathology[34] in preclinical models of Alzheimer's disease, highlighting key differences with CNS autoimmunity where immune checkpoint blockade worsens CNS pathology[35], probably reflecting the targeting of different T cell subsets and also the existence of a broader repertoire of activated CNS-reactive T cells in the latter. These findings highlight challenges linked to the therapeutic exploitation of interoceptive T cells, which could be circumvented by the use of mRNA-engineered T cells bearing selected self-reactive T cell receptors (TCRs) to control their specificity and phenotype[36].

T cell interactions with glial cells such as astrocytes[13] also have important roles in CNS inflammation and neurodegeneration[37,38]. This is exemplified by the activation of pathogenic astrocyte responses by T cell-derived granulocyte–macrophage colony-stimulating factor (GM-CSF)[39] and, conversely, by the activation of cytotoxic $CD8^+$ T cells by astrocytes[40]. Even so, neuroimmune interactions between specific T cell and astrocyte subsets can also limit CNS pathology. A subset of astrocytes lining CNS borders in mice and humans express TNF-related apoptosis-inducing ligand (TRAIL), which induces apoptosis in pro-inflammatory T cells as they access the CNS[41]. Alternatively, IL-10 and other anti-inflammatory molecules produced by regulatory T cells suppress disease-promoting glial responses in mice[42,43]. Similar roles in CNS pathology and repair have also been described for neuroimmune interactions involving other peripheral immune cells, such as B cells[44], natural killer (NK) cells[41], monocytes[45] and neutrophils[46].

Bidirectional neuroimmune interactions involving CNS-resident immune cells have also been described. Microglial products can either promote or suppress astrocyte pro-inflammatory responses[47–50]. Conversely, astrocyte surface molecules such as EPHB3 (ref. 51) and astrocyte production of GM-CSF[52,53] or the related cytokine IL-3 (ref. 54) boost pathogenic microglial responses in experimental autoimmune encephalomyelitis (EAE) and MS. Of note, IL-3-mediated astrocyte–microglia communication is protective in models of Alzheimer's disease[55], indicating that there are context-dependent effects of neuroimmune circuits that probably involve other CNS resident cells, such as oligodendrocytes and neurons[56–61].

Together, these studies implicate multiple immune cell lineages in neuroimmune interactions. A significant challenge in the field is to understand the totality of the neuroimmune connectome and its disease-associated perturbations that promote CNS pathology in human diseases and their preclinical models. Future studies should leverage the power of single-cell genomics and in situ biology to identify and map interacting cell subsets and interaction mechanisms, in combination with cell-tracing approaches to define the origin of the interacting immune cells; for example, immune cells originating from the gut[41] or skull bone marrow[6,7,62].

Neural circuit–immune cell cross-talk

The neuroimmune interactions described above participate in the direct and indirect control of neural circuit integrity. However, neuroimmune interactions also mediate the control of the immune response by specific neural circuits, as well as the regulation of neural circuit activity by the immune response. Inside-out (from the CNS to the peripheral immune system) and outside-in (from peripheral immune cells to the CNS) neuroimmune signalling differ in the mechanisms of communication involved. Inside-out neuroimmune signalling involves signals emanating from the CNS through neural projections that act on immune cells either directly, or indirectly through intermediary peripheral neurons[63]. These mechanisms contrast with those used by outside-in neuroimmune signalling, which usually involve local ligands and receptors interacting in the absence of cellular processes that span the body. The architecture of these interactions enables the modulation of immunity by CNS-derived signals (Fig. 1).

Inside-out signalling

A classic example of peripheral immune cell modulation by the CNS is the sympathetic reflex arc that controls T cell activation during sepsis[64]. In this case, activation of the vagus nerve releases acetylcholine onto sympathetic neurons in the coeliac ganglion, the fibres of which release noradrenaline onto splenic T cells, which then secrete acetylcholine in the spleen to limit endotoxin-induced inflammation in mice and humans[65,66]. Similar mechanisms control B cells in mice, in which B cell follicle formation and plasma cell maturation are reported to be regulated in an acetylcholine-dependent manner by splenic nerve activity driven by the central amygdala or the paraventricular nucleus of the hypothalamus[67]. Beyond autonomic neurons, sensory neurons cross-talk with NK cells and neutrophils in mouse inguinal lymph nodes[68]. Nociceptor-derived calcitonin gene-related peptide (CGRP) boosts skin dendritic cell antigen presentation through IL-1β production[69]. Related studies have uncovered important links between sensory neuron peptides, innate lymphoid cells and T cells[70–73].

Finally, an elegant study has identified central circuits in the brain that control monocyte, lymphocyte and neutrophil circulation and homing after acute stress in mice[74], with similar findings in humans[75]. Hypothalamic paraventricular nucleus neurons mediated these effects in mice through glucocorticoid receptor signalling acting on $CD4^+$ T cells, $CD19^+$ B cells and inflammatory monocytes to induce bone marrow homing, and motor cortex activity on muscle induced C-X-C motif chemokine ligand 1 (CXCL1) production, which drove neutrophil egress from the bone marrow and into tissues[74]. Interestingly, even short perinatal exposure of mice to glucocorticoids can induce long-lasting alterations of the hypothalamic–pituitary–adrenal axis that impair $CD8^+$ T cell-mediated anti-tumour immunity in adulthood[76], identifying a potential mechanism by which the activation of stress-responsive circuits early in life can induce persistent perturbations of the neuroimmune circuits that control the immune response.

Outside-in signalling

The inside-out and outside-in neuroimmune circuits associated with specific environmental stimuli or stressors are intricately related, as further illustrated by stress models. A study of the immune response linked to psychological stress in mice and humans established that monocyte-derived matrix metalloproteinase 8 disrupts the stability of the blood–brain barrier (BBB) in the nucleus accumbens, leading to social deficits induced by chronic stress[77]. These changes in social behaviour were controlled by IL-6 (refs. 78,79), a cytokine produced by brown adipocytes during chronic stress[80]. Related work has shown that IL-13 produced by meningeal type 2 innate lymphoid cells contributes to inhibitory synapse formation during development, which is important for normal social behaviour[81]. Strikingly, these data may suggest specificity on both the central circuits involved and their upstream immune cell partners.

One of the most exciting findings related to outside-in signalling is the ability of the brain to encode and recapitulate previous immune experiences. Specifically, it was reported that mouse insular cortex neurons are activated by intestinal inflammation; their chemogenetic reactivation recalls the intestinal immune responses that initially triggered them[82]. More recently, neuron activity in the vagal nucleus or caudal nucleus of the solitary tract brainstem was shown to attenuate multiple types of peripheral inflammation, and silencing it resulted in dysregulated inflammatory responses[83]. Conversely, activity in a Dbh^+ subpopulation of brainstem neurons in the nucleus of the solitary tract and nucleus ambiguus worsened allergic lung inflammation[84]. These findings indicate that select neural circuits have a role not only in the regulation of the immune response, but also in immune memory, through unexplored mechanisms. For example, recent work identified epigenetic memory programs in astrocytes that alter their subsequent response to immune restimulation[85], and similar mechanisms probably operate in other CNS cells[86]. Thus, it is important to define how memories of peripheral and CNS inflammation, the neuroimmune interactions that modify them, and the potential engrams[87] that constitute them are connected and linked to behaviour.

Together, these studies highlight important roles for the nervous system in immune regulation. Although we focused in the CNS, similar mechanisms operate in the periphery, for example involving the enteric[88] and sensory[89] nervous systems. These and other studies suggest the following common principles: first, central and peripheral neurons control immunity; second, immune cells can serve as neural surrogates by releasing neurotransmitters; and third, neurons can store immune experiences. Nevertheless, there are still some outstanding questions. For instance, it is not known whether only certain neurons are capable of storing and retrieving immune memories. There is uncertainty over the role of glial cells in encoding memories of peripheral immune state changes. Further work is needed to explore the full spectrum of immune responses induced by neuropeptides, akin to the cytokine dictionaries of the immune system[90]. Finally, the totality of cellular partners in the immune system regulated by neural activity remains to be completely defined. Similar questions remain about whether all neurons and glia can respond to immune stimuli, or whether specialized subsets of cells participate in neuroimmune interactions instead.

Behaviour

The neuroimmune connectome has a central role in multiple aspects of behaviour, including sickness and depression[91,92] (Fig. 2). For example, discrete neural circuits express receptors for immune mediators produced during peripheral inflammatory responses[91]. Neurons localized to limbic areas or circumventricular organs that sense these peripheral cues orchestrate complex behavioural responses to sickness. Moreover, immune cells adjacent to or inside the brain influence behavioural responses during chronic stress, stroke or inflammatory challenges. Below, we discuss how behaviour is shaped by peripheral inflammatory responses and immune cell recruitment to the CNS.

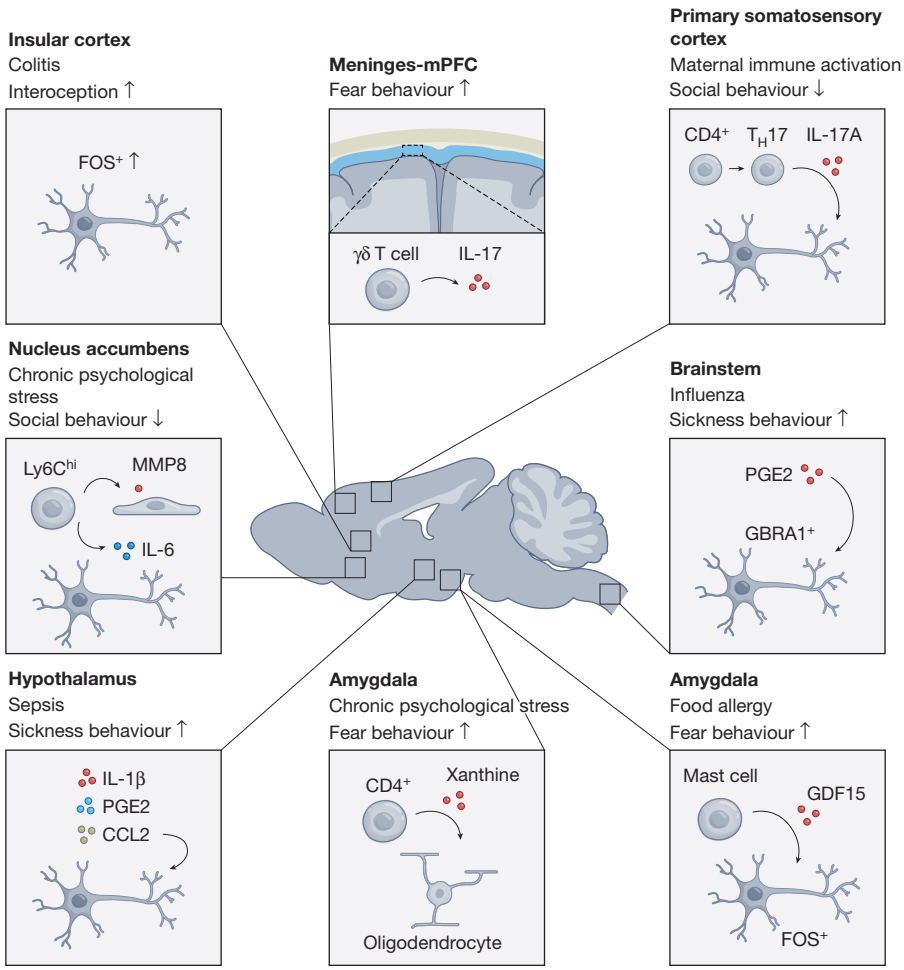

Fig. 2 | Brain areas responsive to immune cues. Brain nuclei and the mechanisms that regulate them in the context of immunological or behavioural perturbations. γδ T cell, γδ TCR-expressing T cell; GBRA1, $GABA_A$ receptor subunit 1; GDF15, growth/differentiation factor 15; Ly6C^{hi}, pro-inflammatory monocyte; MMP8, matrix metalloproteinase 8; mPFC, medial prefrontal cortex; PGE2, prostaglandin E2.

Non-sickness behaviours

It has been shown that xanthine produced by CD4$^+$ T cells promotes stress-induced anxiety-like behaviour through a mechanism involving oligodendrocytes[93]. These findings are consistent with reports of increased fear responses linked to dysregulated T cell responses in the absence of immune checkpoint molecules such as PD-1 (ref. 94). Similarly, activation of CD4$^+$ T cells in maternal immune activation (MIA) paradigms induces T_H17-dependent social behaviour deficits in the F_1 progeny by disrupting the sensory cortex[95]. Other studies support a role for IL-17 in the control of behaviour, because IL-17 produced by meningeal γδ TCR-expressing T cells reportedly boosts fear responses through its effects on medial prefrontal cortex neurons[96].

Beyond T_H17 cells, CX3CR1$^+$ monocytes were linked to MIA-associated impairments in motor learning through synaptic pruning, potentially through TNF[97]. Furthermore, monocyte CNS infiltration has been linked to increased fear behaviour and altered memory in a myocardial infarction model[98], potentially explaining the reported links between cardiac activity and affective behaviour[99]. Similar mechanisms operate in human and experimental Langerhans cell histocytosis, in which myeloid cell infiltration was linked to increased fear behaviour[100], highlighting important roles of monocytes in the control of fear-related neural circuits.

Besides these outside-in neuroimmune mechanisms mediated by immune cells, stress-induced immune cell products in the circulation can directly control behaviour-related neural circuits in limbic nuclei[101,102]. For example, stress-induced BBB breakdown facilitates IL-6 entry into the nucleus accumbens to induce anhedonic behaviour[78]. Moreover, astrocyte responses driven by NF-κB, which is a transcription factor activated by pro-inflammatory cytokines such as IL-6, have been shown to promote anhedonic phenotypes in mice[103].

Conversely, some immune cell products protect against behavioural deficits. IFNγ and IL-13 derived from meningeal immune cells promotes social behaviour by tuning GABAergic interneurons[81,104], and T cell-derived IL-4 supports learning and memory[105]. Together, these studies illustrate the interplay between peripheral immune activation and its effects on defined neural circuits mediated by specific immune cell products (such as metabolites and cytokines). However, most studies analysed individual immune cell products in isolation. Based on the immunometabolic regulation of CNS cells[106] and immune cells[107,108], future study is needed on the effects of complex combinations of metabolites and cytokines on behaviour. Indeed, it should also be considered that multiple metabolites important for CNS physiology, such as lactate[109,110], are potent immunomodulators[108,111]. These findings also call for the study of specific immune-responsive neural circuits involved in distinct aspects of behaviour.

Sickness behaviours

The relationship between the activation of specific neural circuits relevant for sickness behaviours and discrete classes of peripheral immune cells has recently been evaluated. For example, allergic sensitization of the gut induces IgE production by B cells[112,113], which, through

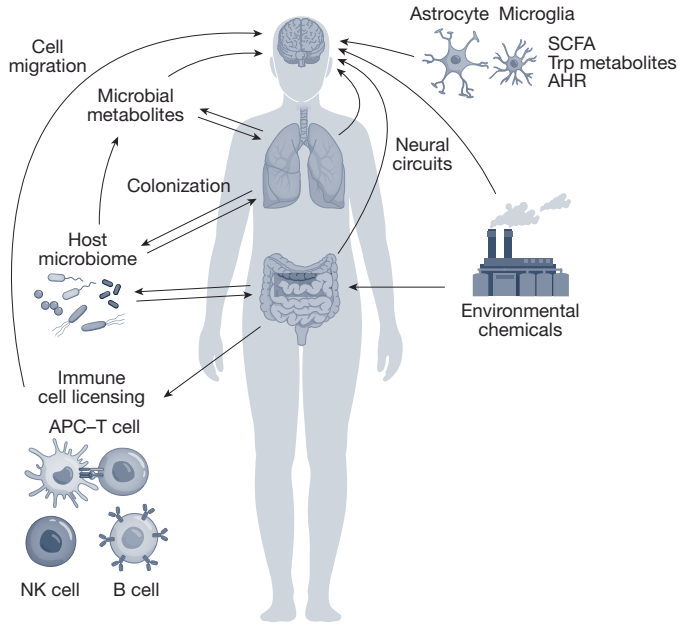

Fig. 3 | Environmental regulation of the neuroimmune connectome. Environmental factors, such as the host microbiome and environmental chemicals, modulate immune and neural cell responses throughout the body. The schematic shows the host microbiome influencing multiple tissues, including the lung and intestines, and producing microbial metabolites that signal to the brain. AHR, aryl hydrocarbon receptor; APC, antigen-presenting cell; SCFA, short-chain fatty acid; Trp, tryptophan.

a mast cell-dependent mechanism, induces antigen avoidance by activating brain areas linked to interoception and fear-related behaviour, including the central amygdala, parabrachial nucleus and nucleus of the solitary tract[112]; the interoceptive pathways underlying these deficits remain under active investigation[113].

These findings complement studies of the circuits underlying sickness behaviour[114]. Intriguingly, in response to lipopolysaccharide or poly(I:C), one study detected activation of the hypothalamic ventromedial preoptic area through IL-1β, prostaglandin E2 or C-C motif chemokine ligand 2 (CCL2). ADCYAP1$^+$ peptidergic neurons in the nucleus of the solitary tract and the area postrema are key mediators of sickness behaviour[115]. The reactivation of these neurons recapitulates the behavioural changes induced by lipopolysaccharide injection. Similarly, prostaglandin E2 produced in response to influenza infection signals to glossopharyngeal sensory neurons innervating the nasopharynx, transmitting these signals to the brainstem[116]. These studies in mice demonstrate the direct sensing of microorganism-triggered immune activity by peripheral and central neurons, which, in combination with immune cells acting on these neural circuits, influence a variety of complex behaviours.

In summary, immune system activation affects specific brain circuits, altering long-term plasticity and behaviour. These findings beg the question of how long-lived the neural responses to peripheral immune signals are, and how they compare with neural responses driven by immune cell CNS infiltration. These responses to peripheral immune factors may be influenced by differences in BBB integrity, for example between areas that lack a BBB[117] to those with induced BBB leakiness such as the nucleus accumbens or amygdala[78,118]. Thus, the activity of a neural circuit may locally affect BBB integrity, and the responsiveness of the circuit to immune modulation may be modulated by the BBB.

Environmental impact on neuroimmune interactions

Environmental factors such as microorganisms and environmental chemicals regulate the activity and interactions of the immune and nervous systems (Fig. 3). Dietary factors, including tryptophan and short-chain fatty acids, have been shown to tune the responses of both CNS and immune cells. However, it is challenging to study the effects of environmental factors on the immune and nervous systems because multiple factors usually operate in parallel, and the signalling mechanisms triggered by each factor are unknown. A further difficulty is that environmental exposures may precede the onset of their pathological effects by decades. Thus, a central challenge in neuroimmunology is to isolate causal relationships between environmental factors and the responses of cells across the CNS and immune system.

Environmental chemicals

The exposome is defined as the totality of the environmental exposures faced by an organism in its lifetime[119], including infections and the commensal flora[120]. Multi-omic approaches have identified environmental exposures that modulate multiple biological processes linked to specific disorders[121], for example aryl hydrocarbon receptor ligands[122,123]. To define the mechanisms through which exposures act, platforms based on the analysis of environmental chemical libraries have been developed[124], using a combination of zebrafish and mouse preclinical models, machine learning and clinical samples[125,126]. This and similar approaches[127] have defined mechanisms and neuroimmune interactions that regulate inflammation and are regulated by environmental factors, including the SigmaR1–XBP1 axis, which controls astrocyte proinflammatory responses[126]. These platforms will help to identify neuroimmune interactions regulated by environmental factors, an important point given the multifactorial contribution of the environment to human disorders[121].

Microbiota

The microbiome associated with different tissues, such as the gastrointestinal tract and the lung, modulates neuroimmune interactions through direct and indirect mechanisms, with important consequences for neurodegeneration, behaviour and immunity. Classical studies showed that the gut microbiome controls spontaneous T cell CNS autoimmunity in mice bearing transgenic self-reactive T cells and B cells[128]. Related studies defined the molecular mechanisms, including microbial metabolites, that are involved in the microbial control of T cell responses in mice[129,130]. Other immune cell types such as B cells[44,131] and NK cells[41] are also modulated by the intestinal microbiome and migrate to the CNS, establishing neuroimmune interactions with resident cells. In the periphery, microbially regulated interactions between T_H17 cells and sensory neurons mediated by IL-17–IL-17RA signalling promote the regeneration of sensory neurons in mice[132], raising some interesting possibilities about the existence of similar mechanisms in the CNS. Although less studied, the commensal microbiome in other tissues besides the gut (notably the lung) has also been shown to control neuroimmune interactions driven by CD4$^+$ and CD8$^+$ T cells, B cells and myeloid cells in the CNS[133,134].

Similar studies established key links between the gut microbiome and perturbed neuroimmune interactions resulting in long-term behavioural deficits. For instance, gut microbiome perturbations induced by MIA[135] license T_H17 cell-driven behavioural abnormalities in mice offspring[136]. The diet also influences neuroimmune interactions, as exemplified by metabolites of dietary tryptophan, which regulate murine and human astrocyte–microglia neuroimmune interactions[48,137] that are also responsive to environmental chemicals[125]. Similarly, a high-salt diet supports intestinal T_H17 cells that promote cognitive deficits[138], and meningeal T_H17 cells that act on border-associated macrophages to promote behavioural deficits in a hypertension mouse model[139]. These studies highlight the direct and indirect environmental control of neuroimmune interactions.

The commensal flora not only regulate CNS neuroimmune interactions directly through BBB-permeable metabolites across species[48,137,140–142], they also regulate CNS activity indirectly through the

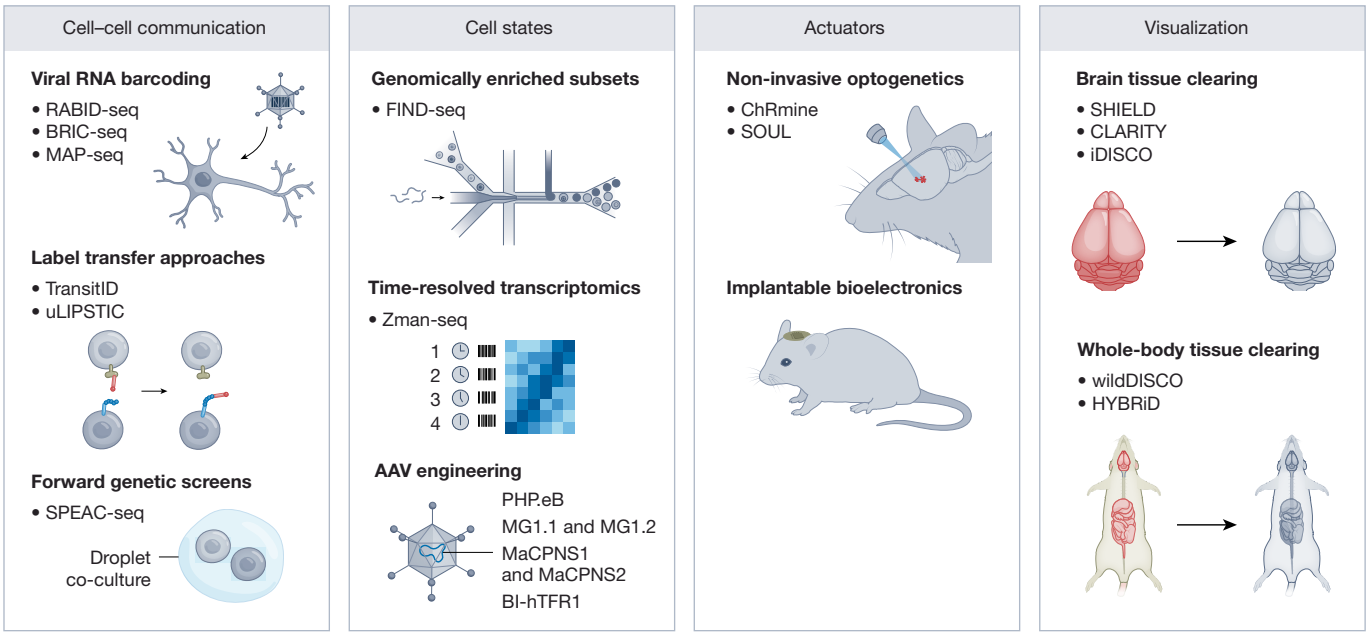

Fig. 4 | Technologies used to study neuroimmune interactions. Many tools exist that have great potential to decipher neuroimmune interactions, but each class of technologies possesses unique strengths and weaknesses. Actuator technologies provide excellent temporal and spatial resolution but lack detailed longitudinal molecular information on the cells targeted (such as the transcriptome). Specialized methods to study cell–cell communication enable connectome studies linked to molecular data but lack high temporal resolution. Visualization strategies enable systematic anatomical mapping but provide only a snapshot of cellular dynamics and are limited in the number of read-out channels. Technologies to investigate cell states enable specialized molecular and temporal analyses but have low spatial resolution. AAV, adeno-associated virus.

control of peripheral neurons. In one study using mice, the microbiome was linked to the motivation to exercise mediated by the ventral striatum, specifically through the peripheral production of endocannabinoids that act on afferent sensory neurons[143]. Together, these studies reveal complex mechanisms by which the microbiota influence neuroimmune interactions that are relevant for CNS development, homeostasis and pathology. Moreover, these studies also suggest therapeutic avenues to target directly or indirectly neuroimmune interactions, based on the depletion[144] or administration of microbial products or their synthetic analogues[145], or engineered probiotics for the production of therapeutic molecules in vivo[108,146].

Sleep

Sleep is recognized as an important environmental factor severely affected by modern life patterns; its perturbation affects multiple aspects of physiology[147], including neuroimmune interactions. Melatonin, a pineal gland hormone involved in the regulation of the sleep–wake cycle, modulates $CD4^+$ T cell polarization and tissue inflammation[148]. Moreover, sleep-induced hypocretin suppresses CSF1 production in mice and, consequently, bone marrow monocyte maturation and atherosclerosis[149], and sleep disruption triggers monocytosis and worsens atherosclerosis. Similarly, in animal models of cardiac disease and in human patients, peripheral macrophages accumulate in the superior cervical ganglia[150], inducing sympathetic denervation of the pineal gland and sleep disruption, potentially driving a positive feedback loop of inflammatory myelopoiesis.

Further links between the immune response and sleep may underscore these findings. For example, prolonged sleep deprivation induces a cytokine storm-like phenotype linked with neutrophil and monocyte mobilization and PGD2 signalling in brain endothelium[151]. Conversely, dysregulated $CD4^+$ and $CD8^+$ T cells targeting hypocretin$^+$ hypothalamic neurons have been linked to the pathogenesis of human narcolepsy[152,153]. Future studies in this area are likely to identify specific mechanisms by which modern lifestyles affect disease-relevant neuroimmune interactions, as well as potential interventions to minimize their impact.

In summary, environmental factors shape the neuroimmune connectome by influencing the activity of immune and CNS cells. One outstanding challenge in the field is to decipher the relative contribution of each environmental factor in the complex mixture of exposures that simultaneously act on humans. Computational approaches, such as those used in systems immunology[154], may help to decipher the links between environmental perturbations and altered neuroimmune interactions. Together, the integration of tools for lineage tracing, spatial profiling, environmental perturbations and computational analysis might help to reveal the effects of specific environmental factors on neuroimmune interactions and the mechanisms involved.

Tools to probe neuroimmune cross-talk

The complexity of cell types and mechanisms that mediate long-term and short-lived neuroimmune interactions calls for the development of new high-dimensional tools for neuroimmunology research. Considering the transient nature of some neuroimmune interactions, coupled with rapid changes in cellular states, approaches designed to label cell–cell interactions while simultaneously analysing cell activation states and their location in tissues are needed to study neuroimmune interactions and the specific cell subsets that participate in them. Finally, tools for the specific manipulation of the chemical and electrical activity of defined cell states are needed to delineate the functional properties of neuroimmune circuits (Fig. 4). Below, we summarize some recently developed technologies for neuroimmune connectome research.

Cell–cell interactions

First, it is important to identify and mechanistically define neuroimmune interactions in tissues[155]. RABID-seq[51], a genetically encoded interactomic method, deploys cellular barcodes between interacting cells using a library of barcoded G-deficient pseudotyped rabies virus[156].

RABID-seq and similar approaches[157–159] integrate connectomic and single-cell transcriptomic data, so specific subsets of interacting cells can be unequivocally identified. Similar tools have been developed to study connections across neural circuits[160], including BRIC-seq and MAP-seq, which use barcoded Sindbis virus to detect interactions between neurons[161,162].

Furthermore, methods for the analysis of peripheral neuroimmune interactions are also needed[163]. One approach is PIC-seq[164], which combines flow cytometry and single-cell RNA sequencing (scRNA-seq) to define mechanisms of cell–cell communication based on the analysis of the transcriptional program of cell doublets[165]. An alternative approach, LIPSTIC[166], is based on the enzymatic labelling of cell interactions in vivo by combining available Cre strains with a Cre-inducible LIPSTIC reporter[167]. These approaches are complemented by in vitro methods such as SPEAC-seq[50], a forward genetic screening method to identify interaction mechanisms in cell pairs cultured in droplets. Collectively, these techniques enable the rapid study of neuroimmune interactions.

Mapping cell types and states

The development of technologies is accelerating the study of neuroimmune connectome-relevant cell subsets. FIND-seq is a microfluidic-based approach that enables the in-depth transcriptional, epigenetic and genomic interrogation of cell subsets defined by the expression of nucleic acid biomarkers[168,169]. Coupling these and similar analytical methods with temporal information would define the timescale and dynamics of neuroimmune interactions. For example, Zman-seq[170] couples time-resolved molecular barcoding with single-cell transcriptomics, providing a granular view of neuroimmune interaction dynamics when applied to the CNS.

Cost-effective methods for the manipulation and high-resolution mapping of cell states in tissues are needed to define the function of neuroimmune interactions, the molecular mechanisms they control and their physiological consequences. Optimized adeno-associated viruses containing new capsids provide possibilities for functional genetic perturbation studies in vivo[171] targeting cell subsets that participate in neuroimmune interactions of interest[172–176]. These investigations are supported by new methods for the spatial profiling of RNA, some of which capture temporal information. Remarkably, one such technique records the electrophysiological properties of excitable cells using a barcoded bioelectronic device[177]. Alternatively, profiling actively translated mRNA by RIBOmap[178] or infusing spatial barcodes into nuclei in intact tissue by Slide-tags[179] enable multi-omic single-cell spatial analysis to identify specific tissue microenvironments in which defined neuroimmune circuits control defined homeostatic or pathological responses.

Reading and actuating cellular activity

Finally, actuator technologies such as optogenetics and chemogenetics enable the control of neuroimmune circuits to study their function[180–182]. Red-shifted opsins such as ChRmine or step-function opsins highly sensitive to blue light (SOUL) can be used to stimulate deep brain nuclei and neurons in peripheral tissues[99,183–185], enabling the non-invasive control of neuroimmune circuits without optical fibre implantation or much tissue heating. Other tools, including bioelectronic implants, can directly link peripheral circuits, such as the enteric nervous system, to CNS responses[186]. These tools may provide unprecedented access to central, peripheral and immune circuits to define their roles in physiology and disease.

Beyond the control of cellular activity, tools have been developed to visualize and record cellular processes. Optical clearing techniques, such as CLARITY[187], SHIELD[188] and iDISCO[189], provide unprecedented resolution into cellular dynamics in the brain. Recent iterations of these tools enabled whole-body clearing, such as with wildDISCO[190] or HYBRiD[191], which can provide insights into neuroimmune interactions across the body, and whole-brain vasculature mapping[192] to link peripheral changes to brain function. Coupled with methods for the alignment of whole-brain cellular and anatomical data, these tools may enable the dissection of neuroimmune interactions at an organismal scale.

Outlook

The connectome is defined in neurobiology as the network of elements and connections in the brain[193]. Neuroimmunology has made great progress in elucidating the nervous and immune mechanisms, cell types and circuits that control physiology and pathology. However, it has not yet generated an integrated view of the neuroimmune connectome to provide a comprehensive understanding of the functional roles and mechanisms that mediate interactions between the relatively fragile and stationary nervous system and the more resilient and dynamic immune system. Basic questions remain unanswered with regard to the neuroimmune connectome and its molecular identity, regulation and function.

First, we need to define and analyse the neuroimmune connectome. At present, we define neuroimmune interactions according to their functional effects on immunity or the nervous system. However, neuroimmune interactions exhibit tissue-specific adaptations and state-dependent outcomes that may not be easily detected with a one-size-fits-all approach. Moreover, neuroimmune interactions involving circulating immune cells are highly dynamic and potentially short-lived, although they may have long-lasting effects. Thus, new tools are needed to record past neuroimmune interactions and their location, temporal dynamics and functional consequences.

Second, we need to know how information is captured and stored in the neuroimmune connectome to modulate the activity of the nervous and immune systems, tissue physiology and even subjective conscious experience. Immune cells and neurons are directly and indirectly responsive to endogenous and exogenous stimuli, such as neurotransmitters, cytokines, environmental chemicals and microbial products that may show combinatorial effects compounded by heterogeneous cell subsets expressing different repertoires of receptors for these stimuli. Thus, analytical and computational methods are needed to integrate this complex and heterogeneous network of stimuli and receptors, and define the environment-modulated neuroimmune circuits associated with specific functions.

Finally, a unique characteristic of both the nervous and immune systems is their ability to establish retrievable memories, including synaptic plasticity or vaccination against pathogens. Indeed, some neuroimmune interactions exhibit memory[82]. We need to know how long-lived the effects of neuroimmune interactions really are. Recent findings indicate that astrocyte activation by immune stimuli induces epigenetic memory programs that alter their subsequent responses to stimulation[85], resembling findings made on immune[194,195] and structural cells[86]; neuroimmune interactions between astrocytes and other cells (for example, microglia) are likely to further contribute to and regulate this astrocyte memory, as well as epigenetic memory programs in other cells of the nervous and immune systems. Defining the durability of neuroimmune interaction-driven responses may therefore provide insights into tissue physiology, while guiding the development of therapeutics to manage inflammation and promote tissue repair and resilience.

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