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Infectious immunity in the central nervous system and brain function

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Abstract

Inflammation is emerging as a critical mechanism underlying neurological disorders of various etiologies, yet its role in altering brain function as a consequence of neuroinfectious disease remains unclear. Although acute alterations in mental status due to inflammation are a hallmark of central nervous system (CNS) infections with neurotropic pathogens, post-infectious neurologic dysfunction has traditionally been attributed to irreversible damage caused by the pathogens themselves. More recently, studies indicate that pathogen eradication within the CNS may require immune responses that interfere with neural cell function and communication without affecting their survival. In this Review we explore inflammatory processes underlying neurological impairments caused by CNS infection and discuss their potential links to established mechanisms of psychiatric and neurodegenerative diseases.

Neuroinfectious diseases are associated with acute changes in mental and motor function that are followed by chronic neurological dysfunction that can persist long after recovery from the infectious event[1–4]. During the acute stage, CNS invasion by neurotropic pathogens activates inflammatory responses that control replication and/or coordinate their elimination. Brain cells, including resident macrophages and microglia, endothelial cells, ependymal cells, neurons and glia (astrocytes and oligodendrocytes) express innate immune molecules that induce the recruitment of leukocytes into infected CNS compartments to promote pathogen clearance. Innate immune responses also induce the expression of inflammatory mediators, which may exert cell- and region-specific influences on brain function (Fig. 1). Thus, initial inflammatory events during pathogen neuroinvasion are often associated with clinical signs that not only identify the CNS site of infection but are the result of

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pathophysiological events that affect blood–brain barrier (BBB) function, cerebral metabolism, oxygen consumption and blood flow. Clinical signs of acute infection induce adaptive changes in behavior, including fatigue, hypersomnia, depressed activity, decreased social interactions and inability to concentrate[5]. These behavioral effects are mediated by cytokines and serve to conserve energy and promote survival. However, inflammatory responses during neuroinfectious diseases may progress to focal neurological deficits, delirium, obtundation or even coma. The role of the inflammatory response in worsening morbidity and mortality during acute infections of the CNS is also evidenced by the standard use of anti-inflammatory agents to limit immune system–mediated effects[6] and the lack of prodromal and focal symptoms observed in immuno-compromised hosts[7].

Historically, post-infection neurological sequelae have been attributed to acute neuronal death caused by the invading pathogen or the immune response to it. Animal models of neuroinfectious diseases support the idea that CNS injury mediated by pathogens or lymphocytes underlies permanent loss of motor and cognitive function[8]. Explanations for the focality of neurological symptoms in patients thus rely on the CNS regions acutely infected, as determined on the basis of initial MRI results[9]. However, neurological dysfunction in patients that survive CNS infections is not always consistent with prior neuroimaging findings[10], and rodent models of neuroinfectious diseases do not always show extensive brain damage in survivors[11]. In addition, chronic complications from neuroinfectious diseases have been linked to ongoing inflammatory processes within the CNS that are acutely induced by innate and adaptive immune responses to infectious agents but may persist in the absence of ongoing pathogen replication and exhibit different cell- or region-specific effects from those of the inciting pathogen[12–14]. Moreover, events triggered in the acute setting of CNS infection may lead to neurological sequelae via mechanisms similar to those observed with normal aging or in noninfectious, neurological disorders such as Alzheimer's disease[12,15]. Thus, in contrast to acute infection, post-infectious, chronic inflammatory processes within the CNS can cause maladaptive behavioral alterations that manifest as depression, decreased cognition, impaired learning or loss of fine adjustments in motor and mental functions. In this Review we explore chronic inflammatory processes underlying neurological impairments due to CNS infection and discuss their potential links to established mechanisms of psychiatric or neurodegenerative disorders.

CNS anatomy dictates immune responses to invading pathogens

The CNS has a high degree of anatomic and cellular heterogeneity that exerts profound effects on most facets of brain function and behavior and may provide insights into various aspects of disease pathogenesis during infections. The meninges, CNS parenchyma and ventricular system each have distinct vascular structural components that may limit the entry of certain pathogens and particular leukocyte subsets while providing abluminal localizing cues that promote immune cell interactions[16]. Fluids from each of these compartments, along with cerebrospinal fluid (CSF), which is formed continuously by the choroid plexus within the fourth ventricle, drain into cervical lymph nodes via lymphatic vessels that may also contain antigen-specific immune cells[17]. Parenchymal interstitial fluids drain through paravenous pathways, which have basement membranes that may limit the egress of immune cells[18]. The CNS parenchyma is divided into forebrain, midbrain and hindbrain regions that

contain gray and white matter areas of neuronal cell bodies and their myelinated tracts, respectively. Neurons, astrocytes, oligodendrocytes and microglia within disparate CNS regions show extensive functional and immunological heterogeneity that may result in regional differences in innate and adaptive immune responses[19,20]. Here we will briefly discuss the vascular specializations and cell- and region-specific proinflammatory responses within CSF and parenchymal compartments that control acute infections and leukocyte recruitment (reviewed in this issue)[21]. These CNS compartment–specific responses may also promote post-infection complications via inflammatory molecule–mediated alterations in neurological pathways that affect motor and cognitive functions such as motivation and reward, memory, learning behaviors and functional fine tuning (Table 1).

Bacteria, fungi, viruses and parasites may initially gain access to the CSF across vessels within the meninges and ventricular system, which are fenestrated and nonrestrictive[22]. In comparison, CNS parenchymal vessels have specializations that provide a barrier to blood-borne pathogens, cells and large molecules. The meningeal arachnoid membrane and ventricular choroid plexus epithelial cells have intercellular tight junctions, comprising claudins 1, 2 and 3 (ref. 23), that help restrict the invasion of pathogens into the CNS parenchyma. CSF circulates throughout the ventricular system and subarachnoid space of the meninges via apertures between these compartments[24], allowing detection of pathogens via meningeal CSF sampling. During pathogen invasion, meningeal cells express the cellular adhesion molecule ICAM-1 and the neutrophil chemoattractant CXCL2 (refs. 25,26), and brain endothelial cells upregulate ICAM-2 and the neutrophil chemoattractants leukotriene B_4 and complement component C5a[27,28]. The infiltration of neutrophils into these compartments is critical for pathogen clearance but leads to the clinical signs of meningitis, a classic triad of headache, neck stiffness (meningismus) and photophobia. These signs are the result of catecholamine expression by phagocytes exposed to bacterial products[29], which promotes mydriasis, leading to excessive transfer of light to the brain and vasospasm[30]. Antigen-presenting cells (APCs) that reside within the choroid plexus and meninges express major histocompatibility complex class II and the C-type lectin receptor DNGR-1, also known as CLEC9A[31], a marker of dendritic cell subsets with functional similarity to lymphoid and tissue dendritic cells. These resident APCs provide a mechanism for local restimulation of infiltrating T cells, which is required for their extravasation into the CNS parenchyma[32,33]. High concentrations of proinflammatory cytokines within the CSF of patients with infectious meningitis are associated with impaired cognition and correlate with poor outcome[34,35]. Resolution of meningitis requires both administration of antimicrobials and immunocompetence[36], the latter of which enables the recruitment of lymphocytes and monocytes in response to upregulation of vascular cell adhesion molecule 1 (VCAM-1) and expression of chemoattractants such as CCL5, CXCL9, CXCL10 and CXCL11 on vessels[37]. Although baseline surveillance of the meninges and choroid plexus by interleukin 4 (IL-4)-expressing $CD4^+$ type 2 helper T (T_H2) cells is critical for the performance of cognitive tasks[38], high concentrations of T_H1 cytokines such as IL-1β, tumor necrosis factor (TNF) and interferon-γ (IFN-γ) may result in continued cognitive impairment after bacterial meningitis, as suggested by studies in animal models using agents that target these molecules[3]. Although the mechanisms that cause cognitive impairment during acute meningitis are incompletely understood, studies suggest involvement of global and regional

disruptions in neurogenesis[39], synaptic coupling[40] and neuronal circuitry[41], all of which underlie various aspects of perception, mood, learning and memory formation.

Within the CNS, the BBB functions as a communication conduit with the immune system. It is a highly selective barrier that separates the CNS parenchyma from the blood at the capillary and post-capillary levels while responding to luminal and abluminal immune signals, coordinating interactions between cells at both interfaces during CNS infections[32]. The cellular constituents of the BBB form the neurovascular unit (NVU), comprising endothelial cells with ensheathing pericytes and astrocyte endfeet, which modulates BBB integrity and responds to infiltrating pathogens, immune cells and the metabolic demands of neurons[42]. The functional integrity of the BBB is achieved by junctional complexes that prevent permeation of solute, cells and pathogens through paracellular routes and connect BBB endothelial cells to each other and to the cytoskeleton via scaffolding proteins. Adherens junctions are comprised of cadherin proteins and link to actin filaments via α-, β- and γ-catenin, while tight junctions, formed by occludins and claudins, link to the cystokeleton via the scaffolding and regulatory proteins ZO-1, ZO-2, ZO-3 and cingulin. Activation of Rho GTPases regulates the length of actin fibers, which in turn controls the integrity of both adherens junction and tight junction complexes. Claudin 3 or claudin 5 is required for tight junction formation and may be decreased in the setting of certain neuroinfectious diseases[43].

Host detection of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) at the NVU directly regulates BBB integrity and tight junction formation via induction of innate cytokines (Table 2), including type I i (IFN-α and IFN-β), type III interferon (IFN-λ), TNF and IL-1β, which differentially activate the small GTPases Rac1 and RhoA[44,45]. Direct signaling of the type I interferon receptor, IFNAR, and of the IFN-λ receptor, IFNLR, at the NVU promotes BBB closure, limiting further entry of neurotropic viruses, whereas TNF and IL-1β open the barrier. Brain endothelial cells and astrocytes also express the TAM receptors Mertk and Axl, receptor tyrosine kinases that diminish host innate immune responses upon binding with their ligands, Gas6 and Protein S. Mertk and Axl recognize phosphatidylserine displayed by the outer membrane of enveloped viruses[46]. IFNAR and Mertk synergistic signaling at the BBB ‘preferentially’ activates the cytoskeletal regulatory GTPase Rac1, which enhances endothelial barrier function and limits the expression of barrier-disrupting inflammatory cytokines, including IL-1β and TNF[47]. Cytokine-mediated disruption of the BBB may impair cognition and motor function via increased leukocyte entry into the hippocampus or basal ganglia, as has been observed in post-surgical patients and in those with Parkinson’s disease or CNS lupus[48–50]. In addition, CXCL10 expressed downstream of IFNAR signaling in brain endothelial cells induces lethargy and cognitive dysfunction during viral infection via impaired presynaptic release of neurotransmitter within the hippocampus, weakening synaptic long-term potentiation[51].

Pathogenic invasion of the CNS parenchyma is met with strong cell- and region-specific local innate immune responses that limit replication and cellular tropism while inducing antimicrobial responses throughout the CNS. The initial immune response depends on the route of entry; viruses may invade via anterograde or retrograde trafficking along neurites from peripheral neurons, including those of the olfactory neuroepithelium and spinal tracts,

whereas other pathogens enter via paracellular or transcellular paths across the BBB[22]. PRRs are expressed along all routes of invasion, inducing interferons upon PAMP-induced activation[52] (Box 1).

Box 1

Enhanced innate immune responses of hindbrain neurons and astrocytes

Astrocytes and neurons in hindbrain regions show enhanced immune signatures at baseline and in response to an inflammatory stimulus. Early *in vitro* experiments demonstrated that brain stem astrocytes had higher expression of major histocompatibility complex class II and ICAM-I than various forebrain structures[58]. Cerebellar and spinal cord astrocytes additionally released higher basal levels of many chemokines and cytokines *in vitro*, including IL-1β, CCL2, IL-6 and IL-9, than cortical astrocytes, and brain region had specific effects on chemokine or cytokine expression after exposure to HIV proteins[175]. *In situ* hybridization studies have shown that interferon-stimulated gene ISG-49 (also known as IFIT-3) is highly expressed in the Purkinje cell layer, corpus callosum and choroid plexus after lymphocytic choriomeningitis virus infection. In contrast, ISG-56 (IFIT-1) is most highly expressed in the olfactory bulb and olfactory neurons. Striking differences in ISG expression occur even in neuronal subpopulations within a given region. For example, whereas ISG-49 is present at high concentrations in Purkinje cells and molecular and granule neurons of the cerebellum, ISG-56 is primarily restricted to the granule neuron layer and ISG-54 (IFIT-2) is found in the Purkinje cell layer. Granule cell neurons also express high amounts of ISG-49 and ISG-56 after WNV infection[176]. Differences in expression of innate immune-associated genes can be seen at baseline. Microarray analysis comparing granule cell neurons of the cerebellum to cortical neurons of the cerebral cortex has shown that expression of interferon-related genes, including *Ifit1*, *Irf7*, *Stat1* and *OasI*, is higher in cerebellar granule cell neurons. Granule cell neurons show increased resistance to viral infection at baseline and in response to IFN-β treatment. The kinetics response to IFN-β treatment is also increased in cerebellar granule cell neurons, as several genes including *Ifit1*, *Rsad2* and *Oas* reached peak expression levels at an earlier time point than did cortical neurons[177].

Astrocytes have a variety of neuroprotective functions, including buffering of ions, glutamate and other neurotransmitters and regulation of synaptic function, neuronal repair and BBB integrity, in addition to producing neurotrophic factors and anti-inflammatory cytokines such as IL-10 (refs. 53,54). Astrocyte heterogeneity during physiological conditions is based on their morphology, function and localization in white and gray matter and is well established[55]. However, studies indicate substantial regional heterogeneity in astrocyte function during neuroinflammatory disease and injury[41,56]. *In vitro* baseline expression of PRRs, cytokines and chemokines varies among astrocytes derived from different regions of the CNS[57,58], supporting *in vivo* observations of differences in susceptibility and clearance between brain regions during neuroinfectious diseases (Box 1). After infection, astrocytes respond to Toll-like receptor and NOD-like receptor signals by expressing complement components, interferons, IL-1β, IL-6 and chemokines[59]. Although

these responses might augment pathogen clearance, they may also negatively affect neuronal function and survival through alterations in astrocyte homeostasis. For example, impaired glutamate uptake contributes to synaptic loss, impairment of neurogenesis and neurotoxicity[60,61], which lead to poor clinical outcome after neuroinflammation.

Microglia, the only resident myeloid cells within the CNS parenchyma, also respond to microbial pathogens via recognition of PAMPs by PRRs, which can result in the transcription of genes encoding IL-1 family cytokines including IL-1β, IL-18 and IL-33 (ref. 62). There is evidence that both local expansion of microglia and recruitment of bone marrow–derived monocytes into the CNS parenchyma can contribute to increased phagocytosis of pathogens during neuroinfectious diseases[63,64]. Thus, although the relative abundance of microglia differs among brain regions, with lower numbers observed in hindbrain[65], this may be altered during CNS infections. However, as microglial activation contributes to local neurodegeneration[66], the relative disparity in numbers may provide additional means for limiting the effects of their secreted cytokines within hindbrain regions. Microglia derived from different brain regions also show differences in levels of nitric oxide (NO), glutamate uptake and TNF expression upon activation with lipopolysaccharide (LPS)[67] and may remain activated after resolution of CNS infection[12].

Infections of CSF compartments and brain function

Acute infection of the CSF compartments by bacteria and fungi causes the classical sickness behaviors described above and, if inadequately treated, can cause permanent CNS injury and damage leading to deficits in vision, hearing, cognition and motor function[68]. Although antimicrobials are critical for limiting CNS damage by proliferating pathogens, antimicrobial treatment without control of inflammation may result in paradoxically worse outcomes by stimulating the release of bacterial or fungal components that further provoke immunopathological responses adjacent to brain parenchyma[69,70]. Consistent with this, survivors of acute bacterial meningitis caused by *Streptococcus pneumoniae* or *Neisseria meningitides* may show persistent neurological deficits, including cognitive dysfunction or dementia, even if they received a timely diagnosis and treatment[71]. Monocyte-derived macrophages in the CNS, particularly meningeal and perivascular macrophages, have a protective role during bacterial meningitis[72]. However, microglial recognition of pathogens or pathogen components through Toll-like receptors induces neurotoxicity through the release of cell death signals, such as oxidants, or activation of inflammasome components, including caspase-1, which cleaves pro-IL-1β to the biologically active IL-1β (ref. 73). Indeed, caspase-1 deficiency or *in vivo* use of broad caspase inhibitors in experimental models of bacterial meningitis reduces neuronal damage with mitigation of lethargy and improved motor function[74,75].

Although the innate immune response has a major role in neuronal damage during acute bacterial meningitis, adaptive immune responses may underlie ongoing neurological deficits during and after recovery from more indolent infections of the CSF compartment, such as those caused by *Mycobacterium tuberculosis* (Mtb) and *Cryptococcus neoformans* (Fig. 2). Tuberculous meningitis (TBM) represents approximately 1% of active tuberculosis cases and may present with or without concurrent pulmonary tuberculosis[76]. Patients with TBM

often present with behavioral abnormalities or psychiatric disorders in addition to other neurological symptoms[77], with ongoing neurological sequelae occurring at high frequency in survivors. Similarly, chronic meningitis due to *C. neoformans*, a pathogenic yeast that can infect the meningeal compartment in immunocompetent individuals, who account for one-third of cases[78], may present with psychosis or mania; deficits in attention, concentration and visuospatial skills[79]; or a frontal network syndrome characterized by apathy, disinhibition and decreased executive function[80]. Cryptococcal meningitis is associated with up to 30% mortality despite optimal antimicrobial therapy[81], and survivors may continue to experience neuropsychological consequences despite resolution of initial imaging abnormalities[79].

Early clinical signs in patients with TBM, which are similar to those of acute bacterial meningitis, are consistent with an early neutrophilic response. However, CSF neutrophils are replaced early in the course of TBM by T and B cells[82], and T cells may persist within the CSF compartment with or without bacterial clearance[83]. In a study that measured the numbers of Mtb antigens ESAT-6– and CFP-10–specific, IFN-γ–producing T cells within the CSF during 6 months of antibiotic treatment, patients whose T cell counts increased over time experienced a worsening of clinical symptoms, even with complete sterilization of CSF[84]. Similarly, T_H1-polarizing immunity is critical for clearance of meningeal infection with *C. neoformans* and, although concentrations of CSF IFN-γ positively correlate with survival[85], they are also associated with severe neurological disease. In addition, CNS biopsies from patients with tuberculosis or cryptococcal meningitis revealed extensive parenchymal infiltration of T cells and extensive activation of astrocytes and microglia[86]. These data suggest a role for IFN-γ–expressing T cells in ongoing neurological abnormalities in patients with chronic meningitis due to Mtb or *C. neoformans* via effects on non-neuronal cells.

Studies in animal models show that IFN-γ activation of the JAK–STAT pathway promotes microglial activation[87], which alters the activity of neuronal networks via production of cytokines, reactive oxygen species and nitrogen species[88]. However, coactivation of Toll-like receptor TLR4 and IFN-γ receptors results in neuronal dysfunction and death caused mainly by enhanced microglial expression of inducible nitric oxide synthase (iNOS) and NO release. Taken together, these studies provide a mechanism for alterations in brain function and behavior in patients with infections of the CSF compartment. Of interest, experiments using positron emission tomography (PET) tracers to quantify 18-kDa translocator protein (TSPO), a hallmark of microglial activation, show higher abundance of TSPO in patients with schizophrenia and in people with subclinical symptoms who are at high risk of psychosis[89]. Although the etiology of psychotic disorders is multifactorial and may include genetic and noninfectious environmental causes, the similarities in symptomatology and inflammatory processes between such disorders and neuroinfectious diseases are interesting and suggest generalizable innate and adaptive immune mechanisms for many types of CNS diseases. Further studies evaluating the function and antigen specificity of persistent T cells within the CNS may provide new links between microbe-specific immunity and psychiatric diseases.

Inflammation-induced CNS dysfunction in parenchymal infection

DNA and RNA viruses of different families can infect the CNS, leading to the clinical syndromes of meningitis, encephalitis or meningoencephalitis. Many DNA viruses and a few RNA viruses replicate in the nucleus, establishing latency by integrating into the cellular DNA, whereas most RNA viruses replicate primarily in the cytosol and generally do not establish latency[90]. Herpes simplex encephalitis (HSE), caused by the DNA virus HSV-1, is the most common acute, sporadic encephalitis in the United States and worldwide[91]. Arthropod-born viruses, or arboviruses, are another important cause of encephalitis[92]. West Nile virus (WNV), a positive sense RNA flavivirus, is the most widely distributed arbovirus worldwide, with cases reported on every continent but Antarctica[93]. The pathophysiology, diagnosis and management of acute HSE and WNV have been reviewed[7]. Patients with viral encephalitis of any etiology typically present with fever, headache, confusion and altered mental status but may also present with seizures or focal neurological signs. Animal and human studies have demonstrated that both innate immune responses and lymphocyte trafficking to the CNS are important mechanisms of virologic control[94,95]. Neurological and neuropsychiatric sequelae can persist or develop after encephalitis due to a variety of neurotropic pathogens, which has become a prioritized area of research[96]. Patients surviving HSE or WNV encephalitis show high rates of neurological sequelae, including memory impairment (60%), speech disorders (35%) and cognitive impairment (29%)[97]. Of the 90% of patients who survive WNV, about 50% experience cognitive sequelae deficits, including depression, fatigue, memory impairment and changes in executive function that may persist for years[98,99]. Here we will focus on mechanisms underlying neurological sequelae in HSE and WNV encephalitis in individuals with intact immunity.

Increasing evidence suggests that developmental pathways regulating synaptic plasticity by microglia and astrocytes can be reactivated during disease states. Alterations, caused by aberrant activation of glia, in synapse homeostasis may contribute to the cognitive dysfunction in many neurocognitive disorders, including autism spectrum disorders and a variety of dementias including Alzheimer's disease[100,101]. The complement system, part of innate immunity that initiates adaptive responses to clear virus peripherally[102], influences synapse homeostasis during development[103,104] and can promote synapse elimination during neurodegenerative and neuroinfectious diseases[12,15]. In a model of Alzheimer's disease using J20 transgenic mice that harbor a familial mutant of human amyloid precursor protein[105], C1q deposition preceded synapse elimination and plaque formation, and mice deficient in complement signaling had fewer phagocytic microglia and reduced synaptic elimination[15]. Loss of C1q also protected mice from synaptic elimination and downstream behavioral phenotypes in a model of dementia caused by deficiency of progranulin, a pleotropic protein that has a major role in genetic causes of frontotemporal dementia[106]. Progranulin-deficient microglia show increased lysosomal activity and complement production, leading to preferential elimination of inhibitory neurons[107]. In a model of WNV-induced memory impairment, phagocytic microglia persisted for weeks after viral clearance, and gene signatures associated with complement-mediated synapse remodeling were elevated in the hippocampus, a CNS region responsible for memory[12]. Delayed recovery from acute synapse loss correlates with poor spatial learning, and mice with fewer microglia

(*Il34*$^{-/-}$) or complement deficiency (*C3*$^{-/-}$ or *C3ar*$^{-/-}$) were protected from virus-induced synaptic elimination[12] (Fig. 3a), which suggests that aberrant microglial activation and complement-mediated deletion of neuronal communication after viral encephalitis may result in neurological sequelae seen in neurotropic virus-infected survivors.

Instituting intravenous acyclovir as the standard of care for HSE has greatly improved survival rates[108], but patients who survive acute infection are at risk for clinical neurologic relapse and the development of new neuropsychiatric symptoms, including memory loss and epilepsy[109]. PCR analysis of the CSF during relapse at times reveals an absence of CNS viral replication, leading to the hypothesis that these relapses are immune mediated[110]. In recent years, numerous studies and case reports have linked clinical relapses to the development of auto-immune encephalitis, and in particular to anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis[111] (Fig. 3b). Administration of CSF from patients with autoimmune encephalitis, but not healthy controls, to hippocampal cultures leads to a titer-dependent but reversible decrease in NMDAR density without altering the number of synapses or the density of other synaptic proteins, such as PSD-95, GluR1, GluR2 receptor clusters or GABA receptor[112]. Intracerebral infusion of patient CSF or purified IgG similarly increases *in vivo* NMDAR internalization and alteration in glutamate homeostasis and signaling[112,113]. Furthermore, these autoantibodies inhibited the development of long-term synaptic plasticity *in vitro*[114]. The recent development of a rodent model for anti-NMDAR encephalitis demonstrates that continuous infusion of patient autoantibodies can lead to behavioral deficits, providing a platform for preclinical testing[113]. Whether autoantibodies develop via molecular mimicry, secondarily to release of antigens following neuronal lysis or as a primary mechanism of neuroprotection by the immune system requires further study.

CNS infections with certain neurotropic parasites are also known to cause alterations in host behavior. Among the best known is *Toxoplasma gondii*, a common zoonotic parasite with a worldwide seroprevalance of 30–70%. *T. gondii* causes chronic CNS infection and neuroinflammation after ingestion of oocysts in contaminated food or water[115]. Ingested oocysts develop into fast-dividing tachyzoites that invade the gut epithelium and lamina propria, replicate asexually through a process called endodyogeny and then exit and infect myeloid cells, which allow dissemination to multiple tissue sites in the body (including the eye, heart, liver, lung, lymph nodes, muscles and CNS)[116]. The life cycle of *T. gondii* requires infection of feline prey intermediate hosts, whose ingestion leads to infection of feline definitive hosts[117]. Infection of the intermediate host CNS appears to be a critical stage of the *T. gondii* life cycle, ensuring successful predation via modification of the prey's olfactory preferences to reduce its avoidance of predators[118,119]. Epidemiological studies of *T. gondii* infection in humans, which may have evolved when human ancestors were still under feline predation[120], similarly link parasite seropositivity with alterations in olfactory preference and behavioral abnormalities in immunocompetent individuals, the latter of which include those associated with neurodegenerative and psychiatric diseases.

CNS invasion by *T. gondii*[121] leads to infection of all neural cell types, most of which are promptly cleared of parasite via astrocyte and microglial expression of T cell chemoattractants CCL5, CXCL9 and CXCL10, that recruit IFN-γ-expressing CD4^{+} and

CD8$^+$ T cells directed at *T. gondii* antigens[122]. Neurons remain latently infected with slowly replicating bradyzoites throughout the life of the host. In murine studies, behavioral effects of *T. gondii* are associated with direct infection of cortical neurons and astrocytes and modification of their functions, including those that affect innate immunity and dopaminergic and glutamate signaling[123,124]. Direct effects of *T. gondii* on neuronal function—including derailment of neurotransmitter expression, modulation of calcium signaling and loss of myelinated fibers, MAP-2$^+$ neurites and NeuN$^+$ cells—are all suggestive of parasite-mediated impairment or injury[125]. These effects have been proposed to underlie a variety of behavioral alterations and psychiatric diseases and certain neurodegenerative disorders observed in *T. gondii*–infected hosts. However, aversion to cat urine is also observed in rodents after clearance of cysts[126], and observations of low total cyst burden and lack of specific neuronal tropism observed in infected brain regions raise the important possibility that chronic *T. gondii* infection induces inflammatory-mediated dysfunction that does not require the persistence of parasite.

The *T. gondii*–infected CNS shows increased astrocyte expression of TNF, IL-1β and IL-6 (ref. 127), each of which has been implicated in the regulation of neural correlates of memory including adult neurogenesis, synaptic plasticity and modulation of long-term potentiation[128–130]. Molecular interactions between dopaminergic and inflammatory cascades within neurons may underlie behavioral alterations during chronic infection with *T. gondii*. The NR4A transcription factors NR4A1, NR4A2 and NR4A3 (also known as Nur77, Nurr1 and Nor1, respectively) share similar DNA-binding properties and have been implicated in regulation of genes involved in dopamine neurotransmission[131]. Nurr1 induces tyrosine hydroxylase expression during differentiation of dopaminergic neurons and has a key role in the maintenance of the adult brain dopaminergic system. Consistent with this, *NR4A2* polymorphisms are associated with a variety of neurological and psychiatric disorders, including Parkinson's disease, Lewy body dementia, addiction and attention deficit disorder[132,133]. Nurr1 and its coregulating factor, glycogen synthase kinase 3, recruits CoREST, a complex of several proteins that assembles chromatin-modifying enzymes, also interacts with the transcription factor complex NF-κB–p65, protecting dopaminergic neurons during LPS-induced inflammation by reducing expression of, for example, *Tnf*, NO and *Il1b* in microglia and astrocytes[134]. *Nurr1*$^{+/-}$ mice show more exploratory behavior and lower anxiety than wild-type mice, and these changes are exacerbated by chronic infection with *T. gondii* compared with the behaviors of similarly infected wild-type animals[135]. There are no studies examining *NR4A2* polymorphisms in psychiatric patients chronically infected with *T. gondii*, but cognitive deterioration among *T. gondii*–infected patients with bipolar disorder has been reported[136]. Genome-wide analyses may be useful to identify susceptibility genes that predispose individuals to development or worsening of affective disorders after infection with *T. gondii*.

Summary and future perspectives

The intersecting mechanisms of CNS damage discovered for infectious, psychiatric and neurodegenerative diseases are leading to new hypotheses about the roles of immune system molecules in normal brain function and in the etiologies of neurological diseases. Type I interferons, for example, are now known to be critical for normal neuronal homeostasis as a

regulator of autophagy-mediated protein degradation[137], and T cell cytokines IFN-γ and IL-4 are involved in social and cognitive behavior[138,139].

Genetic studies have further identified putative roles for aberrantly expressed innate immune molecules in psychiatric and neurodegenerative diseases[140], supporting the idea that immune function is crucial in maintaining the flow of information in the normal CNS. Although inflammation is critical for CNS pathogen clearance, lasting effects of immune molecules and pathogen by-products may represent an underlying mechanism of neurologic dysfunction. During infectious and noninfectious neurological diseases, innate immune molecules such as complement proteins and cytokines regulate synaptic plasticity and neurogenesis, whereas amyloid-β and α-synuclein, biomarkers of neurodegenerative diseases, show antimicrobial roles[141,142]. These findings suggest that, depending on the pathogen, host genotype or environmental factors, both canonical and noncanonical anti-pathogen pathways may affect interneuronal communication, leading to adaptive or maladaptive effects on brain function. Future efforts to elucidate the molecular mechanisms of neurological illnesses will lead to a more integrated view of how the immune and nervous systems' combined activities contribute to the physiology of each. Understanding the interplay between immunity and neurological function after CNS infection has the potential to shed light on pathway intersection and novel drug targets.

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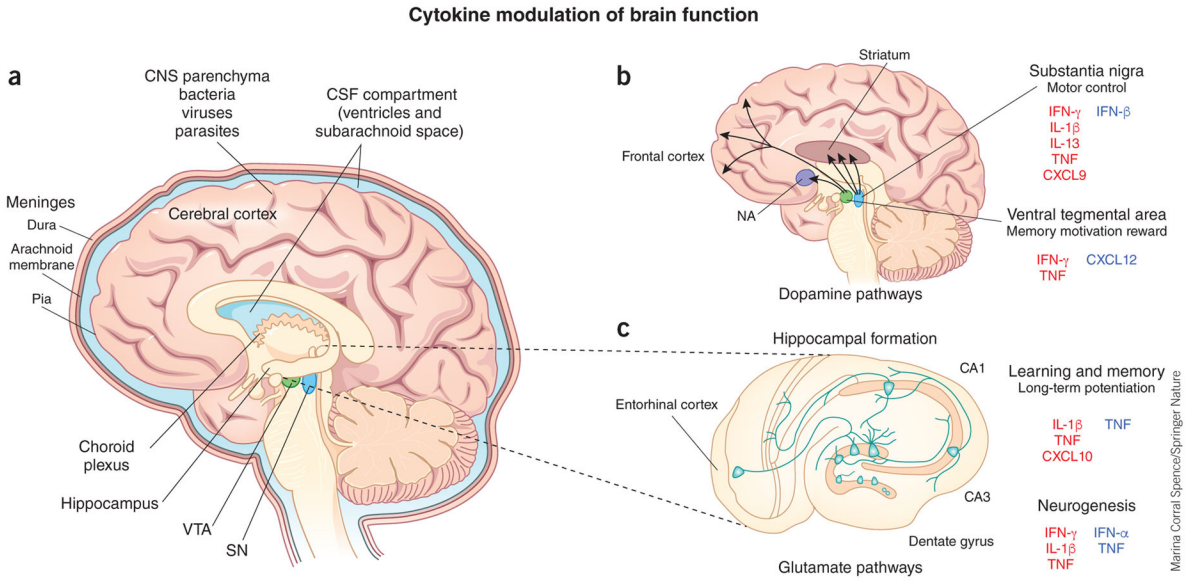

Figure 1.

Neuroinfectious diseases and cytokine modulation of brain functions. (**a**) Neurotropic pathogens gain access to the CNS parenchyma (bacteria, viruses and parasites) or CSF compartments (bacteria, viruses and fungi), the latter of which includes the subarachnoid space and the ventricular system. (**b**, **c**) Increased expression of cytokines and chemokines modulate brain function via effects on dopaminergic pathways (**b**) and glutamatergic pathways (**c**). Dopamine is manufactured in the substantia nigra (SN), which affects motor function, and in the ventral tegmental area (VTA), which is involved in memory, motivation and reward. Dopaminergic neurons of the SN project to the dorsal striatum, and those of the VTA project to the nucleus accumbens (NA) and the prefrontal cortex. Glutamatergic pathways are involved in learning and memory formation, which also require long-term potentiation, characterized by a persistent increase in synaptic strength following high-frequency stimulation, and genesis of new neurons within the dentate gyrus (adult neurogenesis). Molecules labeled in red have inhibitory effects; those labeled in blue have stimulatory effects.

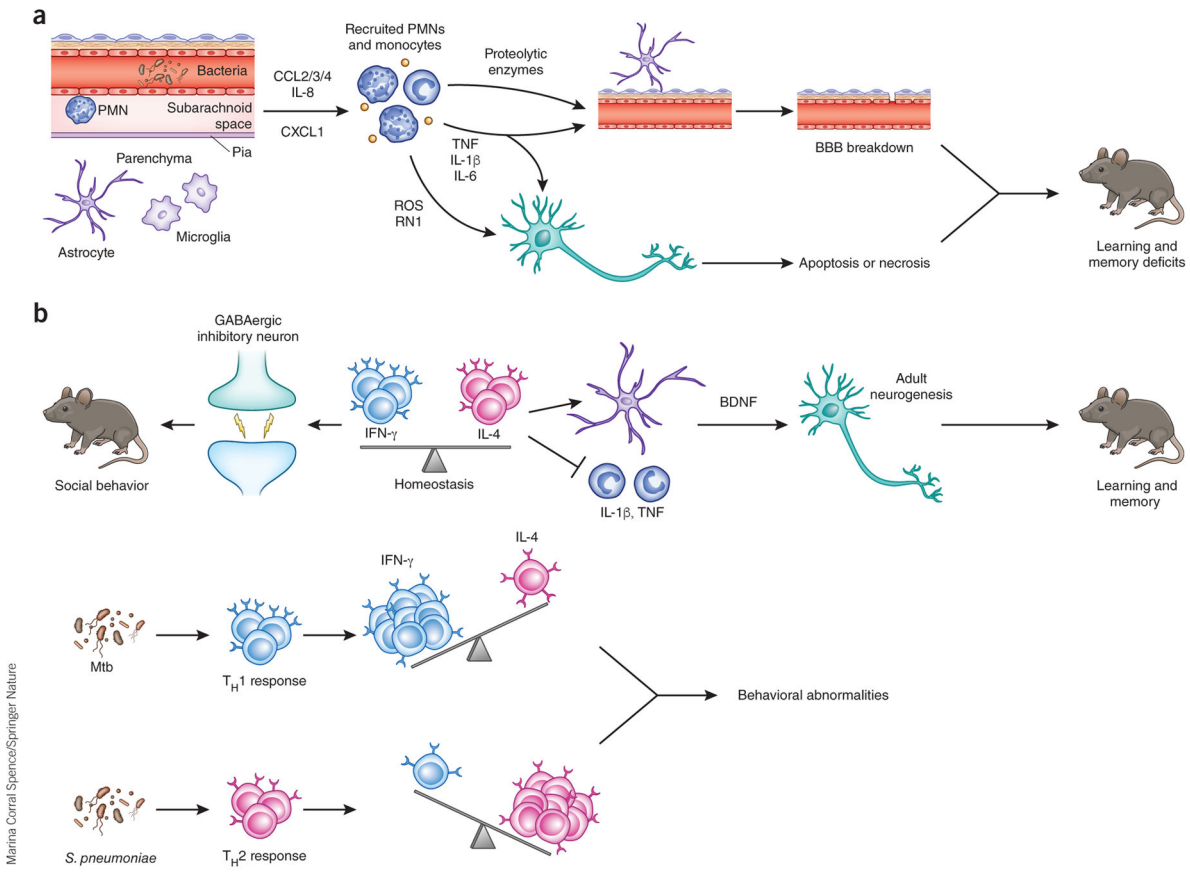

Figure 2.

Potential mechanisms of neurological sequelae subsequent to bacterial and fungal meningoencephalitis. (**a**) Perivascular or meningeal macrophages (PVM) recognize invading pathogens during meningoencephalitis and release a variety of chemoattractants, including CCL2, CCL3, CCL4 (CCL2/3/4), IL-8 and CXCL1, to recruit neutrophils and monocytes to the CSF compartment. Recruited neutrophils release proteolytic enzymes, which contribute to BBB breakdown through loss of tight junctions and degradation of the basement membrane. Reactive oxygen (ROS) and nitrogen (RN1) species can initiate apoptosis or necrosis in neurons. TNF, IL-1β and IL-6 can participate in BBB breakdown and neuronal death. These proinflammatory cytokines are increased in the hippocampus and cortex during experimental meningitis in mouse models and can cause learning and memory deficits in surviving animals. (**b**) Balance between IFN-γ and IL-4 produced by meningeal T cells is necessary for normal behavior. IFN-γ acts on inhibitory neurons to increase GABAergic current and maintain normal social behavior. IL-4 maintains normal learning and memory, potentially through inhibition of proinflammatory cytokine production by meningeal myeloid cells and/or increasing brain-derived neurotrophic factor (BDNF) production by astrocytes, which is crucial for adult neurogenesis. During infection, the balance is disrupted, which may cause behavioral alteration. Chronic infection by Mtb results in T_H1 cell recruitment to the CSF compartment, increasing IFN-γ production. Meningitis caused by *S. pneumoniae* and other acute bacterial pathogens results in the influx of IL-4 producing T_H2 cells, shifting the balance toward an IL-4-dominated cytokine milieu.

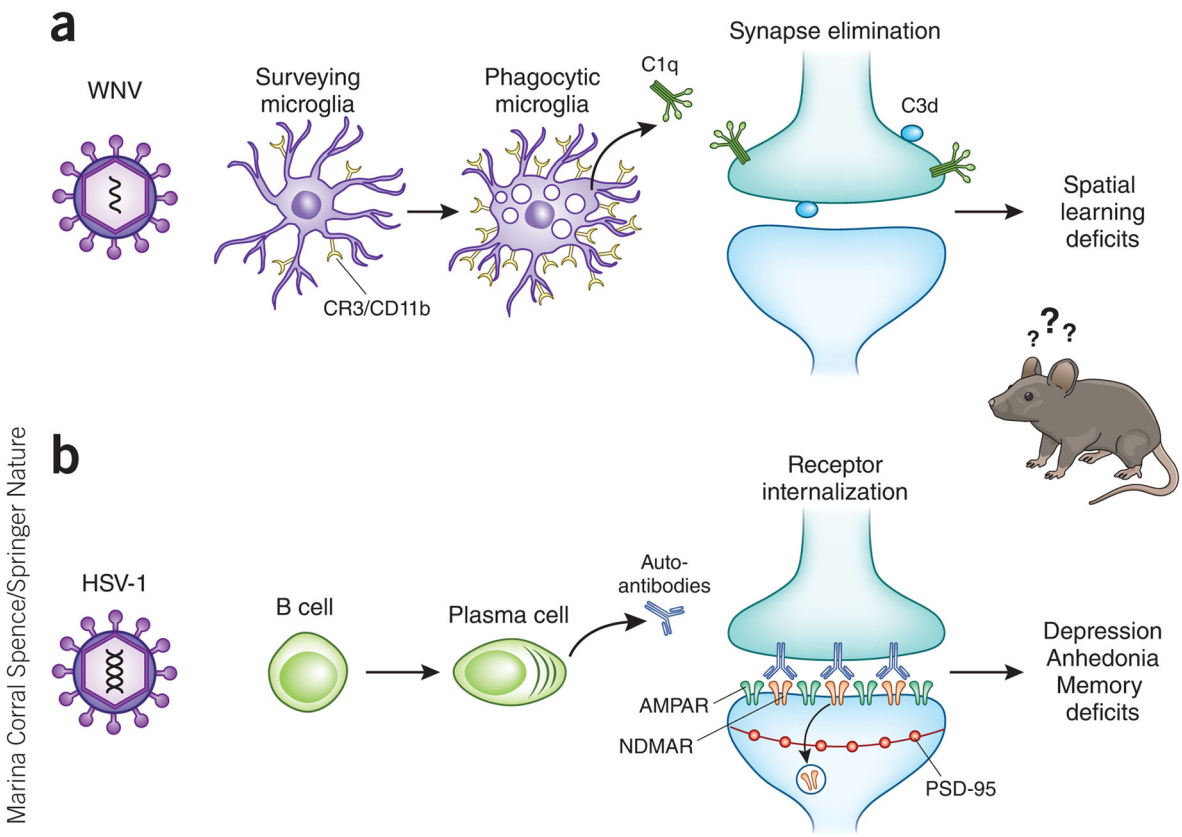

Figure 3.

Mechanisms underlying neurological sequelae in a subset of viral encephalitis survivors. (**a**) Microglia are activated after WNV infection, leading to upregulation of complement receptor 3 (CR3) and expression of complement component C1qa. C1qa and the downstream complement cleavage protein C3d localize to presynaptic terminals in the hippocampus. Complement-mediated engulfment of tagged synapses by microglia leads to selective loss of presynaptic terminals in the CA3 region of the hippocampus and deficits in spatial learning. CD11b, cluster of differentiaton 11b. (**b**) B cells can produce autoantibodies to synaptic proteins, including NMDAR, after HSV-1 mediated encephalitis. Autoantibodies bind to NMDAR on the post-synaptic terminal, which leads to selective internalization of NMDAR, whereas other synaptic components, such as AMPAR and PSD-95, remain intact. Loss of NMDAR in the hippocampus leads to behavioral memory deficits and neuropsychiatric symptoms of depression and anhedonia.

Table 1

Cytokine effects on neurotransmitter systems and neuronal function

Cytokine	Effect
IL-1β	Degeneration of dopaminergic neurons with age-related decline in motor skills, Parkinsonism[143]
	Inhibition of long-term potentiation[144]
	Blocking of cerebellar function[145]
TNF	Induction of death of dopaminergic neurons via miRNA targeting of mitochondrial complex-1 (ref. 146)
	Blocking morphine-induced activation of ventral tegmental (reward) dopaminergic neurons[147]
	Cognitive and motor deficits due to hyperexcitability from increased long-term potentiation[148–150]
	Enhancement (TNFR2) and inhibition (TNFR1) of adult neurogenesis[151]
	Cognitive dysfunction via a mechanism that involves TNFR1 signaling in astrocytes, which modify excitatory synapses within the dentate gyrus[152]
IFN-γ	Induction of CXCL9-mediated damage to dopaminergic neurons[153]
	Induction of CXCL10-mediated depression of long-term potentiation[154]
	Enhancement of adult neurogenesis[155]
	Cerebellar dysfunction[156]
IFN-α	Depression induced via activation of indoleamine-2,3-dioxygenase (IDO), which increases kynurenic acid (KA) and decreases quinolinic acid (QA), both neuroactive metabolites; activation of the kynurenine pathway leads to reduced formation of the neurotransmitters serotonin and dopamine[157]
	Excitotoxicity or decreased glutamatergic signaling caused by binding of NMDA receptors by QA (produced by microglia) or KA (produced by astrocytes), respectively, inhibiting synaptic plasticity and adult neurogenesis[157,158]

Table 2

Infections of the CSF compartment and NVU cytokine expression

Pathogen	Brain endothelial cells	Choroid plexus epithelial cells	Astrocytes	Meninges or CSF
Bacteria				
Mtb	NIA	NIA	TNF, IL-6, ROS[159]	NIA
S. pneumoniae	NO[160,161]; IL-8, CXCL1, CXCL2, CCL20, IL-6 (ref. 27)	NIA	IL-6, TNF[162]	NIA
N. meningitidis	IL-6, IL-8 (ref. 163); IL-6, TNF[164]	CXCL1–3, IL-6, IL-8, TNF, G-CSF and GM-CSF[165]	IL-19 (ref. 166)	IL-6, IL-1, TNF[167]
Fungi				
C. neoformans	High-mobility group box 1 protein[168]	NIA	NO[169]	NIA
Viruses				
Enteroviruses	IL-6, MIF, CCL2 (ref. 170)	CXCL1–3, IL-8, CCL5 (ref. 171)	IL-6, IL-8, CCL5, CXCL10 (ref. 172)	NIA
Herpes simplex viruses	NIA	NIA	IFN-α, IFN-β[173]; TNF, IL-6 (ref. 174)	NIA

NIA, no information available.