Published in final edited form as:

Nat Rev Neurosci. 2017 June ; 18(6): 375–384. doi:10.1038/nrn.2017.39.

How and why do T cells and their derived cytokines affect the injured and healthy brain?

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Abstract

The evolution of adaptive immunity provides enhanced defence against specific pathogens, as well as homeostatic immune surveillance of all tissues. Despite being ‘immune privileged’, the CNS uses the assistance of the immune system in physiological and pathological states. In this Opinion article, we discuss the influence of adaptive immunity on recovery after CNS injury and on cognitive and social brain function. We further extend a hypothesis that the pro-social effects of interferon-regulated genes were initially exploited by pathogens to increase host–host transmission, and that these genes were later recycled by the host to form part of an immune defence programme. In this way, the evolution of adaptive immunity may reflect a host–pathogen ‘arms race’.

During infection, it is readily apparent that the immune system affects the brain and behaviour. The feelings of malaise, fatigue and loss of appetite (among others) were initially thought to be a direct consequence of the pathogen; however, seminal studies have described how sickness behaviour is a well-orchestrated host response to fight infections (reviewed in REF. 1). In the absence of infection, an immune response directed towards the CNS has typically been considered pathogenic. However, it is only recently that we have started to appreciate that immune surveillance of the CNS is crucial for correct brain function and recovery after injury².

In this Opinion article, we review recent works describing the effects mediated by adaptive immunity (primarily T cells and their derived molecules) on the brain. Although the brain itself is considered immune privileged, T cells patrol the borders (meningeal spaces) of the CNS (BOX 1; FIG. 1). We highlight our current understanding of how T cells are involved in response to CNS injury and how, under physiological conditions, they affect learning and social behaviours in mice. As the immune system constantly adapts when exposed to pathogens, different T cell-derived molecules have the capacity to alter the neuroimmune dialogue during different types of infection. Here, we speculate on a novel mechanism of how an anti-pathogen cytokine, interferon- γ (IFN γ), may have evolved to limit the spread

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Competing interests statement

The authors declare no competing interests.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

of pathogens as organisms aggregate, highlighting a potential co-evolutionary ‘arms race’ of pathogens and hosts. Overall, neuroimmune communications are essential for correct brain function, and understanding this complex language will broaden our repertoire for therapeutics through targeting the immune system to treat neurological disorders.

Box 1

Introduction to immunology for neuroscientists

T cells and B cells (collectively known as lymphocytes) are vital constituents of the adaptive arm of the mammalian immune system. Lymphocytes can rearrange their genome to create unique antigen-specific receptors. B cells produce antibodies, which can be either surface-bound receptors or secreted effectors. T cells, through their surface-bound T cell receptor (TCR), detect peptides that have been processed and then presented on major histocompatibility complex (MHC) molecules by other cells. The outcome of TCR MHC recognition can be broadly defined in terms of two T cell subsets: CD8⁺ cytotoxic T cells and CD4⁺ helper T cells.

CD8⁺ T cells detect foreign antigens presented on MHC class I (MHC I) molecules, which are produced by virtually all cells in the body to constantly present peptides that reflect their intracellular contents. When a pathogen infects an MHC I-expressing cell, the presentation of a foreign peptide will activate CD8⁺ T lymphocytes, which then kill the infected cell.

Conversely, CD4⁺ T cells detect antigens presented by MHC II molecules. These antigens are primarily presented by antigen-presenting cells (APCs) — such as dendritic cells, macrophages and B cells¹⁰⁶; APCs phagocytose antigens and present the engulfed and digested products to CD4⁺ T cells in draining lymph nodes¹⁰⁷. Upon activation by their specific peptides, CD4⁺ T cells proliferate and, when exposed to certain secondary stimuli, differentiate to combat the particular threat. CD4⁺ T cells differentiate to numerous subsets, including type 1 T helper cells (T_H1 cells), T_H2, T_H17 and regulatory T cells (T_{reg} cells), each specialized to combat certain types of infection or resolve inflammation. CD4⁺ T cell subsets act largely by secreting cytokines that are specific to their lineage. For example, T_H2 cells produce interleukin-4 (IL-4), IL-13 and IL-5, whereas T_H1 cells produce interferon- γ (IFN γ) and IL-2 (REF. 108). The secreted cytokines can profoundly affect the regulation of the local immune response, the nature of which is highly dependent on the stimulus and the environment. For example, the single-cell parasite *Toxoplasma gondii* induces a type 1 (mainly T_H1-driven) response, whereas infections by parasitic worms induce a type 2 (mainly T_H2-driven) response^{109,110}.

The CNS parenchyma in its naive state does not contain lymphocytes, but T cells reside in the meninges and are proposed to influence brain function from there (FIG. 1). According to currently proposed models, T cells enter the meninges and the CSF through blood vessels in the leptomeninges (the pia mater and arachnoid), through meningeal blood vessels in the dura, or through the choroid plexus^{111,112}, and exit to the deep cervical lymph nodes through meningeal lymphatic vessels^{2,113,114}. Using intravital two-

photon microscopy, Schläger *et al.*¹¹¹ observed T cells extravasating from blood vessels into the leptomeninges, where they gained access to the CSF in the subarachnoid space.

Following acute infection or injury in the CNS, as in peripheral tissues, T cells are recruited from the bloodstream through a chemokine gradient and upregulation of adhesion molecules on the luminal surface of the vascular endothelium¹¹⁵, which bind to integrins activated on the surface of circulating T cells, to promote extravasation. Adhesion molecules have some degree of specificity for particular tissues, and, during the presentation of an antigen, the profiles of integrins on T cells are imprinted in the draining lymph nodes of a tissue recruiting a T cell response¹¹⁶. For example, binding of very late antigen 4 (VLA4) to vascular cell adhesion molecule 1 (VCAM1) is important for extravasation of T cells and their homing to the CNS and meninges¹¹⁷. Inhibition of this interaction by a neutralizing antibody (in disease or steady state) attenuates T cell extravasation, thereby depleting the meningeal T cell population within days^{46,117}. Under physiological conditions, T cell accumulation in the meninges seems to be antigen dependent⁴⁸, although the antigen specificity of meningeal T cells is not known. Meningeal lymphatic vessels are supposedly the major traffic route for the exit of meningeal immune cells¹¹⁴, although further *in vivo* experiments tracking labelled cells exiting the meninges are required to substantiate this claim.

T cells and the injured brain

Although in multiple sclerosis and other autoimmune neuroinflammatory diseases the activity of infiltrating T cells is unequivocally pathological³, experimental evidence over the past two decades suggests that the effects of T cells after CNS injury probably depend on the type of injury and appropriate regulation of the infiltrating T cells.

T cells after ischaemia–reperfusion injury

Evidence suggests that T cells are overall detrimental following ischaemia–reperfusion (I/R) injury. In models of brain I/R, T cells enter the lesion site as early as 1 day post-injury (DPI), initially clustered around blood vessels, and increase in numbers in the parenchyma between 3 and 7 DPI⁴. After an I/R injury, *Rag*^{−/−} mice, which lack T cells and B cells and thus are deficient for adaptive immunity, show decreased lesion volumes and neurological deficit compared with injured wild-type mice⁵. Furthermore, adding splenocytes to *Rag*^{−/−} animals to repopulate the T cell and B cell compartments reverses the effect⁵. Similar results were obtained using severe combined immunodeficiency (SCID) mice (which also lack T cells and B cells)^{6,7}.

The mechanisms that underlie the detrimental activities of T cells in I/R injury remain incompletely understood. After ischaemic injury, infiltrating T cells are predominantly skewed to type 1 T helper (T_H1) and T_H17 phenotypes⁸, and adoptive transfer of T cells skewed towards T_H1 and T_H17 phenotypes worsened behavioural scores after middle cerebral artery ligation and reperfusion (a model of ischaemic stroke)⁹. A working theory is that their canonical cytokines — IFN γ , interleukin-17 (IL-17), IL-21 and IL-23 — contribute to neuronal degeneration (FIG. 2a–c); thus, manipulating T cell phenotypes may

be a promising avenue for future work. For example, systemic treatment with the alarmin IL-33 was beneficial in a stroke model and was associated with an increase in T_H2-derived cytokines and in the ratio of T_H2 cells to T_H1 and T_H17 cells in lesion sites^{8,10}.

T cells after traumatic CNS injuries

In contrast to I/R injuries, recovery after traumatic CNS injuries, including facial nerve transection¹¹, traumatic brain injury¹², optic nerve crush injury^{13–15} and spinal cord contusion¹⁶, seems to benefit from T cell assistance. After traumatic CNS injury, T cells are rapidly recruited, starting at 1 DPI and peaking at 4–10 DPI, depending on the type of injury^{14,17}. Athymic nude mice, *Rag*^{−/−} mice and SCID mice all show impaired neuronal survival following injury compared with injured wild-type mice^{11,18–20}. This impairment is attenuated when T cell-deficient mice are supplied with splenocytes. T cells can produce neurotrophic factors (including brain-derived neurotrophic factor (BDNF), neurotrophin 3 and nerve growth factor) at the site of injury, possibly explaining some of their neuroprotective effects²¹ (FIG. 2d–f). Together, these studies point to a beneficial effect of T cells after traumatic CNS injury¹⁸.

Possible mechanisms

A series of early investigations have suggested a counterintuitive mechanism of the beneficial effect of T cells after traumatic CNS injury, suggesting that the effect is mediated by autoreactive T cells specific for brain antigens^{13,19,22–24}. Injecting mice with myelin basic protein (MBP)-specific T cells immediately after optic nerve crush (a model of CNS injury) limited continuous secondary degeneration of retinal ganglion cells and improved optic nerve conductance compared with untreated injured controls¹³. Similar results were obtained after spinal cord injury in rodents²³: injected MBP-specific T cells accumulated at the injury site and improved outcomes^{13,22}.

Autoimmune responses are implicated in both improved and impaired recovery in stroke²⁵. The number of MBP-responsive T_H1 cells in particular seems to be a marker for worse outcome in patients after stroke^{26,27}, whereas, interestingly, reactivity to neuronal antigens was conversely associated with improvement²⁸. Preconditioning rats with MBP antigen intranasally before I/R injury also resulted in an improved outcome and was associated with an increased ratio of MBP-reactive regulatory T cells (T_{reg} cells) to MBP-reactive T_H1 cells²⁹.

The conditions that determine whether autoimmune responses are harmful or beneficial remain unclear. Current data suggest that these conditions are primarily affected by the type of insult, and this may explain the differences in the effects of T cells after I/R versus traumatic CNS injuries. Autoimmune responses probably exist in a delicate balance, with both too much and too little activity leading to suboptimal recovery.

In addition to the theory of protective autoimmunity, recent work from our group has pointed to an antigen-independent mechanism of T cell neuroprotection after trauma¹⁴. To test whether the beneficial effects of T cells depended wholly on T cell receptor (TCR)–major histocompatibility complex class II (MHC II) engagement, mice that lack MHC II proteins (known as MHC II-deficient mice), which normally lack CD4⁺ T cells, were injected with

CD4⁺ T cells at 1 and 8 DPI. If antigen specificity were indeed important for the neuroprotective actions of T cells, as suggested by earlier studies, these injections would be expected to have no effect. However, injecting T cells in MHC II-deficient mice markedly improved neuronal survival after injury¹⁴. Although the beneficial response was thus independent of TCR–MHC II interactions, it was dependent on myeloid differentiation primary response protein 88 (MYD88) and T cell-derived IL-4 (REF. 14). Therefore, the beneficial actions of T cells after CNS injury may occur through multiple mechanisms — some that are antigen dependent, and others that are not. It is possible that the availability of antigens and danger molecules (molecules used by the immune system to recognize tissue damage³⁰) released from the site of injury endow T cells with either neuroprotective or neurodestructive properties.

Many studies have investigated the role of T_{reg} cells after CNS injury. T_{reg} cells suppress the response of other T cells by producing anti-inflammatory cytokines, such as IL-10, and by competing for the T cell survival signal IL-2 (REF. 31). Depletion of T_{reg} cells using a CD25-specific antibody before I/R injury was associated with increased infarct volume, neutrophil infiltration, microglial activation and cytokine production³². Many of these findings could be recapitulated by IL-10 injections, which suggests that IL-10 is an important T_{reg} cell product for these effects³². Interestingly, other studies show an apparently opposite role for T_{reg} cells. Depletion of T_{reg} cells in DERE mice (in which the diphtheria toxin receptor is expressed under the *Foxp2* promoter, and thus injection of diphtheria toxin selectively kills T_{reg} cells) actually improved recovery after injury. Notably, the mechanism of impairment induced by T_{reg} cells has been suggested to be independent of their modulatory effects on other T cells, as the addition of T_{reg} cells to T cell-deficient *Rag*^{-/-} mice also led to impairment, and T_{reg} cells were linked to increased pathologic cerebral vascular events³³.

A similarly complicated picture of the involvement of T_{reg} cells has been described in traumatic CNS injury. As mentioned above, repopulating athymic nude mice with splenocytes promoted neuronal survival after injury, but there was further benefit in adding splenocyte populations partially depleted of T_{reg} cells¹⁸. Moreover, partially depleting T_{reg} cells after optic nerve crush (modelled using the DERE mice) improved neuronal survival. Interestingly, increasing T_{reg} cells worsened neuronal survival and was associated with a decrease in alternatively activated (that is, tissue-healing) macrophages at the injury site³⁴. For optimal recovery, the number of T_{reg} cells must be strictly controlled: if there are too few T_{reg} cells, damage can result from excessive inflammation, whereas if there are too many T_{reg} cells, the beneficial activity of neuroprotective T cells is suppressed. Both of these dysregulated conditions lead to pathological changes in innate immune cells, linking T_{reg} cell-mediated over-suppression or under-suppression to dysfunction of the innate immune system^{14,35} (FIG. 2c,f). Thus, although the net effect of T cells after CNS injury can clearly be beneficial, their activity must be carefully controlled by means of an appropriate T_{reg} cell response¹⁴.

Much work is still needed to fully understand the nature of the protective and detrimental functions of T cells in various models^{35,36} (FIG. 2). Particularly confusing are contrasting data from the ischaemia and traumatic CNS injury models, in which — with a few

exceptions — T cell activity tends to be detrimental and beneficial, respectively. One possible reason for this difference is the unique inflammatory milieu that is present in each injury site. For example, IL-33 — which is secreted at high levels after traumatic spinal cord injury³⁷ — encourages a protective T_H2 cell phenotype when given exogenously after stroke¹⁰. Although a more detailed characterization of IL-33 is required in each of these models, it is possible that differing levels of several factors at the injury site contribute to unique T cell responses. Future studies should focus on understanding and ultimately harnessing these milieus to drive the optimal circumstances for T cell-mediated neuroprotection. Further work is also needed to address the relative importance of antigen-dependent versus antigen-independent activation of T cells in CNS injury, the therapeutic potential of T_H2-derived cytokines, such as IL-4, and the complex interactions between lymphocytes and other immune cells at the injury site.

T cell influences on the brain

The vital part played by the immune system in recovery from CNS injury, as described above, prompts the question of how the immune and nervous systems interact under physiological conditions.

T cell effects on learning and behaviour

The immune system, particularly through T cells, affects CNS function in health and in disease. Early work demonstrated that SCID mice perform poorly in the Morris water maze and other spatial learning and memory tasks^{38,39}. Notably, learning and memory in SCID mice can be rescued by reconstituting the T cell compartment³⁸. Further supporting the specific influence of T cells on learning behaviour, learning is not impaired in mice that specifically lack B cells⁴⁰.

Behavioural deficits observed in T cell-deficient mice are not restricted to learning and memory impairments. It was recently observed that SCID mice show impaired social behaviour in the three-chamber sociability assay⁴¹, which determines the preference of a test mouse to investigate a novel mouse over a novel object⁴². As with learning, deficits in social behaviour were rescued 4 weeks after repopulation with wild-type lymphocytes; however, it has not been reported how long these effects last. Mice that lack T cells also exhibit heightened susceptibility in a model of post-traumatic stress disorder⁴³, show impaired maternal behaviour⁴⁴ and exhibit compulsive grooming⁴⁵.

Mechanisms that underlie T cell influences on the healthy brain

How do T cells manifest their effects on the function of the healthy brain? As mentioned above, under healthy conditions, T cells do not enter the brain parenchyma. However, a considerable number of T cells are found in the healthy meninges, the three-layer membrane lining that surrounds the brain. These meningeal T cells seem to be crucial for correct brain function.

For example, mice treated with antibodies specific for very late antigen 4 (VLA4; also known as $\alpha 4\beta 1$ integrin), which effectively block T cell migration to the meninges (and leukocyte migration to other tissues, including mucosal tissues, bone marrow and spleen),

exhibit learning deficits in the Morris water maze^{40,46,47} and impaired social behaviour in the three-chamber assay⁴¹. The antigen specificity of the T cells seems to be relevant in this model. Transgenic OT-II mice, which express CD4⁺ T cells that are specifically reactive to the non-self antigen ovalbumin, are impaired in the Morris water maze compared with wild-type mice⁴⁰. This deficit can be ameliorated by the addition of wild-type splenocytes or T cells that are specific to a brain antigen (in this case, myelin oligodendrocyte glycoprotein)⁴⁰. Removal of the deep cervical lymph nodes (the major CNS-draining lymph nodes) also impairs learning, supporting the contention that TCR–MHC II interaction in these lymph nodes may be required for normal learning⁴⁸.

Meningeal T cells are in proximity to, but do not directly contact, the brain tissue; thus, how they affect brain function remains unclear. It is likely that T cells release soluble cytokines that, through paracrine signalling, directly affect neurons and other CNS cells to influence CNS function and behaviours (including sickness behaviour, sociability and cognition^{1,41,49}). The diverse cytokine profiles presented to neurons presumably have different effects on circuits and behaviours, but the effects of specific cytokines on most behaviours have yet to be addressed.

As mentioned above, meningeal T cells are crucial for normal social behaviour in mice. To identify cytokines that might participate in social behaviour, publically available gene-signature data from immune cells (and fibroblasts) exposed to different cytokines or combinations of cytokines (specifically, IFN γ , IL-4 and IL-13, IL-17, or IL-10 and transforming growth factor- β (TGF β)) were compared with gene-signature data from rodent brains after exposure to different conditions (for example, a social environment, stress, sleep deprivation, psychostimulants, antidepressants, anticonvulsants or antipsychotics)⁴¹. The analysis showed that exposure to a social environment induced changes in gene expression that are similar to those triggered by exposure to IFN γ , which suggests that IFN γ has a role in social behaviour. Subsequent experiments confirmed that mice that lacked T cells or IFN γ had social deficits in the three-chamber sociability assay⁴¹. In contrast to mice deficient for IFN γ , mice deficient for IL-4 were more social than wild-type mice. This was surprising because, following a learning task, IL-4-producing T cells accumulate in the meninges, and mice deficient for IL-4 exhibit learning deficits⁴⁶. These data emphasize the possibility that specific cytokines may differentially regulate specific neuronal circuits.

Mice deficient in T cells or in T cell-derived IFN γ also display aberrant hyperconnectivity in the prefrontal cortex (PFC), as measured by resting-state functional MRI. Intriguingly, hyper-connectivity in the PFC is also observed in patients with autism spectrum disorder (ASD)⁵⁰, and direct, optogenetic hyperactivation of the PFC in mice results in social withdrawal⁵¹. Reconstitution of the T cell compartment in SCID mice (for at least 4 weeks) or injection of recombinant IFN γ into the CSF of IFN γ -deficient mice restores normal social behaviour and connectivity. In addition, injection of IFN γ into the CSF of wild-type mice enhanced the activation of layer I PFC neurons (as assessed using immunohistochemistry for FOS, an immediate early gene product), which are almost entirely inhibitory⁵². Moreover, application of IFN γ increased tonic inhibition of layer II/III pyramidal neurons in acutely prepared PFC slices. These IFN γ -induced effects are mediated by neurons, and genetically blocking the ability of neurons to respond to IFN γ —by

injecting a Cre recombinase-encoding adeno-associated virus into the PFC of mice that lacked IFN γ receptor 1 (*Ifngr*^{fl/fl} mice) to specifically target neurons or by conditionally deleting *Ifngr* in vesicular GABA transporter (VGAT)-expressing inhibitory neurons using *Vgat*^{Cre}*Ifngr*^{fl/fl} mice — was sufficient to induce social deficits and inhibit IFN γ -induced tonic inhibition⁴¹. Thus, a lack of IFN γ can lead to a disinhibition of the PFC and thus result in social deficits. Interestingly, social preference in IFN γ -deficient mice can be rescued by boosting GABAergic circuits with diazepam. These data suggest that IFN γ acts as a rheostat for controlling baseline activation in the PFC to support appropriate social behaviour (FIG. 3).

The findings described above indicate a link between social behaviour and T cell-derived IFN γ . Together with reports of altered levels of IFN γ in individuals with depression or ASD^{53–57}, these findings could suggest that immune dysfunction may contribute to the pathology of neurological disorders that present with social withdrawal. In a post-mortem study, Clark *et al.*⁵³ revealed that IFN γ levels were reduced in the ventrolateral PFC of individuals diagnosed with depression compared with controls; by contrast, other studies reported increased circulating levels of IFN γ in people with depression⁵⁴. Whether these differences are due to variability in the cohorts or, more intriguingly, to differential expression of IFN γ in the blood versus the CNS is not known. Similarly, although ASD is a heterogeneous disorder, individuals with ASD often exhibit abnormalities of the immune system and of IFN γ production. In children who are diagnosed with ASD, the number of terminally differentiated T cells is decreased⁵⁸, and, when stimulated experimentally with phorbol myristate acetate and ionomycin, T cells isolated from these individuals produce lower amounts of IFN γ than do T cells from age-matched control individuals⁵⁵. However, in other studies, IFN γ levels were found to be increased in the brains⁵⁶ and blood⁵⁷ of individuals diagnosed with ASD and in a mouse model of ASD (BTBR mice)⁵⁹. These results reflect the heterogeneity of ASD⁶⁰, and it is most likely that a disruption in immunity in any direction has deleterious consequences.

The potential effect of increased IFN γ on social behaviour is as yet untested. An interesting hypothesis is that chronically increased IFN γ levels could overwhelm the system and occlude the small responses to IFN γ that are needed to correctly inhibit local circuits⁶¹. Also, as with many cytokines, strong feedback inhibition mechanisms inhibit signalling molecules downstream of the IFN γ receptor during prolonged IFN γ signalling. For example, the effects of IFN γ signalling may be attenuated by decreasing or upregulating the expression of IFN γ receptor subunits or of suppressors of cytokine signalling (SOCS) protein family members, respectively⁶². By contrast, in the periphery, sub-threshold IFN γ levels can sensitize macrophages to subsequent IFN γ exposure⁶³. This sensitization programmes or changes the responses of macrophages and dendritic cells to IFN γ ^{63,64}. Sensitization of neurons by IFN γ has not yet been investigated.

Meningeal T cells can produce various molecules that can affect the CNS, including neurotransmitters (for example, GABA), neuromodulators (such as serotonin) and growth factors (for instance, BDNF), in addition to cytokines^{65–67}. Whether many of these effector molecules can influence neuronal function in physiological conditions is not known, and how they reach their parenchymal targets remains unclear. However, it is possible that small

molecules that are released into the CSF, including ~20–25 kDa cytokines, may enter the brain parenchyma through para-arterial flux^{68–70}. This was demonstrated when a fluorescently conjugated ovalbumin tracer (~45 kDa) was injected into the CSF; within 10 minutes, fluorescence was observed to cross from paravascular spaces, across astrocyte end-feet, into the brain parenchyma⁶⁸.

Sickness behaviour

The interactions between microorganisms and the immune system may also have important influences on the brain. Given that changes in the microbiota have such profound effects on the immune system⁷¹, it is tempting to speculate that some of the effects on the brain and many different aspects of behaviour that are caused by changes in the gut microbiota⁷² may be mediated by changes in the immune system, although the possible mechanisms are unclear.

Pathogens that invade the body cause robust activation of immune response mechanisms, including the stimulation of innate immune cells, the activation of lymphocytes and an increase in pro-inflammatory cytokines^{1,73}. One of the most salient behavioural responses to infection is sickness behaviour: a collection of behaviours including lethargy, social withdrawal, increased sleep and decreased appetite that are designed to promote survival by decreasing energy expenditure and promoting pathogen clearance. These behaviours, which are crucial for survival of the infected individual and of their group, are an outcome of complex neuroimmune interactions.

Sickness behaviour is initiated by pro-inflammatory cytokines such as IL-6, tumour necrosis factor (TNF) and, predominately, IL-1 β ^{1,74,75}. These cytokines transmit information from the site of infection to the CNS by inducing signalling through vagal afferents or by humoral transmission through the circumventricular organs (which lack a complete blood–brain barrier) and endothelial cells in brain blood vessels^{1,76}. Peripheral signals are transduced to the parenchyma and propagate by further local production of cytokines by perivascular macrophages and microglia^{70,77–79}. Although some aspects of sickness behaviour, such as decreased social interactions, may be attenuated by neutralizing brain IL-1 β (for example, by injecting an IL-1 β antagonist into the cerebral ventricles), others, such as decreased food-motivated behaviours, are not⁸⁰. This suggests that the circuits involved in sickness behaviour are complex, and the molecular mechanisms that underlie how peripheral cytokines affect these neural circuits are unclear.

A virus-versus-host competition

Social or aggregation behaviour is crucial not only for survival and evolution but also for the spread of transmissible organisms. Therefore, coordinated immunity and sickness behaviour have evolved to acutely limit the spread of pathogens. In 1988, Hart⁸¹ first argued that sickness behaviour is not a maladaptive response to infection but rather a coordinated behavioural strategy to promote host survival. A more recent hypothesis attributes sickness behaviour to altruism and kin selection⁸²; that is, sickness behaviour provides an evolutionary advantage to survival of the herd^{83,84}. Interestingly, it has been reported that, if

the infected host does not elicit overt sickness behaviour, they may increase their propensity to aggregate⁸⁵. For example, using a protocol to model influenza challenge — a vaccination containing haemagglutinin from three strains of influenza virus, which did not induce sickness behaviour — Reiber *et al.*⁸⁶ observed increased social interactions for 48 hours in humans who were given the vaccine. How, then, can an increase in pathogen-induced social aggregation be reconciled with social withdrawal being a component of sickness behaviour? Recent work from our group offers a plausible hypothesis that pathogen-induced pro- social behaviour and host-induced sickness behaviour are evolutionarily linked and can be viewed as the result of an evolutionary ‘arms race’ between pathogens and hosts⁴¹.

During an infection, the host response is complex, and behavioural output may be influenced by the types of cytokine that are produced and by their cellular targets. Moreover, peripherally derived cytokines may target cells and/or neuroanatomical sites that are different from those targeted by cytokines that are secreted locally into the CSF or directly in the CNS^{87,88}. IFN γ derived from meningeal T cells promotes social behaviour⁴¹, and the same (or additional) sources of IFN γ may be responsible for anti-pathogen responses in the CNS⁸⁹. However, in addition to the IFN γ response to pathogens, host defence includes an innate immune response that involves TNF, IL-1 β and IL-6 — cytokines that are known to induce sickness behaviour and social withdrawal¹. Therefore, most infections would induce opposing cytokine-induced behavioural responses: IFN γ -driven aggregation and a robust sickness response that is driven by TNF, IL-1 β and IL-6. Essentially, to be maximally successful, a virus must infect a host, limit the antiviral mechanisms and sickness behaviour of the host, and promote aggregation of the host with other conspecifics (FIG. 4). One way in which a virus would secure the transmission of genetic information might be to silently evade the immune response of the host and become incorporated into the host genome.

Endogenous retroviruses (ERVs) are provirus genes that reside in the genome of the host. It is suggested that they derive from ancient infections, and have since become integrated into germline cells and are now inherited as chromosomal DNA⁹⁰. Sequences derived from ERVs comprise up to 10% of the human genome⁹¹. ERVs do not produce functional viruses, at least not in humans, and usually do not generate protein, owing to early embryonic silencing by heavy *de novo* methylation patterns. Exceptions are the syncytins, provirus ancestral polyproteins that form the viral envelope and that are thought to have contributed to the evolution of eutherians (placental mammals)⁹². Besides these and some other exceptions, do other ERVs simply reside in the genome of the host as ‘junk DNA’? Recent evidence suggests that this is not the case and instead indicates that ERVs play an active part in the host.

Altering histone-methylation patterns can result in aberrant expression of ERVs. Thus, for example, neural precursor cells from mice that lack tripartite motif containing 28 (*Trim28*), which encodes a transcriptional co-repressor that recruits histone-modifying enzymes, show aberrant expression of the ERVs *MMERVK10C* (*Mus musculus* ERV using tRNA^{Lys} type 10C) and *IAP1* (intracisternal A-particles class 1)⁹³. The consequence is aberrant expression of nearby genes (and non-coding RNAs) on the chromosome and behavioural hyperactivity. In humans, increased levels of ERV mRNA have been associated with ageing and psychiatric disorders such as schizophrenia and bipolar disorder^{94–97}. Even when silenced,

the presumably benign ERV sequences can influence the transcription of nearby genes through several mechanisms — for example, by providing promoters for protein-encoding genes or by facilitating the production of microRNAs, long non-coding RNAs and antisense RNAs^{98–100}. This suggests that ERVs can potentially modulate not only gene networks in neurons but also their functions.

ERVs were recently shown to amplify the expression of IFN γ -inducible genes through the binding of signal transducer and activator of transcription 1 (STAT1) — a transcription factor that is expressed following interferon receptor activation — to ERV elements¹⁰¹, although the precise relevant mechanisms have yet to be elucidated. Chuong *et al.*¹⁰¹ analysed available data sets obtained by chromatin immunoprecipitation followed by sequencing (ChIP-seq) from three human immune cell lines treated with IFN γ (K562 cells, which are derived from myeloid leukaemia; HeLa cells; and primary CD14⁺ macrophages). Intriguingly, many long terminal repeats of ancient ERV sequences were found to be enriched for binding sites for STAT1 and interferon regulatory factor 1 (IRF1) — transcription factors that mediate the expression of IFN γ -inducible genes. The ERV sequence *MER41* was bound directly by STAT1. Surprisingly, when the *MER41* sequence was deleted from HeLa cells, IFN γ was unable to induce expression of the IFN γ -inducible protein absent in melanoma 2 (AIM2), a component of the inflammasome pathway. Why would a virus-derived sequence upregulate *AIM2* and other IFN γ -dependent genes, given that this response is detrimental for the virus? The authors comment that “It would be ironic if viral molecular adaptations had been evolutionarily recycled to fuel innovation and turnover of the host immune repertoire” (REF. 101).

Given the pro-social effects of IFN γ described above, it is intriguing to speculate that organisms would increase their fitness and natural selection by expanding the effects of IFN γ , which promotes social aggregation, to also include the expression of anti-pathogen genes. Retroviral insertion, transposition and gene duplication might also have contributed, in evolutionary terms, to the diversity of genes that encode MHC proteins and TCRs, again suggesting a productive evolutionary ‘arms race’ between host and pathogen^{102–104}.

As outlined above, IFN γ -inducible genes in the brain drive sociability (which has been used to predict increased reproduction¹⁰⁵) and aggregation⁴¹. Thus, it is conceivable that viral induction of pro-social genes that are regulated by IFN γ in the brain would increase social interactions between the host and its conspecifics, benefiting the spread of the viral genome. Higher-order species have evolved means for IFN γ to also promote inflammation and therefore combat viruses more efficiently. This would ensure that an anti-pathogen response is promoted during the periods of aggregation needed for the survival of a species.

To further investigate this possibility, brain transcriptomes of rats, mice, zebrafish and flies housed in social or isolated conditions were analysed⁴¹. In the social condition, organisms exhibited increased expression of IFN γ -inducible genes, even in the absence of infection. This remained true even in flies, which have the primordial Janus kinase (JAK)–STAT signalling pathway but lack IFN γ itself and adaptive immunity (both of which developed more recently with the evolution of jawed vertebrates).

Overall, if transposed ERVs enhanced the social behaviour of the host by upregulating social genes (such as IFN γ -dependent pro-social genes), both the social fitness of the organism and the probability of vertical transfer of the ERV sequence would be increased. Furthermore, by evolving an immune IFN γ signalling pathway that is more efficient, organisms remain social while mounting a more effective antiviral response (FIG. 4). Future work is needed to assess how IFN γ fits into this evolutionary interaction between pathogens and host regarding social behaviour and the anti-pathogen response. For example, mapping the genes that are necessary for IFN γ -driven pro-social behaviour and identifying which of these intersect with genes that are involved in the IFN γ -dependent immune response will be important to understand how IFN γ might have evolved to influence these two important functions.

Concluding remarks

Immune cells and their derived molecules can have a prodigious effect on behaviour. Some of the relevant signalling pathways that culminate in the expressions of these effects, such as sickness behaviour, have been well studied, but the mechanisms by which most immune cell-derived molecules affect behaviour are unclear. More than 100 different molecules with 'cytokine' activity are currently known, and immune cells produce numerous neuroactive compounds, including neurotransmitters and neuromodulators. This abundant pool of immune agents constitutes a huge potential reservoir through which immune cells and their derived molecules can globally or selectively influence neural circuits. Many fundamental questions in neuroimmunology remain unanswered. What is the precise nature of the protective and the detrimental functions of T cells and of their effects on recovery from CNS disease or injury? Besides T cells, are there other meningeal immune cells that can signal to neurons? If so, how do these signals gain access to the parenchyma? How rapidly can these signals operate? Are all neural circuits amenable to modulation by immune molecules? Can disruption of neuroimmune communications alter disease progression?

Finding the answers to these questions will provide a more profound understanding of the interactions between the immune and the nervous systems and will open new doors for the development of novel therapeutic modalities that target the immune system and benefit the brain.

Acknowledgments

The authors thank S. Smith for editing the manuscript and A. Impagliazzo for helping with the artwork. The authors also thank all the members of the Kipnis laboratory for their insightful comments and enlightening ideas. This work was supported by grants from the US National Institutes of Health (AG034113, NS096967 and MH108156 to J.K., and T32-AI007496 to A.J.F.) and the Hartwell Foundation (to A.J.F.).

References

1. Dantzer R. Cytokine, sickness behavior, and depression. *Immunol Allergy Clin North Am.* 2009; 29:247–264. [PubMed: 19389580]
2. Kipnis J. Multifaceted interactions between adaptive immunity and the central nervous system. *Science.* 2016; 353:766–771. [PubMed: 27540163]
3. Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. *Nat Rev Immunol.* 2015; 15:545–558. [PubMed: 26250739]

4. Jander S, Kraemer M, Schroeter M, Witte OW, Stoll G. Lymphocytic infiltration and expression of intercellular-adhesion molecule-1 in photochemically induced ischemia of the rat cortex. *J Cereb Blood Flow Metab.* 1995; 15:42–51. [PubMed: 7528223]
5. Yilmaz G, Arumugam TV, Stokes KY, Granger DN. Role of T lymphocytes and interferon- γ in ischemic stroke. *Circulation.* 2006; 113:2105–2112. [PubMed: 16636173]
6. Hurn PD, et al. T⁺ and B-cell-deficient mice with experimental stroke have reduced lesion size and inflammation. *J Cereb Blood Flow Metab.* 2007; 27:1798–1805. [PubMed: 17392692]
7. Subramanian S, et al. Recombinant T cell receptor ligand treats experimental stroke. *Stroke.* 2009; 40:2539–2545. [PubMed: 19443805]
8. Luo Y, et al. Interleukin-33 ameliorates ischemic brain injury in experimental stroke through promoting Th2 response and suppressing Th17 response. *Brain Res.* 2015; 1597:86–94. [PubMed: 25500143]
9. Zierath D, et al. The immunologic profile of adoptively transferred lymphocytes influences stroke outcome of recipients. *J Neuroimmunol.* 2013; 263:28–34. [PubMed: 23948692]
10. Korhonen P, et al. Immunomodulation by interleukin-33 is protective in stroke through modulation of inflammation. *Brain Behav Immun.* 2015; 49:322–336. [PubMed: 26111431]
11. Serpe CJ, Kohm AP, Huppenbauer CB, Sanders VM, Jones KJ. Exacerbation of facial motoneuron loss after facial nerve transection in severe combined immunodeficient (*scid*) mice. *J Neurosci.* 1999; 19:RC7. [PubMed: 10341268]
12. Kipnis J, et al. Therapeutic vaccination for closed head injury. *J Neurotrauma.* 2003; 20:559–569. [PubMed: 12906740]
13. Moalem G, et al. Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. *Nat Med.* 1999; 5:49–55. [PubMed: 9883839]
14. Walsh JT, et al. MHCII-independent CD4⁺ T cells protect injured CNS neurons via IL-4. *J Clin Invest.* 2015; 125:699–714. [PubMed: 25607842]
15. Kipnis J, et al. Low-dose γ -irradiation promotes survival of injured neurons in the central nervous system via homeostasis-driven proliferation of T cells. *Eur J Neurosci.* 2004; 19:1191–1198. [PubMed: 15016077]
16. Hauben E, et al. Vaccination with dendritic cells pulsed with peptides of myelin basic protein promotes functional recovery from spinal cord injury. *J Neurosci.* 2003; 23:8808–8819. [PubMed: 14507981]
17. Raivich G, et al. Immune surveillance in the injured nervous system: T-lymphocytes invade the axotomized mouse facial motor nucleus and aggregate around sites of neuronal degeneration. *J Neurosci.* 1998; 18:5804–5816. [PubMed: 9671668]
18. Kipnis J, et al. Neuroprotective autoimmunity: naturally occurring CD4⁺CD25⁺ regulatory T cells suppress the ability to withstand injury to the central nervous system. *Proc Natl Acad Sci USA.* 2002; 26:15620–15625.
19. Kipnis J, et al. Neuronal survival after CNS insult is determined by a genetically encoded autoimmune response. *J Neurosci.* 2001; 21:4564–4571. [PubMed: 11425884]
20. Serpe CJ, Sanders VM, Jones KJ. Kinetics of facial motoneuron loss following facial nerve transection in severe combined immunodeficient mice. *J Neurosci Res.* 2000; 62:273–278. [PubMed: 11020219]
21. Barouch R, Schwartz M. Autoreactive T cells induce neurotrophin production by immune and neural cells in injured rat optic nerve: implications for protective autoimmunity. *FASEB J.* 2002; 16:1304–1306. [PubMed: 12154003]
22. Kipnis J, et al. T cell immunity to copolymer 1 confers neuroprotection on the damaged optic nerve: possible therapy for optic neuropathies. *Proc Natl Acad Sci USA.* 2000; 97:7446–7451. [PubMed: 10861010]
23. Hauben E, et al. Passive or active immunization with myelin basic protein promotes recovery from spinal cord contusion. *J Neurosci.* 2000; 20:6421–6430. [PubMed: 10964948]
24. Yoles E, et al. Protective autoimmunity is a physiological response to CNS trauma. *J Neurosci.* 2001; 21:3740–3748. [PubMed: 11356861]
25. Urra X, Miro F, Chamorro A, Planas AM. Antigen-specific immune reactions to ischemic stroke. *Front Cell Neurosci.* 2014; 8:278. [PubMed: 25309322]

26. Becker KJ, et al. Autoimmune responses to the brain after stroke are associated with worse outcome. *Stroke*. 2011; 42:2763–2769. [PubMed: 21799171]
27. Zierath D, et al. CNS immune responses following experimental stroke. *Neurocrit Care*. 2010; 12:274–284. [PubMed: 19714497]
28. Planas AM, et al. Brain-derived antigens in lymphoid tissue of patients with acute stroke. *J Immunol*. 2012; 188:2156–2163. [PubMed: 22287710]
29. Gee JM, Kalil A, Thullbery M, Becker KJ. Induction of immunologic tolerance to myelin basic protein prevents central nervous system autoimmunity and improves outcome after stroke. *Stroke*. 2008; 39:1575–1582. [PubMed: 18323496]
30. Seong SY, Matzinger P. Hydrophobicity: an ancient damage-associated molecular pattern that initiates innate immune responses. *Nat Rev Immunol*. 2004; 4:469–478. [PubMed: 15173835]
31. Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. *Annu Rev Immunol*. 2012; 30:531–564. [PubMed: 22224781]
32. Liesz A, et al. Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke. *Nat Med*. 2009; 15:192–199. [PubMed: 19169263]
33. Kleinschnitz C, et al. Regulatory T cells are strong promoters of acute ischemic stroke in mice by inducing dysfunction of the cerebral microvasculature. *Blood*. 2013; 121:679–691. [PubMed: 23160472]
34. Walsh JT, et al. Regulatory T cells in central nervous system injury: a double-edged sword. *J Immunol*. 2014; 193:5013–5022. [PubMed: 25320276]
35. Walsh JT, Kipnis J. Regulatory T cells in CNS injury: the simple, the complex and the confused. *Trends Mol Med*. 2011; 17:541–547. [PubMed: 21741881]
36. Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. *Nat Med*. 2011; 17:796–808. [PubMed: 21738161]
37. Gadani SP, Walsh JT, Smirnov I, Zheng J, Kipnis J. The glia-derived alarmin IL-33 orchestrates the immune response and promotes recovery following CNS injury. *Neuron*. 2015; 85:703–709. [PubMed: 25661185]
38. Bryniskikh A, Warren T, Zhu J, Kipnis J. Adaptive immunity affects learning behavior in mice. *Brain Behav Immun*. 2008; 22:861–869. [PubMed: 18249087]
39. Kipnis J, Cohen H, Cardon M, Ziv Y, Schwartz M. T cell deficiency leads to cognitive dysfunction: implications for therapeutic vaccination for schizophrenia and other psychiatric conditions. *Proc Natl Acad Sci USA*. 2004; 101:8180–8185. [PubMed: 15141078]
40. Radjavi A, Smirnov I, Kipnis J. Brain antigen-reactive CD4⁺ T cells are sufficient to support learning behavior in mice with limited T cell repertoire. *Brain Behav Immun*. 2014; 35:58–63. [PubMed: 24012647]
41. Filiano AJ, et al. Unexpected role of interferon- γ in regulating neuronal connectivity and social behaviour. *Nature*. 2016; 535:425–429. [PubMed: 27409813]
42. Moy SS, et al. Sociability and preference for social novelty in five inbred strains: an approach to assess autistic-like behavior in mice. *Genes Brain Behav*. 2004; 3:287–302. [PubMed: 15344922]
43. Cohen H, et al. Maladaptation to mental stress mitigated by the adaptive immune system via depletion of naturally occurring regulatory CD4⁺CD25⁺ cells. *J Neurobiol*. 2006; 66:552–563. [PubMed: 16555237]
44. Quinlins KM, Cox KH, Rissman EF. Immune deficiency influences juvenile social behavior and maternal behavior. *Behav Neurosci*. 2015; 129:331–338. [PubMed: 26030431]
45. Rattazzi L, et al. CD4⁺ but not CD8⁺ T cells revert the impaired emotional behavior of immunocompromised *RAG-1*-deficient mice. *Transl Psychiatry*. 2013; 3:e280. [PubMed: 23838891]
46. Derecki NC, et al. Regulation of learning and memory by meningeal immunity: a key role for IL-4. *J Exp Med*. 2010; 207:1067–1080. [PubMed: 20439540]
47. Wolf SA, et al. CD4-positive T lymphocytes provide a neuroimmunological link in the control of adult hippocampal neurogenesis. *J Immunol*. 2009; 182:3979–3984. [PubMed: 19299695]

48. Radjavi A, Smirnov I, Derecki N, Kipnis J. Dynamics of the meningeal CD4⁺ T-cell repertoire are defined by the cervical lymph nodes and facilitate cognitive task performance in mice. *Mol Psychiatry*. 2014; 19:531–533. [PubMed: 23752249]
49. Balschun D, et al. Interleukin-6: a cytokine to forget. *FASEB J*. 2004; 18:1788–1790. [PubMed: 15345694]
50. Supekar K, et al. Brain hyperconnectivity in children with autism and its links to social deficits. *Cell Rep*. 2013; 5:738–747. [PubMed: 24210821]
51. Yizhar O, et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*. 2011; 477:171–178. [PubMed: 21796121]
52. Prieto JJ, Peterson BA, Winer JA. Morphology and spatial distribution of GABAergic neurons in cat primary auditory cortex (AI). *J Comp Neurol*. 1994; 344:349–382. [PubMed: 7914896]
53. Clark SM, et al. Reduced kynurenine pathway metabolism and cytokine expression in the prefrontal cortex of depressed individuals. *J Psychiatry Neurosci*. 2016; 41:386–394. [PubMed: 27070351]
54. Dahl J, et al. The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. *Psychoneuroendocrinology*. 2014; 45:77–86. [PubMed: 24845179]
55. Gupta S, Aggarwal S, Roshanravan B, Lee T. Th1- and Th2-like cytokines in CD4⁺ and CD8⁺ T cells in autism. *J Neuroimmunol*. 1998; 85:106–109. [PubMed: 9627004]
56. Li X, et al. Elevated immune response in the brain of autistic patients. *J Neuroimmunol*. 2009; 207:111–116. [PubMed: 19157572]
57. Masi A, et al. Cytokine aberrations in autism spectrum disorder: a systematic review and meta-analysis. *Mol Psychiatry*. 2015; 20:440–446. [PubMed: 24934179]
58. Saresella M, et al. An autistic endophenotype results in complex immune dysfunction in healthy siblings of autistic children. *Biol Psychiatry*. 2009; 66:978–984. [PubMed: 19699471]
59. Heo Y, Zhang Y, Gao D, Miller VM, Lawrence DA. Aberrant immune responses in a mouse with behavioral disorders. *PLoS ONE*. 2011; 6:e20912. [PubMed: 21799730]
60. Careaga M, et al. Immune endophenotypes in children with autism spectrum disorder. *Biol Psychiatry*. 2015; 81:434–441. [PubMed: 26493496]
61. Zhu PJ, et al. Suppression of PKR promotes network excitability and enhanced cognition by interferon- γ mediated disinhibition. *Cell*. 2011; 147:1384–1396. [PubMed: 22153080]
62. Schroder K, Hertzog PJ, Ravasi T, Hume DA. Interferon- γ : an overview of signals, mechanisms and functions. *J Leukoc Biol*. 2004; 75:163–189. [PubMed: 14525967]
63. Hu X, et al. Sensitization of IFN- γ Jak-STAT signaling during macrophage activation. *Nat Immunol*. 2002; 3:859–866. [PubMed: 12172544]
64. Lemoine R, et al. Interferon gamma licensing of human dendritic cells in T-helper-independent CD8⁺ alloimmunity. *Blood*. 2010; 116:3089–3098. [PubMed: 20644110]
65. Bhat R, et al. Inhibitory role for GABA in autoimmune inflammation. *Proc Natl Acad Sci USA*. 2010; 107:2580–2585. [PubMed: 20133656]
66. Kerschensteiner M, et al. Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor *in vitro* and in inflammatory brain lesions: a neuroprotective role of inflammation? *J Exp Med*. 1999; 189:865–870. [PubMed: 10049950]
67. Leon-Ponte M, Ahern GP, O'Connell PJ. Serotonin provides an accessory signal to enhance T-cell activation by signaling through the 5-HT₇ receptor. *Blood*. 2007; 109:3139–3146. [PubMed: 17158224]
68. Iliff JJ, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Sci Transl Med*. 2012; 4:147ra111.
69. Konsman JP, Tridon V, Dantzer R. Diffusion and action of intracerebroventricularly injected interleukin-1 in the CNS. *Neuroscience*. 2000; 101:957–967. [PubMed: 11113345]
70. Vitkovic L, et al. Cytokine signals propagate through the brain. *Mol Psychiatry*. 2000; 5:604–615. [PubMed: 11126391]
71. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell*. 2014; 157:121–141. [PubMed: 24679531]

72. Dinan TG, Cryan JF. The impact of gut microbiota on brain and behaviour: implications for psychiatry. *Curr Opin Clin Nutr Metab Care*. 2015; 18:552–558. [PubMed: 26372511]
73. Kelley KW, et al. Cytokine-induced sickness behavior. *Brain Behav Immun*. 2003; 17(Suppl 1):S112–S118. [PubMed: 12615196]
74. Bluthé RM, Michaud B, Poli V, Dantzer R. Role of IL-6 in cytokine-induced sickness behavior: a study with IL-6 deficient mice. *Physiol Behav*. 2000; 70:367–373. [PubMed: 11006436]
75. Bluthé RM, et al. Synergy between tumor necrosis factor alpha and interleukin-1 in the induction of sickness behavior in mice. *Psychoneuroendocrinology*. 1994; 19:197–207. [PubMed: 8190839]
76. Blank T, et al. Brain endothelial- and epithelial-specific interferon receptor chain 1 drives virus-induced sickness behavior and cognitive impairment. *Immunity*. 2016; 44:901–912. [PubMed: 27096319]
77. Quan N, Stern EL, Whiteside MB, Herkenham M. Induction of pro-inflammatory cytokine mRNAs in the brain after peripheral injection of subseptic doses of lipopolysaccharide in the rat. *J Neuroimmunol*. 1999; 93:72–80. [PubMed: 10378870]
78. Tonelli LH, Postolache TT. Tumor necrosis factor alpha, interleukin-1 beta, interleukin-6 and major histocompatibility complex molecules in the normal brain and after peripheral immune challenge. *Neurol Res*. 2005; 27:679–684. [PubMed: 16197804]
79. van Dam AM, Brouns M, Louisse S, Berkenbosch F. Appearance of interleukin-1 in macrophages and in ramified microglia in the brain of endotoxin-treated rats: a pathway for the induction of non-specific symptoms of sickness? *Brain Res*. 1992; 588:291–296. [PubMed: 1393581]
80. Bluthé RM, Dantzer R, Kelley KW. Effects of interleukin-1 receptor antagonist on the behavioral effects of lipopolysaccharide in rat. *Brain Res*. 1992; 573:318–320. [PubMed: 1387028]
81. Hart BL. Biological basis of the behavior of sick animals. *Neurosci Biobehav Rev*. 1988; 12:123–137. [PubMed: 3050629]
82. Shakhar K, Shakhar G. Why do we feel sick when infected — can altruism play a role? *PLoS Biol*. 2015; 13:e1002276. [PubMed: 26474156]
83. Bos N, Lefevre T, Jensen AB, d'Ettorre P. Sick ants become unsociable. *J Evol Biol*. 2012; 25:342–351. [PubMed: 22122288]
84. Kazlauskas N, Klappenbach M, Depino AM, Locatelli FF. Sickness behavior in honey bees. *Front Physiol*. 2016; 7:261. [PubMed: 27445851]
85. Klein SL. Parasite manipulation of the proximate mechanisms that mediate social behavior in vertebrates. *Physiol Behav*. 2003; 79:441–449. [PubMed: 12954438]
86. Reiber C, et al. Change in human social behavior in response to a common vaccine. *Ann Epidemiol*. 2010; 20:729–733. [PubMed: 20816312]
87. Campbell IL, Hofer MJ, Pagenstecher A. Transgenic models for cytokine-induced neurological disease. *Biochim Biophys Acta*. 2010; 1802:903–917. [PubMed: 19835956]
88. Ottum PA, Arellano G, Reyes LI, Iruretagoyena M, Naves R. Opposing roles of interferon-gamma on cells of the central nervous system in autoimmune neuroinflammation. *Front Immunol*. 2015; 6:539. [PubMed: 26579119]
89. Chesler DA, Reiss CS. The role of IFN- γ in immune responses to viral infections of the central nervous system. *Cytokine Growth Factor Rev*. 2002; 13:441–454. [PubMed: 12401479]
90. Boeke, JD., Stoye, JP. Retroviruses. Coffin, JM. Hughes, SH., Varmus, HE., editors. Cold Spring Harbor Laboratory Press; 1997.
91. Mouse Genome Sequencing Consortium et al. Initial sequencing and comparative analysis of the mouse genome. *Nature*. 2002; 420:520–562. [PubMed: 12466850]
92. Mi S, et al. Syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. *Nature*. 2000; 403:785–789. [PubMed: 10693809]
93. Fasching L, et al. TRIM28 represses transcription of endogenous retroviruses in neural progenitor cells. *Cell Rep*. 2015; 10:20–28. [PubMed: 25543143]
94. Frank O, et al. Human endogenous retrovirus expression profiles in samples from brains of patients with schizophrenia and bipolar disorders. *J Virol*. 2005; 79:10890–10901. [PubMed: 16103141]
95. Christensen T. Human endogenous retroviruses in neurologic disease. *APMIS*. 2016; 124:116–126. [PubMed: 26818266]

96. Li W, et al. Human endogenous retrovirus-K contributes to motor neuron disease. *Sci Transl Med*. 2015; 7:307ra153.
97. Slokar G, Hasler G. Human endogenous retroviruses as pathogenic factors in the development of schizophrenia. *Front Psychiatry*. 2015; 6:183. [PubMed: 26793126]
98. Gogvadze E, Stukacheva E, Buzdin A, Sverdlov E. Human-specific modulation of transcriptional activity provided by endogenous retroviral insertions. *J Virol*. 2009; 83:6098–6105. [PubMed: 19339349]
99. Fort A, et al. Deep transcriptome profiling of mammalian stem cells supports a regulatory role for retrotransposons in pluripotency maintenance. *Nat Genet*. 2014; 46:558–566. [PubMed: 24777452]
100. Macfarlan TS, et al. Embryonic stem cell potency fluctuates with endogenous retrovirus activity. *Nature*. 2012; 487:57–63. [PubMed: 22722858]
101. Chuong EB, Elde NC, Feschotte C. Regulatory evolution of innate immunity through co-option of endogenous retroviruses. *Science*. 2016; 351:1083–1087. [PubMed: 26941318]
102. Flajnik MF, Kasahara M. Origin and evolution of the adaptive immune system: genetic events and selective pressures. *Nat Rev Genet*. 2010; 11:47–59. [PubMed: 19997068]
103. Huang S, et al. Discovery of an active RAG transposon illuminates the origins of V(D)J recombination. *Cell*. 2016; 166:102–114. [PubMed: 27293192]
104. Cooper MD, Herrin BR. How did our complex immune system evolve? *Nat Rev Immunol*. 2010; 10:2–3. [PubMed: 20039476]
105. Kohn GM, King AP, Dohme R, Meredith GR, West MJ. In the company of cowbirds, *Molothrus ater ater*: robust patterns of sociability predict reproductive performance. *J Comp Psychol*. 2013; 127:40–48. [PubMed: 23025262]
106. Davis MM, et al. Ligand recognition by $\alpha\beta$ T cell receptors. *Annu Rev Immunol*. 1998; 16:523–544. [PubMed: 9597140]
107. Itano AA, Jenkins MK. Antigen presentation to naive CD4 T cells in the lymph node. *Nat Immunol*. 2003; 4:733–739. [PubMed: 12888794]
108. O'Shea JJ, Paul WE. Mechanisms underlying lineage commitment and plasticity of helper CD4⁺ T cells. *Science*. 2010; 327:1098–1102. [PubMed: 20185720]
109. Curry AJ, et al. Evidence that cytokine-mediated immune interactions induced by *Schistosoma mansoni* alter disease outcome in mice concurrently infected with *Trichuris muris*. *J Exp Med*. 1995; 181:769–774. [PubMed: 7836929]
110. Hunter CA, Candolfi E, Subauste C, Van Cleave V, Remington JS. Studies on the role of interleukin-12 in acute murine toxoplasmosis. *Immunology*. 1995; 84:16–20. [PubMed: 7890300]
111. Schlager C, et al. Effector T-cell trafficking between the leptomeninges and the cerebrospinal fluid. *Nature*. 2016; 530:349–353. [PubMed: 26863192]
112. Kivisakk P, et al. Human cerebrospinal fluid central memory CD4⁺ T cells: evidence for trafficking through choroid plexus and meninges via P-selectin. *Proc Natl Acad Sci USA*. 2003; 100:8389–8394. [PubMed: 12829791]
113. Aspelund A, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med*. 2015; 212:991–999. [PubMed: 26077718]
114. Louveau A, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature*. 2015; 523:337–341. [PubMed: 26030524]
115. Engelhardt B, Ransohoff RM. Capture, crawl, cross: the T cell code to breach the blood–brain barriers. *Trends Immunol*. 2012; 33:579–589. [PubMed: 22926201]
116. Kunkel EJ, Butcher EC. Chemokines and the tissue-specific migration of lymphocytes. *Immunity*. 2002; 16:1–4. [PubMed: 11825560]
117. Yednock TA, et al. Prevention of experimental autoimmune encephalomyelitis by antibodies against $\alpha\beta$ 1 integrin. *Nature*. 1992; 356:63–66. [PubMed: 1538783]
118. Bosch I, Oehmichen M. Eosinophilic granulocytes in cerebrospinal fluid: analysis of 94 cerebrospinal fluid specimens and review of the literature. *J Neurol*. 1978; 219:93–105. [PubMed: 81295]

119. Degn M, et al. Increased prevalence of lymphoid tissue inducer cells in the cerebrospinal fluid of patients with early multiple sclerosis. *Mult Scler*. 2016; 22:1013–1020. [PubMed: 26453677]
120. Gadani SP, Smirnov I, Smith AT, Overall CC, Kipnis J. Characterization of meningeal type 2 innate lymphocytes and their response to CNS injury. *J Exp Med*. 2016; 214:285–296. [PubMed: 27994070]
121. Kowarik MC, et al. Immune cell subtyping in the cerebrospinal fluid of patients with neurological diseases. *J Neurol*. 2014; 261:130–143. [PubMed: 24162037]
122. Laperchia C, et al. Two-photon microscopy imaging of *thy1*GFP-M transgenic mice: a novel animal model to investigate brain dendritic cell subsets *in vivo*. *PLoS ONE*. 2013; 8:e56144. [PubMed: 23409142]
123. McGavern DB, Kang SS. Illuminating viral infections in the nervous system. *Nat Rev Immunol*. 2011; 11:318–329. [PubMed: 21508982]
124. Reuter U, et al. Delayed inflammation in rat meninges: implications for migraine pathophysiology. *Brain*. 2001; 124:2490–2502. [PubMed: 11701602]
125. Sayed BA, Christy AL, Walker ME, Brown MA. Meningeal mast cells affect early T cell central nervous system infiltration and blood-brain barrier integrity through TNF: a role for neutrophil recruitment? *J Immunol*. 2010; 184:6891–6900. [PubMed: 20488789]
126. Garcia E, Aguilar-Cevallos J, Silva-Garcia R, Ibarra A. Cytokine and growth factor activation *in vivo* and *in vitro* after spinal cord injury. *Mediators Inflamm*. 2016; 2016:9476020. [PubMed: 27418745]

Figure 1. Immune cells reside in meningeal spaces

The schematic representation shows the three membranes that comprise the meninges: the dura, arachnoid and pia. A full complement of immune cells has been observed in the dura and subarachnoid layers of the meninges and in the cerebrospinal fluid (CSF)^{112,114,118–125}. DC, dendritic cell.

Figure 2. A summary of T cell activity in the injured CNS

Effector T cells (T_{eff} cells) have diverse effects on outcome following CNS injury; they are capable of promoting either neuroprotection or neurodegeneration. In turn, T_{eff} cell activity is inhibited by regulatory T cells (T_{reg} cells), and thus T_{reg} cells can have either beneficial or detrimental effects on outcome. Several mechanisms of T cell-derived harm (parts **a–c**) and benefit (parts **d–f**) have been proposed. **a** | T cells that acquire either the type 1 T helper (T_H1) or T_H17 phenotypes after CNS injury can secrete cytokines such as interleukin-17 (IL-17), IL-23 and interferon- γ (IFN γ), which have detrimental actions¹²⁶. **b** | In certain circumstances, T cells can acquire detrimental auto-immune activity, skewing to a T_H1 phenotype and resulting in increased tissue injury. **c** | T_H1-derived and T_H17-derived cytokines direct local myeloid cells towards a pathological phenotype. Opposite mechanisms have been attributed to beneficial T cells and are typically associated with the T_H2 phenotype. **d** | Following CNS injury, T cells are activated by a major histocompatibility complex class II (MHC II)-independent, myeloid differentiation primary response protein 88 (MYD88)-dependent signal that promotes T_H2 skew and IL-4 production. IL-4 and brain-derived neurotrophic factor (BDNF), which is produced by CD4⁺ T cells, are directly neuroprotective. **e** | Certain autoreactive T cells are known to have special neuroprotective qualities. In particular, they more readily accumulate to sites of injury than do other T cells, and they are neuroprotective at these sites. **f** | T_H2 cells modulate myeloid cells at the injury site, promoting a tissue-healing phenotype. T_H2-derived IL-4 is a promising candidate to mediate macrophage skew, but more work is needed to better understand the molecular mechanisms of these interactions. APC, antigen-presenting cell; TCR, T cell receptor.

Figure 3. IFN γ is necessary for social behaviour

A large proportion of meningeal T cells can produce interferon- γ (IFN γ); which is encoded by *Ifng*; from the meninges, IFN γ presumably reaches the cerebrospinal fluid (CSF) (dashed arrows). From here, small molecules (<40 kDa) can enter the brain parenchyma through paravascular influx across astrocyte end-feet. IFN γ in the CSF can directly activate layer I inhibitory neurons and boost tonic inhibition of excitatory neurons in the prefrontal cortex (PFC). Mice that lack T cells or IFN γ have aberrant hyperconnectivity (represented by red markings; lower panels) in the PFC and social deficits. Normal social behaviour can be rescued in IFN γ -deficient mice by injecting IFN γ into the CSF or by boosting GABAergic inhibition. AAV, adeno-associated virus; Cre, Cre recombinase; *Ifngr1*, gene that encodes IFN γ receptor 1; *Prkdc*, protein kinase, DNA-activated, catalytic polypeptide; *Syn*, synectin; *Vgat*, vesicular GABA transporter; VLA4, very late antigen 4.

Figure 4. Proposed mechanisms for the role of IFN γ in a hypothesized evolutionary ‘arms race’ Signal transducer and activator of transcription (STAT)-induced genes are enriched in primitive social organisms such as *Drosophila* spp. Viruses (shown in green in this schematic) infect a host and upregulate STAT-dependent transcription of pro-social genes; this promotes aggregation and enhances the spread of the viral genes. Retroviruses can integrate into the host genome, and germline integration of the viral sequences results in vertical transmission and passage of viral DNA. As viral sequences integrated into a host genome can transfer through vertical transmission, these sequences can transmit without inducing sickness behaviour in the host (unlike an acute infection). If transposition results in an upregulation of STAT-dependent transcription of pro-social genes, this could increase the reproductive fitness of the host and further promote increased vertical transmission of viral sequences using natural selection. Further positive selection could arise if transposition of endogenous retroviruses (ERVs) expanded to include target genes for anti-pathogen responses. This would ensure greater immunity (for example, in response to the red virus in the schematic) and increased fitness during times of aggregation and mating. Beyond this, transposition of viral DNA leads to the evolution of adaptive immunity (including the assembly of variable, diversity and joining (VDJ) genes for antigen receptors) and to increased efficiency for defence against pathogens. IFN γ , interferon- γ .