Journal of Neuroinflammation

REVIEW

Open Access

Neuroimmune modulation in liver pathophysiology

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Abstract

The liver, the largest organ in the human body, plays a multifaceted role in digestion, coagulation, synthesis, metabolism, detoxification, and immune defense. Changes in liver function often coincide with disruptions in both the central and peripheral nervous systems. The intricate interplay between the nervous and immune systems is vital for maintaining tissue balance and combating diseases. Signaling molecules and pathways, including cytokines, inflammatory mediators, neuropeptides, neurotransmitters, chemoreceptors, and neural pathways, facilitate this complex communication. They establish feedback loops among diverse immune cell populations and the central, peripheral, sympathetic, parasympathetic, and enteric nervous systems within the liver. In this concise review, we provide an overview of the structural and compositional aspects of the hepatic neural and immune systems. We further explore the molecular mechanisms and pathways that govern neuroimmune communication, highlighting their significance in liver pathology. Finally, we summarize the current clinical implications of therapeutic approaches targeting neuroimmune interactions and present prospects for future research in this area.

Keywords Liver disease, Autonomic nervous system, Sympathetic nervous system, Parasympathetic nervous system, Neuroimmune system

Introduction

The nervous and immune systems are crucial for survival. Traditionally, these systems were believed to function independently; however, accumulating scientific evidence suggests an active and beneficial dialogue between them [1]. The liver, innervated by autonomic and sensory fibers of the sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS), plays a pivotal role in various life-sustaining functions, including digestion, coagulation, synthesis, metabolism, detoxification, and immune defense [2, 3]. Liver injury, responsible for approximately 2 million deaths worldwide annually, can result from toxins, metabolic disorders, infections, and genetic diseases [4]. The initial presentation of most chronic and many non-fulminant acute liver diseases is often asymptomatic or involves nonspecific signs and symptoms, such as fatigue, anorexia, and weight loss [5–7]. It is only when the liver capsule or intrahepatic bile duct is involved in inflammation, such as in Fitz-Hugh-Curtis syndrome [8] and hepatolithiasis, [9] that patients complain of right upper quadrant pain. Liver transplantation leads to effective liver denervation, which may contribute to higher rates of obesity, dyslipidemia, and diabetes in liver transplant recipients [10–13]. These observations suggest a strong communication between the liver (including the liver capsule, hilar region, portal region, and liver parenchyma) and the nervous system.

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Although the role of the hepatic nervous system in liver homeostasis is increasingly appreciated, much remains unknown about the specific mechanisms by which hepatic nerves influence and are influenced by liver diseases. Both human and rodent livers are innervated by the autonomic nervous system (ANS). While the human liver is innervated by the SNS and PSNS, the rodent liver may be innervated only by the former [14]. The liver possesses a finely tuned cellular immune system, including innate immune cells such as Kupffer cells (KCs), monocyte-derived macrophages, dendritic cells (DCs), natural killer (NK) cells, natural killer T cells, and adaptive immune cells, such as T and B cells**.** Disruption of the hepatic immune system can cause autoimmune hepatitis, steatohepatitis, cirrhosis, and liver cancer [15]. Although the positional relationships between the nerves and immune cells in the liver are unclear, the role of neuroimmunology in liver diseases has been explored through surgical and genetic techniques. Given the fundamental connection between the nervous system and liver, understanding the role of neuroimmune innervation in liver dysfunction holds promise for developing novel therapeutic approaches for liver diseases.

In this concise review, we provide a brief description of the structure and composition of the hepatic neural and immune systems. Subsequently, we introduce the molecular mechanisms and pathways that mediate neuroimmune communications and discuss their significance in liver ailments. Lastly, we summarize the current clinical implications of therapeutic strategies targeting neuroimmune interactions and propose future research directions.

Hepatic nervous and immune systems

Hepatic neuroanatomy

The neural circuitry connecting the nervous system and liver is intricate. The centrifugal neural circuits are divided into the central nervous system (CNS), which includes the brain and spinal cord, and the peripheral nervous system (PNS), comprising somatic and autonomic nerves [16]. The somatic nerves, originating from the CNS, regulate skeletal muscles and elicit voluntary movements [17]. The ANS consists of the SNS, PSNS, and enteric nervous system (Fig. 1) [18]. The afferent neural circuits are broadly divided into afferent vagus and spinal sensory nerves [19]. The cell bodies of the afferent vagus nerves are situated in two nodose ganglia on either side of the neck, with the left and right vagus nerves innervating visceral organs asymmetrically [20].

Autonomic nerves, both afferent and efferent, innervate various parts of the liver, including the portal vein, hepatic artery, bile ducts, and liver hilum [21]. The anterior plexus, originating from the left portion of the celiac plexus and the right abdominal branch of the vagus, forms a network of nerves surrounding the hepatic artery. The posterior plexus, derived from the right portion of the celiac plexus, surrounds the portal vein, occasionally extending innervations accompanying the hepatic vein (Fig. 2A). The distribution of nerves within the liver is highly species-specific, with most species exhibiting innervation of the portal tract [13]. For instance, while the human liver exhibits both intra-acinar and portal tract innervation, mice and rats primarily display portal tract innervation (Fig. 2B) [14]. The distribution of nerves within the liver in various species, such as rats, rabbits, monkeys, guinea pigs, pigeons, quail, golden hamsters, and turtles, has been thoroughly reviewed in previous studies [13].

Hepatic immune system

The mammalian liver is a multifaceted organ with diverse cell types that perform numerous physiological functions, [22–24] including digestion, synthesis, metabolism, and detoxification. Additionally, the liver plays a vital role in immune processes, such as anti-infection, maintaining autoimmune stability, and supporting antitumor activities (Fig. 3A) [25–27]. One of the liver's unique immunological advantages stems from its parenchymal and nonparenchymal cells, which actively contribute to immunoregulation and the maintenance of overall homeostasis. As a fundamental immune organ, the liver receives blood directly through the portal vein, which drains not only the peritoneum but also the gastrointestinal (GI) tract, pancreas, and spleen [28]. This direct blood supply bypasses classic immune surveillance sites such as lymph nodes [29]. Notably, the liver is more exposed to microorganisms and endotoxins than other organs, given its distinctive anatomical location and unique blood composition (mainly derived from the portal vein and enriched with antigens from the GI tract) [30]. Consequently, the liver typically maintains a tolerogenic immune state to prevent unnecessary immune activation and excessive autoimmune responses [31, 32]. However, during acute and chronic infections, the liver transitions from a tolerant state to an active immune state, constituting a crucial line of defense against invading microorganisms [33–36]. Hepatic defenses depend on a complex network of immune cells, including KCs, DCs, neutrophils, NK cells, and B and T lymphocytes [37]. Furthermore, non-immune cells, such as hepatocytes, cholangiocytes, hepatic stellate cells (HSCs), and liver sinusoidal endothelial cells play pivotal roles

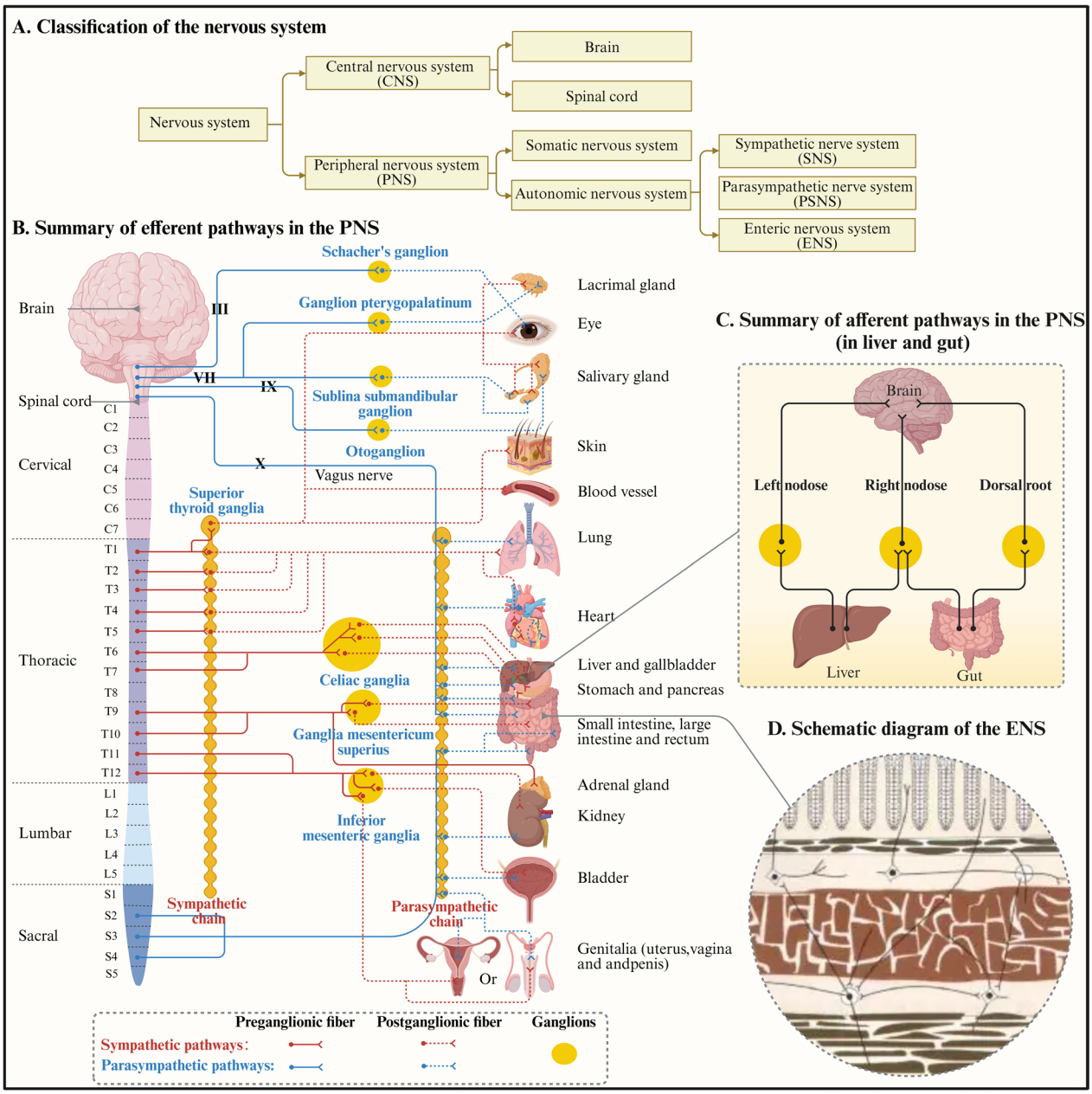

Fig. 1 The classification of the nervous system and the summary of peripheral nervous system (PNS). **A** Classification of the nervous system. **B** Summary of efferent pathways in the PNS. The autonomic nervous system is organized in three anatomical and biochemical distinct systems, the sympathetic nervous system (SNS, in red), the parasympathetic nervous system (PNS, in blue) and the enteric nervous system (ENS, Fig. 1D), respectively. **C** Summary of the afferent pathways in the PNS (in the liver and gut). **D** Schematic diagram of the ENS. The ENS is located within intestinal tissues and has a characteristic architecture. *CNS* central nervous system, *ENS* enteric nervous system, *PNS* peripheral nervous system, *PSNS* parasympathetic nerve system, *SNS* sympathetic nerve system, *III* the third cranial nerve, *VII* the seventh cranial nerve, *IX* the ninth cranial nerve, *X* the tenth cranial nerve

in recruiting proinflammatory immune cells and concurrently producing inflammatory cytokines, including acute-phase proteins, complement factors, and cell adhesion molecules (Fig. 3B) [38–40].

Mechanisms of neuroimmune interaction in the liver

The interactions between neurons and immune cells are intricate and multifaceted, necessitating a sophisticated

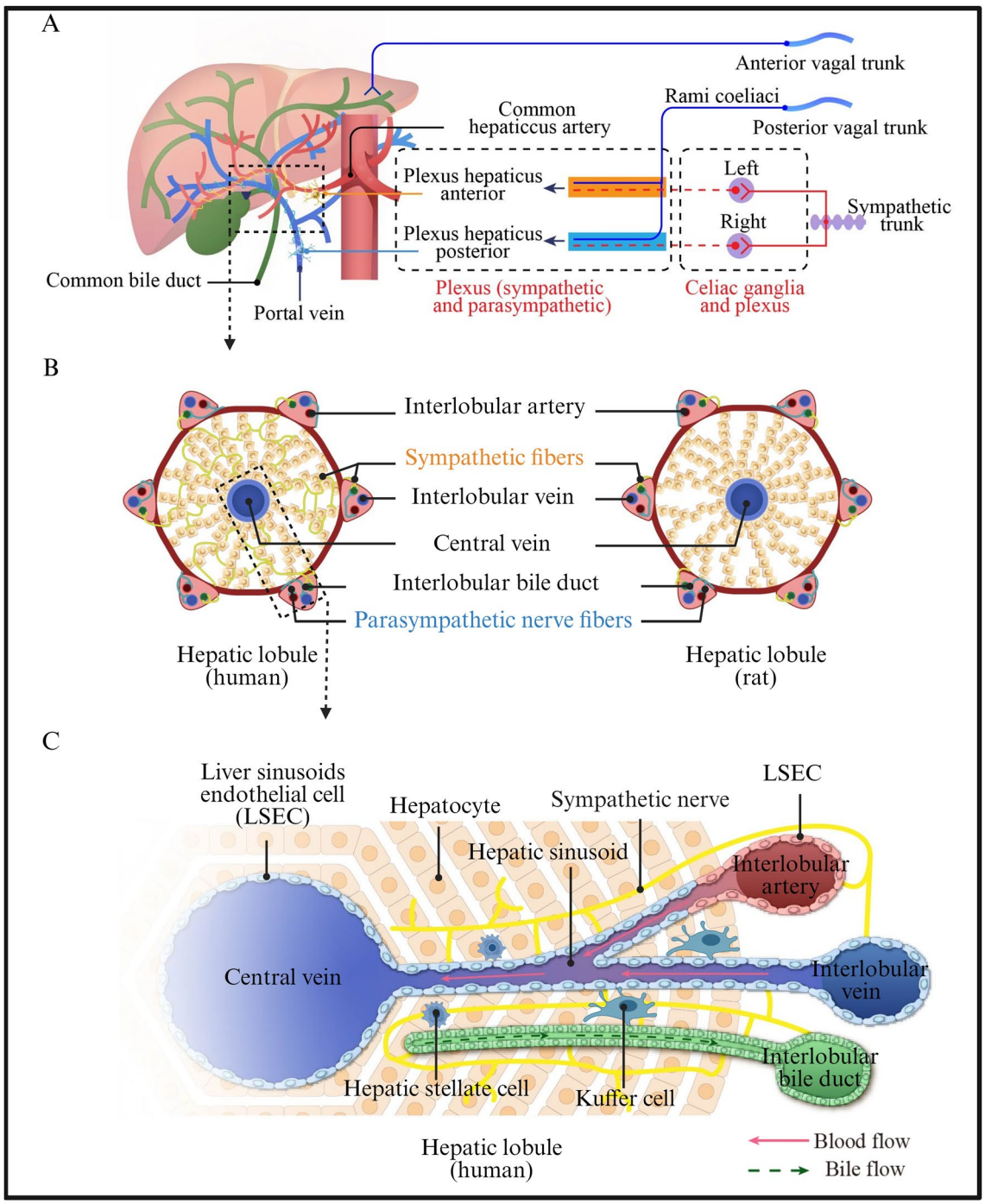

Fig. 2 Hepatic neuroanatomy. **A** Origin and concomitant of hepatic plexus. The anterior plexus, originating from the left portion of the celiac plexus and the right abdominal branch of the vagus, forms a network of nerves surrounding the hepatic artery. Meanwhile, the posterior plexus, derived from the right portion of the celiac plexus, is located around the portal vein with occasional innervations accompanying the hepatic vein. **B** Anatomy of the intrinsic sympathetic and parasympathetic nerve fibers. In all mammalian species, sympathetic and parasympathetic fibers surround the portal are an humans and guinea pigs but not rats. sympathetic fibers course into liver sinusoids. **C** Innervation of the human liver. Within the liver, nerves are found around the hepatic artery, portal vein, and bile ducts. Sympathetic nerves, but not parasympathetic nerves, synapse on hepatocytes as well. *LSEC* liver sinusoids endothelial cell

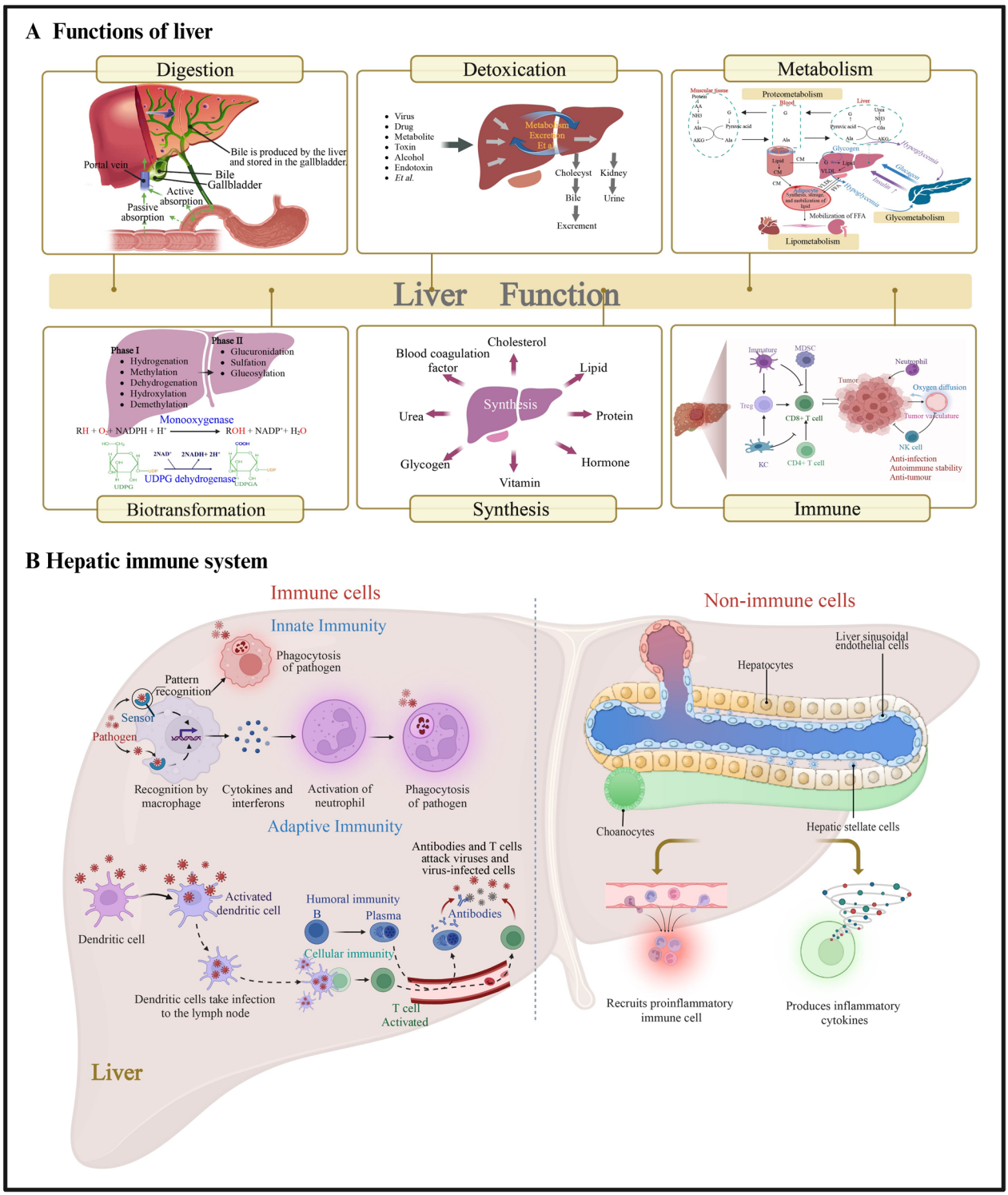

Fig. 3 Hepatic immune system and functions. **A** Functions of the liver. The mammalian liveris a complex organ consisting of diverse cell types that perform multiple physiologicalfunctions including digestion, detoxication, metabolism, biotransformation,and immune. **B** Hepatic immune system. The liver's immune defense mechanism primarily depends on a complex network of immune cells and non-immune cells, the latter of which play immune roles by recruiting proinflammatory immune cells and simultaneously producing inflammatory cytokines

infrastructure to enable signal propagation between these two systems. In the following sections, we delve into the principal pathways through which the nervous and peripheral immune systems communicate and influence each other (Fig. 4A). Each pathway serves as a distinct conduit for transmitting specific information, employing unique mechanisms to convey messages.

Endocrine pathways

The endocrine system is a powerful tool at the brain's disposal, regulating many physiological processes. Hormones, controlled by the brain, are released into the bloodstream and transported to target tissues and immune cells. This rapid and efficient pathway simultaneously delivers information to various organs and synchronizes physiological processes. At the center of this system is the hypothalamus, which communicates extensively with other brain regions and governs vital processes, such as hunger, thirst, body temperature, circadian rhythm, and sleep.

The hypothalamus regulates two primary endocrine pathways: the hypothalamic–neurohypophyseal system and the hypothalamic–hypophyseal portal system. In the hypothalamic–neurohypophyseal system, hormones, including oxytocin [41] and arginine-vasopressin (AVP), [42] are produced and secreted. Oxytocin suppresses proinflammatory cytokines [43, 44] and promotes wound healing, [45] while AVP exerts anti-inflammatory effects during sepsis [46]. The activation of AVP-producing neurons by inflammatory cytokines indicates that this endocrine pathway can respond to changes in immune system activity [47].

The hypothalamic–hypophyseal portal system secretes hypothalamic hormones into the bloodstream to ultimately reach the target organ, inducing the release of the final effector hormone. There are five main axes, [1] including the (1) hypothalamic–pituitary–adrenal axis; (2) hypothalamic–pituitary–thyroid axis; (3) hypothalamic–pituitary–gonadal axis; (4) hypothalamic–pituitary–somatotropic axis; and (5) hypothalamic–pituitary–prolactin axis. These endocrine pathways coordinate physiological and developmental events that necessitate adjustments in immune activity, thus influencing the immune response. For instance, sex hormones play a role in the programming of the immune system [48, 49]. Testosterone generally has an immunosuppressive effect, whereas estrogen enhances immune responses [50]. The immunoenhancing effects of estrogens include promotion of neutrophil infiltration, elevation of macrophage phagocytic activity, enhancement of DC antigen-presenting function, promotion of Th2 differentiation, and contributions from T-lymphocytes, B-lymphocytes, cytotoxic CD8 cells, NK cells, and ILC-2 cells [51–53]. Consequently, females exhibit increased antibody production [54, 55] and are less susceptible to viral infections but more prone to autoimmune diseases [56, 57]. Androgens suppress the immune response through mechanisms such as influencing neutrophil maturation and function, decreasing TNF-α and IL-1β expression and secretion in macrophages, negatively regulating B- and T-cell development, reducing toll-like receptor expression, and decreasing cytokine production [51, 58]. These mechanisms partly explain the increased susceptibility of males to various parasitic, [59] bacterial, [60] and viral infections [61, 62]. Similarly, androgen-mediated suppression of immune reactivity and inflammation lowers the threshold for cancer, making men more susceptible to cancer than women [63]. Diseases such as primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH) have a strong female predominance, whereas primary sclerosing cholangitis (PSC) has a higher incidence in males with a more severe course [64]. The strong association between sex and the development and course of autoimmune liver diseases could be partially explained by differences in sex hormones [65]. Another example is the hypothalamic–pituitary–thyroid axis, which boosts metabolic activity and is linked to immune activation [66]. Thyroid hormones induce lymphocyte proliferation [67]. Consequently, the immune response is suppressed by thyroidectomy, [68] and patients

(See figure on next page.)

Fig. 4 Neuronal regulation of immune activation. **A** Outline. An overview of inter-regulation of the nervous system and the immune system. **B** Endocrine pathways. The endocrine signals enable the synchronization of complex physiological processes and immune activity. **C** Neuronal efferent pathways. Noradrenaline (recognized by α-adrenergic and β-adrenergic receptors) is the primary neurotransmitter of the SNS, while acetylcholine (ACh; recognized by nicotinic and muscarinic ACh receptors) is the primary PSNS neurotransmitter. Both of which can affect activity of immune organs and immune cells. **D** Meningeal lymphatic vessels. The meningeal lymphatic system can impact both the central and peripheral immune response by transporting immune cells and antigens from the brain to the peripheral immune system. *ACTH* adrenocorticotropic hormone, *ANS* autonomic nervous system, *Ach* acetylcholine, *AI* Alzheimer's disease, *AVP* arginine vasopressin, *CNS* central nervous system, *CCL21* C–C motif chemokine ligand 21, *Epi* epinephrine, *FSH* follicle-stimulating hormone, *GH* growth hormone, *LH* luteinizing hormone, *M-R* muscarinic cholinergic receptor, *MS* multiple sclerosis, N1-R nicotinic cholinergic receptor type 1, *NA* norepinephrine, *OXT* oxytocin, *PVN* paraventricular nucleus, *PRL* prolactin, *PNS* peripheral nervous system, *PSNS* parasympathetic nerve system, *PROX1* prospero homeobox 1, *SON* supraoptic nucleus, *TSH* thyroid stimulating hormone, *VEGFR3* also known as "FLT4," fms related receptor tyrosine kinase 4, *α/β-R* adrenergic cholinergic receptor

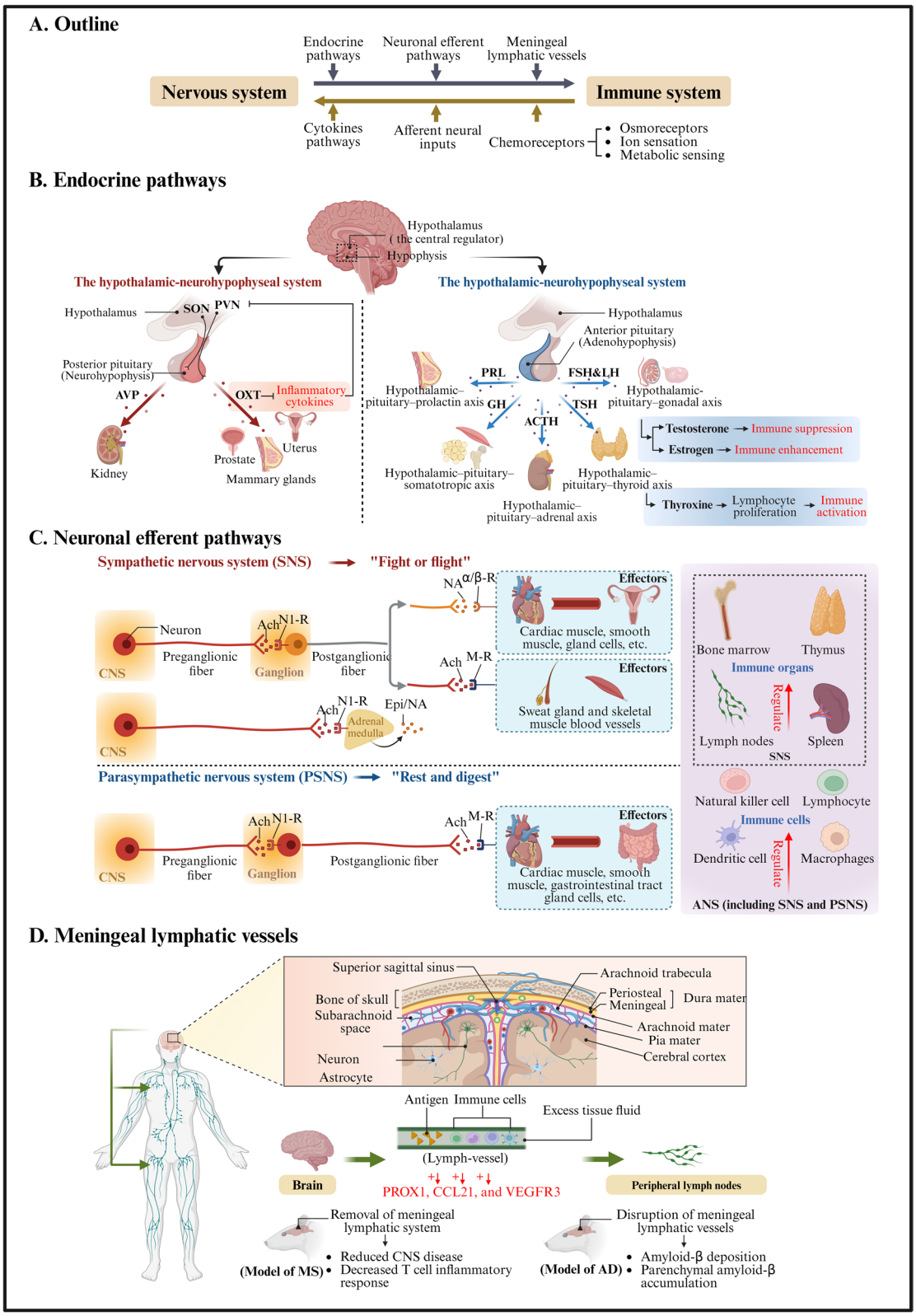

Fig. 4 (See legend on previous page.)

with hypothyroidism are more susceptible to infection [69, 70]. Thus, endocrine signals synchronize complex physiological processes and immune activity (Fig. 4B).

Neuronal efferent pathways

The human CNS communicates rapidly and directly with peripheral tissues through the PNS, comprising 12 cranial nerves, 31 spinal nerves, and the ANS [71]. The ANS regulates functions not under conscious control, such as blood pressure, heart rate, and GI motility and function. The SNS and PSNS have opposing effects on various physiological processes; the SNS regulates the "fight or flight" response, while the PSNS regulates the "rest and digest" state. Many organs, including the bone marrow, lymphatic tissues and organs, joints, blood vessels, lungs, GI tract, liver, kidneys, and spleen, are innervated by the ANS [17].

Noradrenaline, acting through α-adrenergic and β-adrenergic receptors, is the primary neurotransmitter of the SNS, whereas acetylcholine (ACh), acting through nicotinic and muscarinic receptors, is the primary neurotransmitter of the PSNS. Although both systems can influence immune activity, immune organs such as the bone marrow, thymus, lymph nodes, and spleen are predominantly innervated by the SNS [72]. Immune cells, such as NK cells, DCs, T cells, and macrophages, express receptors for neurotransmitters and neuropeptides secreted by the ANS [73, 74]. Notably, immune cells themselves can also secrete various neuronal factors, [74–76] revealing an intricate interplay between the nervous system and immunity (Fig. 4C).

Meningeal lymphatic vessels

The brain can regulate immune responses by introducing brain-specific antigens to the peripheral immune system. Immune cells continually monitor all tissues, residing or patrolling within them to gather information about the tissue's condition and potential threats. These cells then travel through lymphatic vessels to the lymph nodes, where they present antigens and trigger a relevant immune response [77]. Recent research has identified dural lymphatic vessels that transport antigens and immune cells from the brain to the lymph nodes and express lymphatic endothelial markers, such as PROX1, CCL21, and VEGFR3 [78]. The lymphatic system envelops the brain, facilitating the drainage of excess fluid, proteins, and immune cells from the brain tissue to peripheral lymph nodes [79]. In a mouse model of multiple sclerosis, the removal of this meningeal lymphatic system led to a reduction in CNS disease and a decrease in T cell inflammatory responses [79]. Similarly, in a transgenic mouse model of Alzheimer's disease, disruptions in meningeal lymphatic vessels promoted meningeal amyloid-β deposition and increased parenchymal amyloid-β accumulation (Fig. 4D) [80]. Therefore, by transporting immune cells and antigens from the brain to the periphery, the meningeal lymphatic system can impact both central and peripheral immune responses.

Immune regulations of neuronal function

Cytokine pathways

The recognition of immune influences on the nervous system has become more evident, though it initially lagged behind our understanding of how the nervous system regulates the immune system. This delay was primarily due to the recent discovery of the molecular mechanisms governing immune communication signals and pathways, particularly cytokines [81]. Cytokines, primarily released by immune cells, notably T cells and myeloid cells, play a pivotal role in active immune responses [81]. Afferent fibers of the ANS can detect cytokines and transmit this information to the brain, forming a "neural" communication pathway [82]. For instance, in adult mice, the intraperitoneal administration of tumor necrosis factor (TNF) or interleukin-1β significantly alters the action potentials originating from the cervical vagus nerve [83]. Cytokines can also directly activate and sensitize neurons, leading to the generation of action potentials that convey information to the brain (Fig. 5) [84–87]. Under inflammatory conditions, cytokines may directly reach parenchymal brain centers via a "humoral" route, particularly when the blood–brain barrier (BBB) exhibits increased permeability [88].

Afferent neural inputs

Peripheral primary afferent neurons express receptors for microbial constituents and inflammatory products, indicating their role as a hardwired neural connection that signals inflammation or infection from the periphery to the CNS (Fig. 5). The sensory nervous system is a crucial component of afferent neural circuits, transmitting signals from peripheral tissues to the brain and spinal cord [89]. Various pathogen-associated molecular patterns, such as unmethylated cytosine and guanine and lipopolysaccharide (LPS), as well as danger-associated molecular patterns including DNA, histones, HMGB1, adenosine triphosphate, uric acid, and cytokines, can be detected by sensory nerves [90]. In regions of infection or injury, the activation of peripheral immune cells and the release of cytokines and other inflammatory molecules influence sensory neurons, either triggering or altering signals sent to the spinal cord and brain [91].

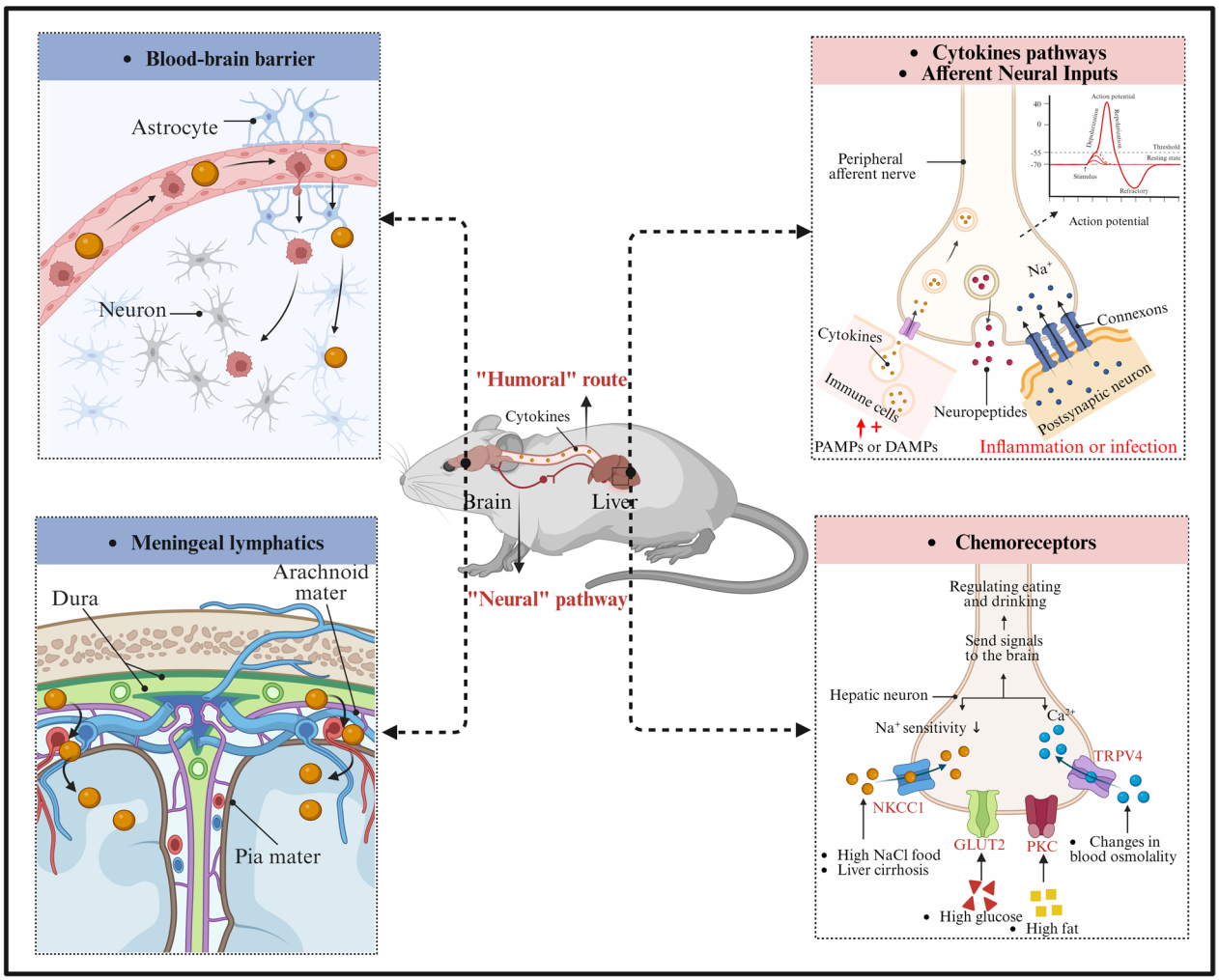

Fig. 5 Immune regulation of neuronal function. The pathways in which immune influences on the nervous system consist of cytokines, afferent neural inputs, and chemoreceptors (including osmoreceptors, ion receptors, and metabolic substance receptors). *DAPMs* damage-associated molecule patterns, GLUT2 glucose transporter 2, *NKCC1* Na^+-K^+-$2Cl^-$ cotransporter, *PKC* protein kinase C, *PAMPs* pathogen-associated molecular patterns, *TRPV4* transient receptor potential vanilloid 4

Furthermore, sensory neurons in the liver play a role in detecting nutritional and absorptive hormones known as incretins. One prominent incretin, glucagon-like peptide 1 (GLP-1), is sensed by afferent nerves in the portal vein. Activation of GLP-1 receptors stimulates hepatic vagal afferent nerves, leading to changes in pancreatic insulin release through efferent sympathetic nerve signals originating in the brain [92, 93]. Hepatic afferent fibers also express receptors for several hormones secreted by the GI tract, including somatostatin, [94] leptin, [95] and cholecystokinin [96].

In addition to their primary function of transmitting information to the brain, these neurons locally release neuropeptides. Sensory fibers have been extensively studied for their ability to communicate with immune cells, [97] particularly in barrier tissues, such as the skin, [98, 99] lungs, [100] and gut, [101, 102] where immune cells are abundant. These sensory innervations directly affect immune cell activity, providing protection against endotoxemia [103] and sepsis [104]. Therefore, the sensory nervous system has both systemic and local effects on immunity, conveying sensory inputs to the brain to regulate the peripheral immune response and secreting neuropeptides directly into the tissues [104].

Chemoreceptors

The liver serves as an ideal sensor for monitoring osmolality, glucose concentration, and fatty acid levels due to its close connection with the GI tract. Following the absorption of macronutrients from the GI

tract, they travel through the portal vein to reach the liver. Within the liver, numerous chemoreceptors play a critical role in sensing ions and nutrients and subsequently transmit signals to the brain. Additionally, several chemoreceptors are multifacetedly correlated with immune response or even neuro-immune communication. These chemoreceptors encompass osmoreceptors, ion receptors, and receptors for various metabolic substances (Fig. 5) [14].

Osmoreceptors

While the brainstem is responsible for detecting disturbances in osmolarity, the liver harbors peripheral osmoreceptors that are quite effective at detecting changes in blood osmolality. This is particularly relevant because the liver can detect changes in water intake before these changes affect systemic blood osmolality [105]. Neurons adjacent to hepatic blood vessels are responsible for detecting and responding to shifts in osmolality within the liver, [105] relying on osmotically-activated ion channels such as transient receptor potential vanilloid 4 (TRPV4) [105]. TRP channels potentiate the inflammatory response following hepatocellular injury by controlling the functions of Kupffer cells, monocytes, and neutrophils, including cytokine and chemokine production, response to chemokines, adhesion, and migration from the bloodstream to injured hepatic sites [106]. Impaired osmoregulation of vasopressin also occurs in the acute phase of severe sepsis, resulting from a depolarization of osmoreceptors, which leads to sick behaviors caused by brain-immune crosstalk dysfunction in response to stress, indicating a crucial role of osmoreceptors in neuro-immune communication [107]. Activation of hepatic osmoreceptors is linked to various physiological and clinical parameters. For instance, water consumption has been associated with outcomes such as weight loss, [108] hepatic denervation, [109] and orthostatic and postprandial hypotension [105].

Ion sensation

The liver possesses receptors that monitor fluid homeostasis by detecting key physiological ions in the portal blood system. Similar to osmoreception, the hepatic nervous system identifies changes in ion concentrations before they impact the entire system [110]. The liver holds a distinct advantage in ion detection compared to other organs, given that the concentration of absorbed substances in the portal vein is 4–5 times higher than what is observed in the systemic blood [111]. Consequently, the liver serves as an ideal "predictor" of systemic blood ion concentrations, allowing for the anticipation of abnormal fluid homeostasis. Patients with cirrhosis commonly exhibit ion imbalances such as hyponatremia or hypochloremia, stemming from the loss of the hepatorenal reflex. Ions serve as critical neurotransmitters in the neuroimmune network in various organs such as the brain and kidneys. Calcium sensing via microglial UDP-specific type 6 purinergic (P2Y6) signaling pathways was reported to promote microglia phagocytosis and shape neuroimmune responses in epileptogenesis [112]. However, the role of ions in liver neuroimmune communication needs further investigation.

Metabolic sensing

Hepatic afferent fibers establish a negative feedback loop involving feeding behavior and metabolite level alterations. Peripheral glucose sensors are distributed in various locations, including the taste buds, intestines, carotid bodies, and liver [113–115]. Emerging evidence points to the wall of the portal vein as a probable site for glucose sensing [116]. In the liver, GLUT2 serves as a hepatoportal glucose sensor with a role in hyperglycemia detection [35]. A *Glut2*$^{-/-}$ knockout mouse model demonstrated a failed hypoglycemic response to portal glucose infusion [35]. However, the exact molecular pathway responsible for hepatic lipid sensing remains undefined. One potential pathway involves the activation of protein kinase C (PKC) δ, θ, and ε [117]. Notably, lipid activation of PKCs is not limited to the liver, as PKC-δ is activated during lipid sensing in duodenal cells as well [118]. This pathway's activation regulates glucose production through a gut–brain–liver mechanism. A study by Seillet et al. elegantly demonstrated the interdependence of the neuroimmune-metabolic network in steady-state conditions with respect to lipid metabolism [119]. The key finding is that intrinsic cellular rhythms acted in synergy with the cyclic patterns of food intake to drive the production of IL-22 and synchronize the protection of the intestinal epithelium through a vasoactive intestinal peptide (VIP)-vasoactive intestinal peptide receptor 2 (VIPR2) pathway in group 3 innate lymphoid cells (ILC3s). IL-22 released by the ILC3s improves insulin sensitivity and can regulate lipid metabolism in the liver and adipose tissue [120]. The combined input of afferent signals from the gut and liver may trigger hypothalamic activity during food intake [121]. Ongoing research should further investigate the potential intersections of lipid- or other metabolite-induced signaling in the brain, liver, gut, and other organs.

Interaction between liver pathology and neuroimmunity

The interplay between liver pathology and neuroimmune disorders is complex. Although the exact connection between nerves and immune cells within the liver remains elusive, the field of neuroimmunology has

investigated liver diseases through surgical and genetic techniques. Recent findings indicate that the nervous system plays a pivotal role in the onset and progression of various liver diseases. Liver diseases frequently coincide with dysfunction in both the CNS and PNS. Chronic inflammatory liver diseases and severe decompensated cirrhosis are often accompanied by behavioral alterations, including fatigue, mood disorders, cognitive dysfunction, and sleep disturbances. In this section, we review several diseases indicative of the interaction between liver pathology and neuroimmunity.

Neuroimmune crosstalk in liver pathology

Liver injury

The liver is susceptible to various internal and external stressors, often resulting in a cascade of events including inflammation, repair, regeneration, and fibrosis. These processes are typically driven by a chronic inflammatory microenvironment. In studies involving mice, sympathetic nerve ablation using 6-hydroxydopamine (6-OHDA) prior to carbon tetrachloride (CCl_4) treatment has been shown to reduce the expression of pro-inflammatory cytokines, steatosis, and necrosis [122]. Hypertensive rats with increased peripheral sympathetic activity [123] are more susceptible to CCl_4-induced liver toxicity, developing cirrhosis after just 4 weeks of CCl_4 administration, whereas control rats display less severe bridging fibrosis [124]. When hepatocytes are damaged by CCl_4 exposure, they undergo apoptosis, and sympathetic denervation increases hepatocyte apoptosis while reducing hepatocyte proliferation [125]. Preventing apoptosis through sympathetic signaling could lead to the accumulation of damaged cells that produce persistent inflammation and increased fibrosis [125]. Therefore, β-receptor agonists and α_1-receptor antagonists have demonstrated protective effects in models of acetaminophen-induced liver injury [126, 127].

In contrast, parasympathetic neurons exert a protective effect on hepatic inflammation by acting through α7nACh receptors expressed on macrophages. In studies involving mice treated with anti-Fas, hepatic vagotomy significantly increases mortality; however, co-treatment with an α7nACh receptor agonist attenuates this effect [128]. Vagal signaling also decreases inflammation in LPS-induced hepatitis, likely through macrophage-expressed α7nACh receptors [129]. In murine acetaminophen-induced liver injury, acetylcholinesterase inhibitors improve survival and reduce hepatocellular inflammation, damage, and apoptosis [130]. Therefore, in multiple models of chemical liver injury, vagal signaling plays a protective, anti-inflammatory role, whereas sympathetic neurons promote inflammation and liver damage (Fig. 6A).

Liver fibrosis

Despite advances in research on the pathogenesis and treatment of liver diseases, effective therapies for liver fibrosis and cirrhosis remain elusive. Intrinsic parenchymal innervation diminishes in the pre-cirrhotic liver and is nearly absent in the regenerating nodules of established cirrhosis [131, 132]. Nevertheless, nerves persist along fibrous septae and in portal tracts within pre-cirrhotic and cirrhotic livers [131, 132]. Among these, substance P- and neuropeptide Y-positive nerve fibers tend to predominate over calcitonin gene-related peptide-containing fibers [133]. An analysis of 178 biopsy specimens from cirrhosis patients revealed concurrent increases in the densities of nerve fibers and mast cells, regardless of the underlying cause. Importantly, these density increases in inflammatory cells and nerve fibers correlated with the degree of liver fibrosis in these patients [134]. Similar findings were observed in a rat model of cirrhosis, where nerve terminals closely interacted with myofibroblasts in periseptal sinusoids [135]. In contrast to cirrhosis, which is characterized by widespread hypoinnervation, toxic hepatic injury specifically induces the proliferation of portal nerve fibers [136].

The activation of HSCs, also known as transdifferentiation, is the primary source of myofibroblasts that secrete matrix proteins, thus driving liver fibrogenesis [137]. HSC activation is induced directly or indirectly by paracrine signals from a complex immune and fibrotic microenvironment. Neural signals have long been recognized as a crucial factor in HSC activation and fibrosis progression. Patients with cirrhosis have elevated blood catecholamine levels and increased sympathetic nerve activity [138]. Studies on toxic injury models suggest that the

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Fig. 6 The neuroimmune crosstalk in liver pathology. The sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS) play a crucial role in the development and progression of liver diseases, including liver injury (**A**), liver fibrosis (**B**), MAFLD (**C**), and HCC (**D**). The two 3D imagines of immunolabeling in the "NAFLD" part are from ref 158. *HSCs* hepatic stellate cells, *HCC* hepatocellular carcinoma, *IL-6* interleukin 6, *MAOA* monoamine oxidase A, *MAFLD* metabolic dysfunction-associated fatty liver disease, *NAFLD* non-alcoholic fatty liver disease, *PSNS* parasympathetic nervous system, *SNS* sympathetic nervous system, *TNF-α* tumor necrosis factor α, *6-OHDA* 6-hydroxydopamine, α7nAChR α7 nicotinic acetylcholine receptor, *α/β-R* adrenergic cholinergic receptor

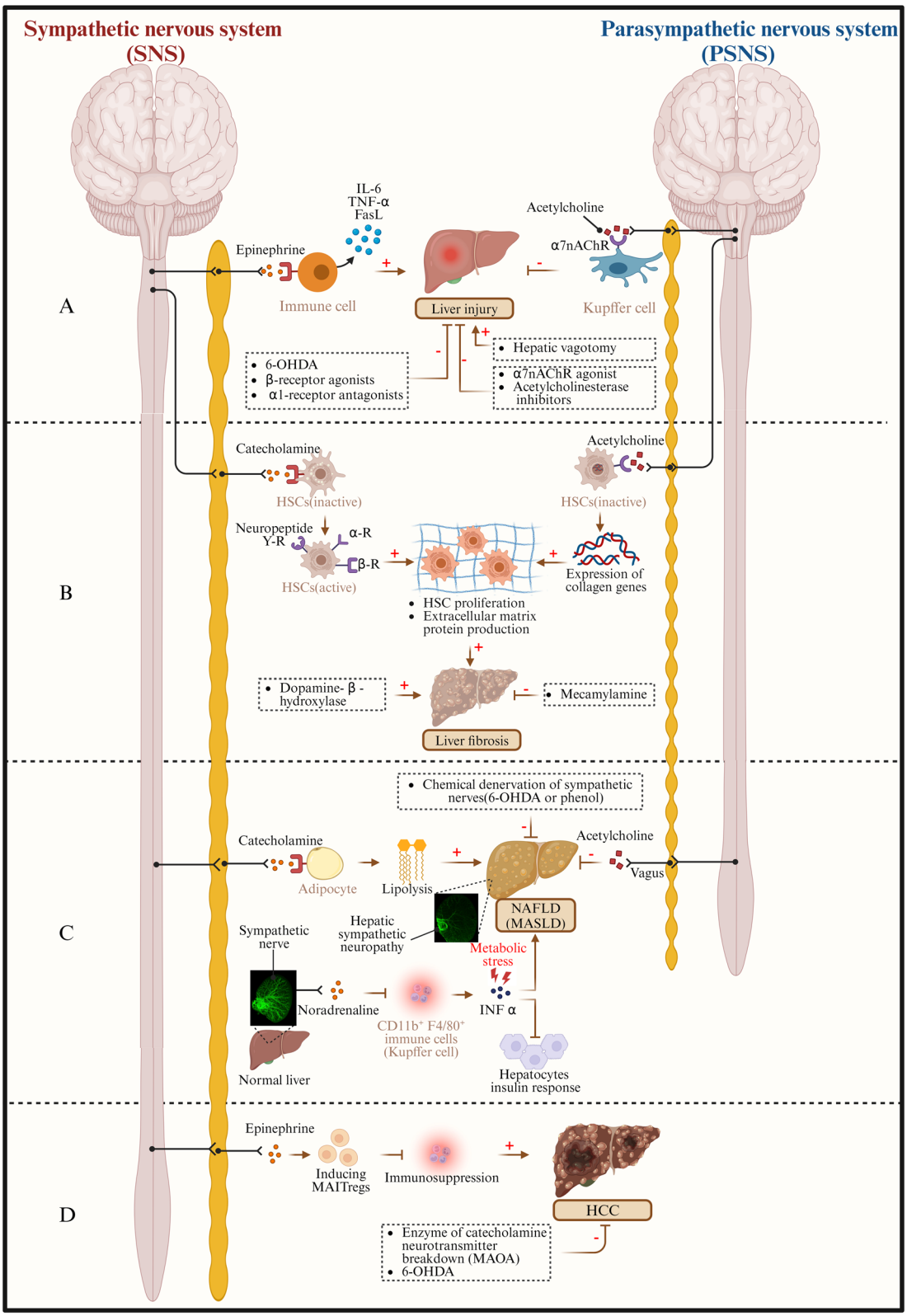

Fig. 6 (See legend on previous page.)

SNS acts on nearby HSCs to exert a proinflammatory and profibrotic effect. Activated HSCs express α-adrenergic, β-adrenergic, and neuropeptide Y receptors, [139] and catecholamines induce HSC proliferation and extracellular matrix protein production in vitro [140, 141]. Mice lacking dopamine-β-hydroxylase, an enzyme essential for norepinephrine production, show reduced accumulation of hepatic α-smooth muscle actin when exposed to an antioxidant-deficient diet that induces fibrosis in control mice [142].

The role of the PSNS in liver fibrosis has not been fully investigated. However, the parasympathetic neurotransmitter Ach promotes the proliferation of myofibroblast-like HSCs and induces the expression of collagen genes in HSCs [143]. These effects are abolished by mecamylamine, an nACh receptor antagonist, suggesting that the influence of Ach on HSC proliferation is partly mediated through nACh receptors (Fig. 6B) [144]. Advanced technologies, such as single-cell and spatial multiomics, multicolor fluorescence, and optogenetics, are needed to better understand the role of neuroimmune crosstalk in the development and progression of liver fibrosis.

Metabolic dysfunction-associated steatotic liver disease

Non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndromes and a major risk factor for liver injury, fibrosis, and even liver cancer [145, 146]. NAFLD is currently estimated to affect 38% of the global population [147] and is expected to become a major indication for liver transplantation [148] over the next 20 years. Recently, important conceptual advances have been made in understanding the complex pathophysiological mechanisms of this highly prevalent liver condition. In 2023, following four rounds of the Delphi survey, three large multinational liver associations proposed that metabolic dysfunction-associated steatotic liver disease (MASLD) should replace the term NAFLD [149]; this proposition garnered wide acclaim, albeit with some dissent [150]. The new nomenclature/criteria of MASLD is more suited for lean patients with NAFLD than the previously suggested metabolic dysfunction-associated fatty liver disease (MAFLD) criteria [151]. This nomenclature change better reflects the pathophysiology and cardiometabolic implications of this common and burdensome liver disease [152]. Emerging evidence suggests an excellent concordance rate between NAFLD and MASLD definitions, with over 99.5% of patients with NAFLD meeting the MASLD criteria [153]. Younossi et al. conducted research showing similar clinical profiles and mortality rates for MASLD and NAFLD, which provided evidence that data generated over the past three decades for NAFLD can be used interchangeably for MASLD [154]. Consequently, it is reasonable to consider that the findings and natural history data from older NAFLD studies remain valid under the new MASLD definition [155].

Increased sympathetic activity is predictive of the development of metabolic abnormalities, whereas reduced parasympathetic activity is linked to metabolic syndrome [156–158]. Autonomic dysfunction is more common in patients with NAFLD (MASLD) than those without [159, 160], suggesting that early autonomic dysfunction may exacerbate the development and progression of NAFLD (MASLD). Chemical sympathetic denervation can decrease the expression of gluconeogenic enzymes and peroxisome proliferator activated receptor alpha in the liver, reducing high-fat diet (HFD)-induced hepatic steatosis [161]. Aging and sympathetic nerve activity are believed to play significant roles in the accumulation of liver fat, with the inhibition of sympathetic activity resulting in increased fat accumulation. The cholinergic anti-inflammatory pathway, regulated by the vagus nerve, provides protection against inflammation associated with obesity and other metabolic complications [162]. KCs, which are liver macrophages, promote liver inflammation through the innate immune response via toll-like receptor (TLR) signaling. Therefore, controlling KC activity may inhibit the progression of NAFLD (MASLD).

Liu et al. used advanced 3D imaging to examine neural distributions in mice, nonhuman primates, and human livers [163]. They observed that neural innervations within the liver are predominantly sympathetic; moreover, they discovered profound and reversible loss of sympathetic innervations during metabolic challenges. This hepatic sympathetic neuropathy was induced by TNFα, produced by $CD11b^{+}$ $F4/80^{+}$ immune cells in response to an HFD. The researchers also found that deleting *Sarm1* alleviated the hepatic sympathetic neuropathy and improved metabolic parameters in mice challenged with an HFD. The study revealed that the sympathetic neurotransmitter norepinephrine suppressed immune cell inflammation, which otherwise would cause insulin insensitivity in hepatocytes (Fig. 6C). These findings shed light on a previously unknown neuropathic event in the liver with metabolic implications [163]. Although the ANS is intricately connected to and interacts with the liver, its precise role in the development and progression of NAFLD (MASLD) remains unclear, especially in the context of the new MASLD definition. Further research is strongly encouraged to develop new neuroimmune biomarkers and drugs against MASLD to ensure patients benefit the most from the changes in disease nomenclature.

Hepatocellular carcinoma (HCC)

Liver cancer stands as the third leading cause of cancer-related mortality worldwide, [164] and HCC accounts for approximately 90% of all liver cancers [165]. The immune components within the tumor microenvironment of HCC are notably intricate, featuring diverse populations of myeloid cells and lymphocytes that play roles in inflammation, immune evasion by cancer, and responses to immunotherapy [166]. HCC is an aggressive cancer, frequently diagnosed late in the disease course when effective treatment options are limited. Fortunately, immunotherapies such as immune-checkpoint inhibitors are revolutionizing cancer management.

The ANS is being increasingly recognized as a significant contributor to tumor progression and metastasis [167, 168]. High sympathetic fiber density in HCC hepatectomy samples is associated with a poorer prognosis [169]. Monoamine oxidase A (MAOA), an enzyme involved in catecholamine neurotransmitter breakdown, is downregulated in HCC, and higher levels of MAOA are associated with improved and disease-free survival [170]. In a rat model of diethyl nitrosamine-induced HCC, sympathetic denervation using 6-OHDA reduced fibrosis and tumor formation [169]. A recent study, combining single-cell RNA sequencing and flow cytometry, identified $FOXP3^+$ $CXCR3^+$ mucosal-associated invariant T (MAIT) cells in patients with HCC as regulatory MAIT cells (MAITregs) with a high immunosuppressive potential [171]. Additionally, the induction and function of MAITregs were promoted by β1 adrenergic receptor signaling in pre-MAITregs and MAITregs, respectively (Fig. 6D). Together, these findings reveal an immunosuppressive subset of MAIT cells that contribute to HCC progression and suggest a control mechanism through neuroimmune crosstalk [171].

Liver pathology affecting the CNS

Hepatic encephalopathy

Hepatic encephalopathy (HE), a serious complication of both chronic liver disease and acute liver failure, is arguably the most clinically relevant entity affecting the crosstalk between liver immunity and the CNS. HE manifests in a wide spectrum of neurocognitive abnormalities, ranging from acute severe cases to more chronic subsyndromal presentations. Patients with fulminant hepatic failure exhibit rigid extremities (and neck muscles), resistance to passive movements (paratonia), worsening confusion, and agitation. These increased reflexes can diminish or be lost in patients with progressive deterioration, such as those in a coma [172, 173]. In subacute forms of HE or less severe presentations, patients may experience frequent falls, fatigue, disinterest, distraction, attention deficits, psychomotor slowing, and, sometimes, impaired driving abilities. This constellation of less-severe symptoms is termed minimal hepatic encephalopathy [172, 173]. The metabolic disturbances and pathogenic mechanisms of HE are multifaceted and complex, with key contributing factors believed to be the elevation of blood toxins such as ammonia and the accumulation of inhibitory neurotransmitters due to disturbances in nitrogenous substance metabolism in the gut [174].

Overwhelming evidence demonstrates that the gut microbiome significantly impacts the crosstalk between liver immunity and brain function in patients with HE (Fig. 7A) [175–177]. The liver–brain–gut axis represents a complex communication system between the gut microbiota, the liver, and the CNS. Dysregulation of this axis has been implicated in the development of several metabolic, inflammatory, neurological, and psychiatric disorders, especially HE [178]. The liver participates in bidirectional communication with the intestine via the portal circulation and bile secretion. Reduced primary bile acid entering the intestine due to liver disease leads to alterations in microbiota composition, bacterial overgrowth, and toxic metabolite production, which in turn exacerbate the course of liver disease [179]. Circulating endotoxins from the gut, together with inflammatory cytokines produced by the gut microbiome and the liver, aggravate systemic inflammation, modulating the impact of ammonia on the brain [180]. Systemic inflammation increases the permeability of the BBB and induces neuroinflammation, leading to microglia activation, astrocyte senescence, and neuronal cell death, subsequently altering neurotransmission and cognitive and motor function in HE [181–183]. In addition to inflammation, enteric pathogens and their metabolites affect cognitive behavior through the direct activation of vagal neurons in the enteric nervous system, altering brain-derived neurotrophic factor, gamma-aminobutyric acid, and oxytocin signaling in the brain [184].

The importance of gut microbial composition and function in the potential pathogenesis of HE is underscored by several gut-centric therapies [175]. Fecal microbiota transplantation, probiotics, prebiotics, and antibiotics can reduce serum ammonia levels and intestinal-derived neurotoxic substances by accelerating intestinal transport and changing the metabolism and abundance of intestinal bacteria [176]. A comprehensive understanding of the mechanisms and importance of the gut–brain–liver axis is imperative for developing innovative therapeutic approaches to address HE [185].

Chronic liver disease (CLD)-associated fatigue

Fatigue is typically the most common complaint and one of the most distressing symptoms reported by patients

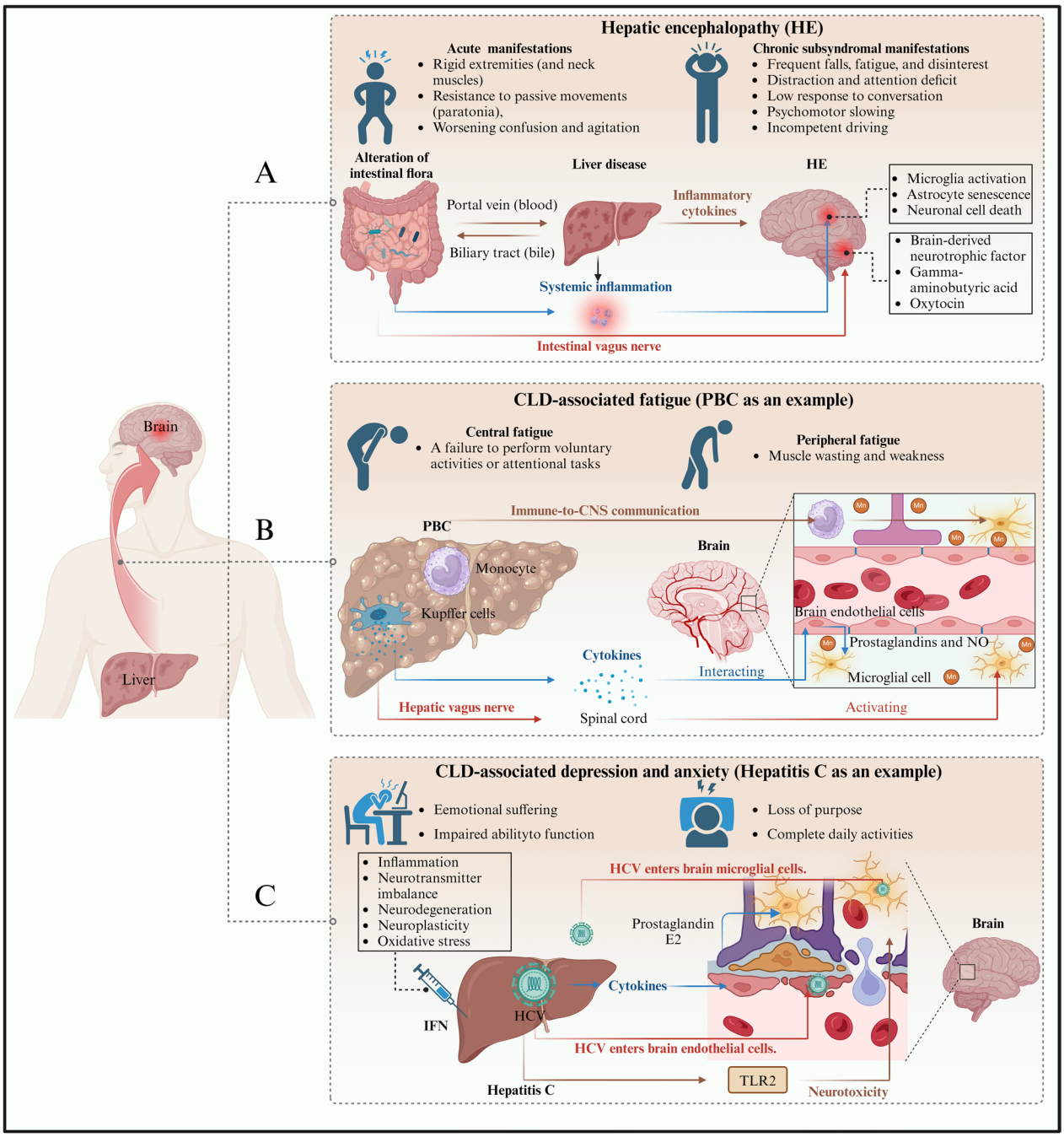

Fig. 7 Liver pathology affecting the CNS. The possible mechanisms of how liver pathology affects brain cognitive function in diseases of hepatic encephalopathy (**A**), chronic liver disease (CLD)-associated fatigue (**B**), depression, and anxiety (**C**). *CLD* chronic liver disease, *CNS* central nervous system, *HE* hepatic encephalopathy, *HCV* hepatitis c virus, *IFN* interferon, *NO* nitric oxide, *PBC* primary biliary cirrhosis, *TLR2* toll-like receptor 2

with CLD. It is closely associated with alterations in mood, such as anxiety and depression [186]. Fatigue is a multidimensional symptom experienced as tiredness in the musculoskeletal system, poor recovery from exercise, decreased motivation for usual activities, cognitive decline, fuzzy thinking, lethargy, and exhaustion [187, 188]. CLD-associated fatigue is generally classified into central (CNS dysfunction, marked by a failure to perform voluntary activities or attentional tasks) and peripheral (neuromuscular failure, characterized by muscle wasting

and weakness) fatigue. [189]. Although the mechanism is poorly understood, 55–85% of patients with PBC have been reported to present with fatigue, [190, 191] with 20% experiencing significant or life-altering fatigue [192].

Defective release of corticotropin releasing hormone [193, 194] and alteration of serotonergic neurotransmission, mediated by 5-HT receptors [195, 196], have been implicated in the genesis of central fatigue occurring in an experimental model of cholestatic liver disease [197]. Clinical evidence reveals that fatigued patients with PBC exhibit stronger resting-state functional neural connectivity between the basal ganglia and motor and premotor cortices, [198] as well as a lower globus pallidus magnetization transfer ratio, [199] compared to non-fatigued patients with PBC. Communication between liver pathology and changes in endocrine function and structure in the CNS is thought to involve two potential pathways: neural and/or humoral. KCs within the liver secrete proinflammatory mediators, subsequently activating vagal afferent nerves that innervate the liver [186]. Nerve impulses are then carried through the spinal cord to the brain, thus altering neurotransmission either directly or indirectly (via microglia activation) [187]. Circulating cytokines from liver inflammation may directly interact with cerebral endothelial cells and generate secondary signals (e.g., prostaglandins and nitric oxide), creating a milieu of neuroinflammation, which can activate microglia [200]. Additionally, another immune-to-CNS communication pathway was identified, involving the entrance of immune cells into the brain. Circulating immune cells were recruited to the brain during liver inflammation to activate resident immune cells within the CNS (i.e., microglia) and amplify neuroinflammation [201]. Activation of microglia can reduce synapses between neurons in the prefrontal cortex of the brain, inhibit neural transduction, and cause behavioral alterations such as anxiety and fatigue [202]. Additionally, the imbalance of manganese homeostasis in the brain as a result of impaired biliary excretion may be an important mechanism in the genesis of fatigue in patients with pre-cirrhotic PBC (Fig. 7B) [199].

Fatigue in patients with PBC also has numerous associated peripheral features. Autonomic dysfunction, typically in the form of vasomotor abnormality, is common at all disease stages of PBC [203]. Autonomic dysfunction is strongly associated with peripheral fatigue by limiting the capacity of the muscle to respond through increased proton/lactate efflux from cells and outflow from tissues [204]. In addition, the anti-mitochondrial antibody has direct muscle-level metabolic effects, leading to over-utilization of anaerobic metabolism [204]. Other symptoms of patients with PBC can also indirectly affect the occurrence of fatigue. Pruritus, another commonly experienced symptom by patients with PBC, can lead to sleep disorders and worsen the feeling of fatigue [205]. Depression and fatigue are mutually causal and may share a common pathogenesis [206–208].

Fatigue in PBC has been mostly assessed with subjective and nonspecific versions of numeric ratings or questionnaires, [209, 210], but no consensus on objective or combined assessments has been reached [188]. Further work is needed to provide more specific and accurate methods to quantify the severity of fatigue and distinguish central from peripheral fatigue. Pharmacological agents to date have not shown to have a significant, reliable effect in reducing fatigue [211]. Consequently, future studies should focus on how the periphery communicates with the brain to mediate changes in central neural activity, enabling the identification of novel therapeutic targets to decrease the burden of debilitating fatigue.

CLD-associated depression and anxiety

Clinical studies have shown that some patients with CLD also experience mental health issues, such anxiety and depression, [212] including symptoms such as emotional suffering, loss of purpose, and impaired ability to function and complete daily activities. For instance, depression and anxiety have high prevalences in patients with hepatitis C [213]. Intracerebral neurobiological changes associated with hepatitis C may potentially explain these symptoms. These changes may arise from infiltration of the brain by peripheral cytokines induced by hepatitis C infection, [214] as well as direct neuropathic effects of hepatitis C viral particles penetrating the BBB. Peripherally-derived cytokines act on the endothelial cells of the BBB, stimulating the secretion of secondary messengers such as prostaglandin E2 into the brain [215]. This stimulates the release of cytokines from activated microglia cells, [216] with subsequent inhibition of neural conduction in the brain [217]. Human brain endothelial cells express specific surface functional receptors (claudin-1, tetraspanin CD81, E-2 glycoprotein, and scavenger receptor-BI) that support hepatitis C viral entry and replication [218]. Viral particles may also be introduced into the brain via infected mononuclear cells and microglia. Activated intracerebral microglia harboring hepatitis C viral infection may have inhibitory or apoptotic effects on neurons through the release of molecules such as pregnalone [219]. Furthermore, the hepatitis C virus core protein promotes neurotoxicity via the sustained activation of extracellular signal-regulated kinase through toll-like receptor 2 signaling [220]. IL-1β polymorphisms have also been confirmed to be associated with depressive symptoms in patients with hepatitis C [221]. Interferons (IFNs), as a highly beneficial therapy in hepatitis C and B, also bring about many neuropsychological disorders such

as depression, anxiety, and other symptoms that affect the patient's quality of life [222]. IFN therapy-related depression can be explained by several mechanisms, including its association with inflammation, neurotransmitter imbalance, neurodegeneration and neuroplasticity, and oxidative stress [223, 224]. Future studies should explore further mechanisms underlying the elevated incidence of depression in patients with hepatitis C, notably IFN-associated depression (Fig. 7C).

PBC, AIH, and PSC represent the three major autoimmune liver diseases [225]. Depression and anxiety have also been observed in patients with PBC and AIH [226]. Depression and anxiety in patients with PBC may have a multifactorial basis. Current supported hypotheses have implicated disrupted neurotransmitter synthesis and changes in brain structure seen on imaging. Tryptophan, as a precursor for the production of the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]), is often associated with depressive mood [227–229]. One study indicated that lower levels of tyrosine and tryptophan were significantly associated with higher levels of fatigue and unexpected depressive condition [191]. It is speculated that treatment with steroids could influence the occurrence of depression and anxiety, since this is a well-known side effect of corticosteroid treatment (Fig. 7) [230, 231].

However, it is still unknown whether depression in turn alters the structure of liver tissue or even aggravates liver function. Further research is needed to identify biomarkers common to both biological processes, to elucidate the potential biological correlations between depression and CLD.

Clinical translations

Ongoing research is shedding light on the communication between the nervous and immune systems, with significant implications for clinical applications [91]. Clinical studies are exploring novel therapeutic approaches for inflammatory and autoimmune conditions, including pharmacological modalities and bioelectronic neuromodulation. Neurotransmitter receptor agonists are a key pharmacological modality. For instance, the anti-inflammatory and disease-ameliorating effects of GTS-21, choline, and other α7nACh receptor agonists have been demonstrated in murine models of endotoxemia, sepsis, postoperative brain inflammation, ischemia and reperfusion injury, and various other inflammatory conditions [232–236]. Centrally-acting acetylcholinesterase inhibitors, such as galantamine, have also been evaluated as anti-inflammatory agents in endotoxemia, inflammatory bowel disease (IBD), arthritis, and other metabolic disorders (Fig. 8) [237–239].

Bioelectronic medicine is an emerging area of neuromodulation that aims to identify molecular disease mechanisms that can be targeted therapeutically using neural signals and bioelectronic devices. This field is grounded in the significant role of the vagus nerve in the inflammatory reflex, which regulates peripheral immune function and inflammation. The therapeutic potential of electrical vagus nerve stimulation (VNS) has been demonstrated in preclinical models of rheumatoid arthritis, [240] IBD, and other inflammatory and autoimmune conditions [238, 241]. Bioelectronic devices, such as VNS, deep brain stimulation, transcranial magnetic stimulation, transcranial direct current stimulation, transcranial ultrasound stimulation [242, 243], and splenic nerve modulation [244], have received clinical approval or are under investigation for conditions like epilepsy, depression, Alzheimer's disease, Parkinson's disease, dystonia, and other neurodegenerative and neuropsychiatric disorders (Fig. 8). The splenic nerve plays an essential role in mediating the anti-inflammatory effects of VNS in LPS-induced endotoxemia [245, 246]. It has been reported that the anti-inflammatory efficacy of nerve stimulation might be improved by directly targeting the splenic nerve instead of the vagus nerve [247, 248]. An interesting animal study verified that splenic nerve denervation could inhibit LPS-induced depression-like behavior [244]. Collectively, research suggests a role for splenic nerve modulation in inflammation-induced abnormalities. Afferent and efferent vagus nerve signaling may contribute to communication between the brain and spleen (the brain–spleen axis), which may also indirectly participate in regulating liver functions that affect health [249]. Therefore, splenic nerve modulation as a potential therapeutic approach provides new insights into the treatment of liver diseases.

Recent progress in understanding the role of neural pathways in controlling inflammation and other physiological functions, along with advances in neuromodulatory technologies, including electrodes, physiological interfaces, and devices, have paved the way for clinical translation of this knowledge. However, several critical considerations must be addressed for clinical translation. First, evaluating intersubject variability in innervation and neuron origins across different species is essential for designing effective therapies that target specific cell populations. Additionally, understanding the influence of chronic inflammation on organ innervation is crucial, as it can lead to neural changes like sprouting, hypertrophy, and altered neurotransmitter release, affecting neural density and function. These gaps highlight the need for ongoing preclinical and clinical studies to assess inflammation's effects on organ innervation. Lastly, a deeper

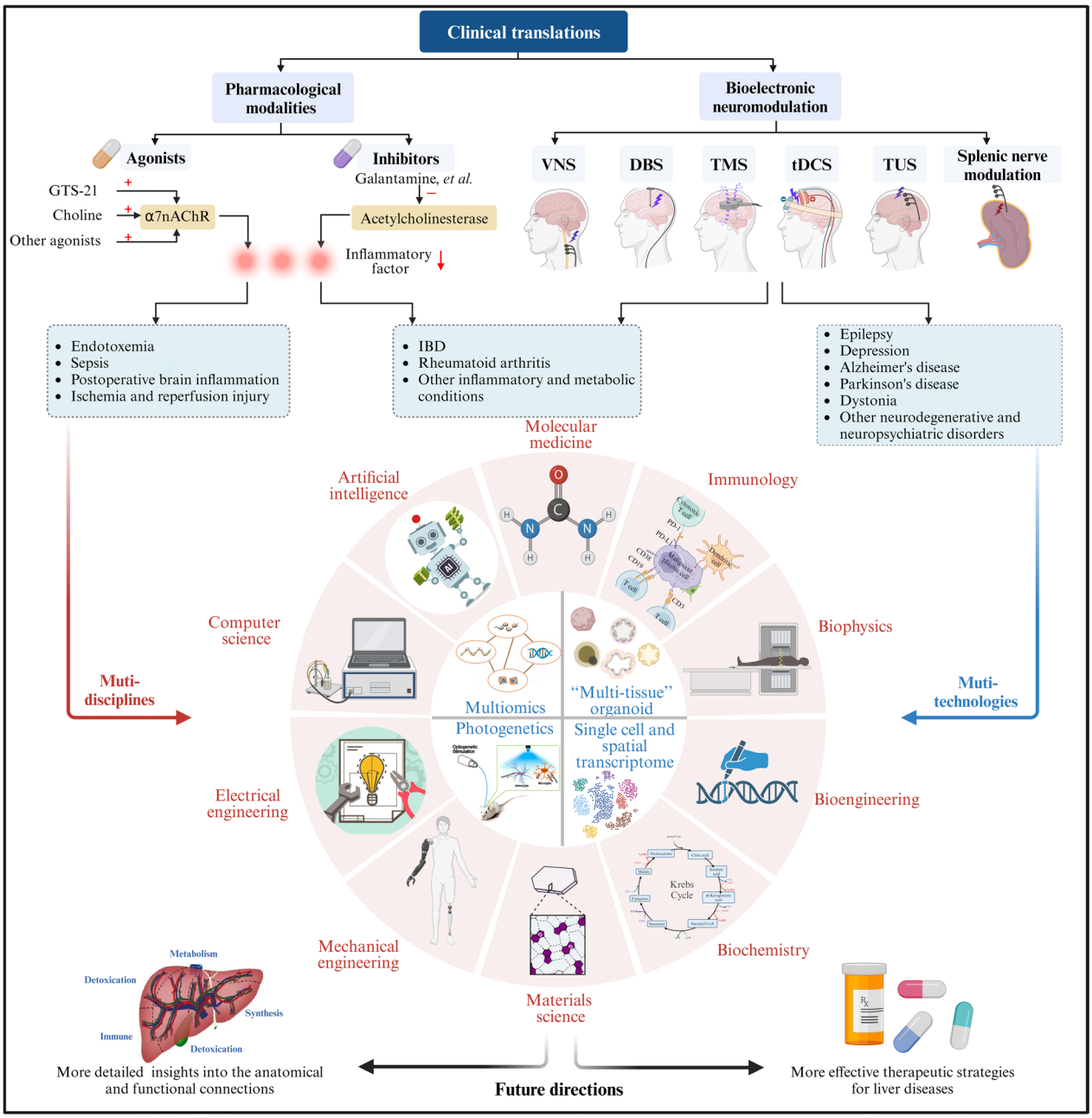

Fig. 8 The Clinical translations and future directions of the neuroimmune crosstalk in the liver. *DBS* deep brain stimulation, *IBD* inflammatory bowel disease, *TMS* transcranial magnetic stimulation, *tDCS* transcranial direct current stimulation, *TUS* transcranial ultrasound stimulation, *VNS* vagus nerve stimulation, *α7nAChR* α7 nicotinic acetylcholine receptor

understanding of the neural circuitry components that regulate specific biological processes is vital for the field of neuroimmune medicine, enabling the simultaneous targeting of multiple sites. Achieving this will require collaborative efforts across various disciplines, including molecular medicine, immunology, biophysics, bioengineering, biochemistry, materials science, mechanical engineering, electrical engineering, computer science, mathematics, and artificial intelligence (Fig. 8).

Conclusions and perspectives

The nervous and immune systems hold pivotal roles in maintaining bodily regulation and defense. In this review, we have explored the experimental evidence showcasing

the intricate interplay between these two systems in the context of liver diseases. As neuroscience and immunology progress, our understanding of the molecular mechanisms governing immune regulation undergoes a profound transformation. Delving into the mechanisms of neuroimmune communication has not only expanded our knowledge but has also paved the way for the evaluation of innovative therapeutic approaches. These approaches, including pharmacological modalities and bioelectronic medicine, have shown promise in preclinical and clinical settings for conditions like sepsis, IBD, and arthritis.

However, it is worth noting that neuroimmune-mediated therapies for liver diseases are still in their infancy. While local neuroimmune interactions have been extensively studied, comprehensive techniques that provide a holistic view of neuroimmune interactions between distant organs and the nervous system in vivo are currently limited. Additionally, the molecular mechanisms governing local immune regulation within the nervous system remain elusive.

The future of this field holds immense promise as cutting-edge technologies, such as multiomics, "multitissue" organoids, optogenetics, and single-cell and spatial transcriptomics, are shedding light on more precise anatomical connections and functional interactions within the neuroimmune network. These advancements will continue to unveil new insights into the anatomical and functional foundations of neuroimmune units at an organismal level.

In conclusion, ongoing research in the field of neuroimmune interactions promises to unravel the mysteries of how these systems collaborate and will likely yield effective therapeutic strategies for liver diseases and beyond. This interdisciplinary journey, bridging neuroscience, immunology, and advanced technologies, heralds a hopeful future where our understanding of neuroimmune communication transforms into tangible clinical benefits.

Abbreviations

ACh	Acetylcholine
AIH	Autoimmune hepatitis
ANS	Autonomic nervous system
AVP	Arginine-vasopressin
CCl_4	Carbon tetrachloride
CLD	Chronic liver disease
CNS	Central nervous system
DCs	Dendritic cells
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
HCC	Hepatocellular carcinoma
HE	Hepatic encephalopathy
HFD	High-fat diet
HSCs	Hepatic stellate cells
IBD	Inflammatory bowel disease
IFN	Interferon
KCs	Kupffer cells
ILC3s	Group 3 innate lymphoid cell
LPS	Lipopolysaccharide
MAFLD	Metabolic dysfunction-associated fatty liver disease
MAIT	Mucosal-associated invariant T
MAITregs	Regulatory MAIT cells
MAOA	Monoamine oxidase A
MASLD	Metabolic dysfunction-associated steatotic liver disease
NAFLD	Non-alcoholic fatty liver disease
NK	Natural killer
P2Y6	UDP-specific type 6 purinergic
PBC	Primary biliary cholangitis
PKC	Protein kinase C
PNS	Peripheral nervous system
PSC	Primary sclerosing cholangitis
PSNS	Parasympathetic nervous system
SNS	Sympathetic nervous system
TRPV4	Transient receptor channel protein vanilloid 4
TNF	Tumor necrosis factor
VIP	Vasoactive intestinal peptide
VIPR2	Vasoactive intestinal peptide receptor 2
5-HT	5-Hydroxytryptamine
6-OHDA	6-Hydroxydopamine

Acknowledgements
We would like to thank Editage for English language editing.

Author contributions
Ruochan Chen: conceptualization, investigation, and writing (original draft, review & editing). Ju Zou: writing and graphics (original draft, review and editing). Jie Li, Xiaoxu Wang, and Daoling Tang: writing (original draft, review and editing).

Funding
This manuscript was supported by grants from the National Natural Sciences Foundation of China (82070613 and 82370638 to R.C.), the Science and Technology Innovation Program of Hunan Province (2022RC1212 to R.C.), and the Natural Science Foundation of Hunan Province China (2023JJ10095 to R.C.).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 11 December 2023 Accepted: 19 July 2024
Published online: 01 August 2024

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