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Review

# Neuroimmune interactions and their roles in neurodegenerative diseases

Bai-Rong Chen[a], Ting Wu[a], Ting-Hui Chen[a], Yun Wang[a,b,*]

[a] Neuroscience Research Institute and Department of Neurobiology, School of Basic Medical Sciences, Key Laboratory for Neuroscience, Ministry of Education/National Health Commission and State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100083, China
[b] PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871, China

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ABSTRACT

The nervous system possesses bidirectional, sophisticated and delicate communications with the immune system. These neuroimmune interactions play a vitally important role in the initiation and development of many disorders, especially neurodegenerative diseases. Although scientific advancements have made tremendous progress in this field during the last few years, neuroimmune communications are still far from being elucidated. By organizing recent research, in this review, we discuss the local and intersystem neuroimmune interactions and their roles in Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Unveiling these will help us gain a better understanding of the process of interplay inside the body and how the organism maintains homeostasis. It will also facilitate a view of the diseases from a holistic, pluralistic and interconnected perspective, thus providing a basis of developing novel and effective methods to diagnose, intervene and treat diseases.

## 1. Introduction

Until recently, the nervous system and the immune system were thought to be two autonomous functional entities that acted independently [1]. However, accumulating evidence has suggested that an intimate crosstalk between the nervous system and the immune system exists.

The nervous system has the capacity to influence the immune system. It can regulate the generation of immune cells by mobilizing hematopoietic stem cells into the blood through glucocorticoids, noradrenaline, and neuropeptide Y, among others [2,3]. By releasing multiple mediators, such as calcitonin gene-related peptide (CGRP), substance P (SP) and TAFA chemokine-like family member 4 (TAFA4), the nervous system can also affect the trafficking and migration of immune cells [4]. To respond to signals derived from the nervous system, immune organs and immune cells also express many kinds of receptors for neurotransmitters, such as adrenergic receptors [5]. Accordingly, via norepinephrine, the sympathetic nervous system (SNS) can regulate many immunological processes by activating different subtypes of adrenergic receptors on immune cells [6,7]. In addition, acetylcholine, dopamine and serotonin can also exert an effect on immune cells (Di Benedetto et al., 2017).

In turn, neurons also express a variety of immune-related receptors, such as receptors for TNF and IL-1 (Pavlov and Tracey, 2017.). By releasing immune mediators to interact with these receptors, the immune system functions as a regulator of the nervous system. For instance, immune cells can regulate the proliferation, differentiation and migration of neural stem and progenitor cells through cytokines and trophic factors, resulting in alterations in neurogenesis [8]. In addition, in the context of pathological pain, TNF, IL-1$\beta$, CCL2 and other immune mediators can powerfully enhance neuronal excitability by strengthening excitatory synaptic transmission and diminishing inhibitory synaptic transmission, contributing to nociceptive hypersensitivity [9].

All the above research implies that the nervous system and the immune system can communicate with each other in distinctive manners, and that they interact in both physiological and pathological states. During inflammation, immune cells release TNF, IL-1, IL-6 and other immune mediators that act on nociceptive sensory neurons, resulting in the generation of pain and its signal transmitted to the central nervous system (CNS) [7,10]. At the same time, these nociceptive sensory neurons secrete several neuropeptides, such as substance P (SP) and vasoactive intestinal peptide (VIP), in turn influencing the functions of immune cells and inflammation [7,10]. To date, a growing body of evidence has demonstrated that these neuroimmune interactions are of vital significance in maintaining homeostasis and play an important role in the initiation and development of many disorders, such as inflammatory bowel

* Corresponding author.
*E-mail address:* wangy66@bjmu.edu.cn (Y. Wang).

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diseases [11], asthma [7], pain [9,10] and neurodegenerative diseases [12–14].

With the advancement of technology, the field of neuroimmune interactions has flourished in recent years and many surprising and exciting breakthroughs have been achieved. However, due to the sophistication of both systems, the neuroimmune dialogs are still complex. The detailed processes and mechanisms underlying neuroimmune interactions remain unclear; thus, more exploration is necessary. Organizing recent research, we highlight the local and intersystem neuroimmune interactions and their roles in Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Unraveling neuroimmune communications and their effects on diseases will substantially broaden our understanding of the operation inside the body as well as the initiation and development of diseases, providing us with new insights into the diagnoses, interventions and treatments for diseases.

## 2. Neuroimmune interactions in local tissues

In local peripheral tissues, neurons and immune cells often coexist at defined anatomical locations [3,7,15], where they interact productively with each other. These functional sites have been defined as neuroimmune cell units (NICUs) [3,15], which may be the anatomical bases for neuroimmune interactions in local peripheral tissues. Similar structures can also be found in the CNS. For example, microglia have close contact with the dendrites and synapses of surrounding neurons [12]. Astrocytes can form tripartite synapses with neurons [16]. These formations may establish the structural foundations for local neuroimmune communications.

### 2.1. Neuroimmune interactions in local peripheral tissues

Neuroimmune interactions in local peripheral tissues consist of communications between neurons in the peripheral nervous system (PNS) and peripheral immune cells. In different peripheral tissues, neuroimmune interactions are diversified, as are their functions and roles in disease.

In the gut, enteric neurons are involved in the regulation of local inflammation [11,17]. Reciprocally, intestinal immune cells and inflammation participate in maintaining homeostasis of the enteric nervous system (ENS) [17]. In the pancreas, the activity of sympathetic nerves is also associated with local inflammation [18]. One example supporting this idea is that sympathetic denervation could halt the immune response in pancreatic islets in RIP-LCMV-GP type I diabetes mice, leading to delayed progression of diabetes [18].

Likewise, in the skin, sensory neurons exhibit bidirectional crosstalk with a wide variety of immune cells, including T cells, neutrophils, mast cells and dendritic cells [15] (Fig. 1). IL-4 secreted from T cells can activate dermal sensory neurons, leading to chronic itch [15]. In turn, signals derived from neurons regulate immune cells. For example, nociceptive sensory neurons can suppress the recruitment of neutrophils and their opsonophagocytic activity via calcitonin gene-related peptide (CGRP) during necrotizing infection [15]. In addition, dermal peptidergic sensory neurons are able to drive mast cell degranulation through substance P (SP), while non-peptidergic sensory neurons inhibit this process via glutamate [5]. These studies suggest that different sensory neurons can interact with different immune cells via diverse mediators. However, their relationships are still elusive, and whether they match by the methods of one-to-one, one-to-many, many-to-one or many-to-many is unknown. It is possible that all of these exist but under different conditions. In addition, it is worth interrogating whether the opposite effects caused by different sensory neurons on the same immunological response can be achieved by altering the contacts between different immune cells rather than releasing different molecules to act on the same immune cell.

To summarize, neuroimmune interactions are complicated in distinct local peripheral tissues. Kabata et al. described the sophistication and specificity of neuroimmune interactions in local peripheral sites, which depend on the tissues, cell types and diseases [7]. The same peripheral innervation can produce different or even opposite effects on immune cells in different tissues, diseases and their progression [5]. As an example, transient receptor potential cation channel subfamily V member 1 (TRPV1)-expressing dorsal root ganglia (DRG) neurons can release calcitonin gene-related peptide (CGRP) to inhibit neutrophil recruitment and reduce bacterial killing in *Streptococcus pyogenes* infection while to induce the secretion of interleukin-23 (IL-23) from dendritic cells and promote defense against candidiasis in the case of *Candida albicans* infection [5]. Due to such spatiotemporal heterogeneity and dynamics, the principles of neuroimmune interactions in one site will not be applicable to another. Additionally, even when in the same region, the principles of communication do not necessarily apply in different diseases or during different disease progressions. Therefore, when dealing with neuroimmune-related diseases in the clinic, these differences should be kept in mind, and individualized rather than generalized treatments should be provided. However, the reasons for these differences remain unknown. Udit et al. suggested that it might be caused by the presence of distinct subtypes of neurons [5]. In addition, the types of immune cells and the methods by which neurons and immune cells interact may be altered. To decipher this question, it is necessary to draw a site atlas and disease atlas of neuroimmune interactions in local peripheral tissues, which will show the specific processes of neuroimmune communications in different sites, diseases and the progression of disease. The creation of these two atlases will assist in a better understanding of the neuroimmune interaction in local tissues and facilitate the development of more effective targeted therapies for disease, which may influence the dialog in one site specifically but not the other.

### 2.2. Neuroimmune interactions in the CNS

When compared to local peripheral tissues, the major feature of neuroimmune interactions in the CNS is the crosstalk between glial cells and neurons (Fig. 1). Microglia, the resident immune cells in the CNS, have been implicated in the regulation of neurogenesis and neurodevelopment via cytokines, which can also change the size of the neural progenitor cell pool through phagocytosis and regulate synaptic plasticity as well as the formation of neural circuits through classical complement cascades [19–21]. Similar to microglia, astrocytes can release a variety of substances, such as ATP, glutamate, D-serine and L-lactate, to modulate the activity of neurons, synaptic transmission and plasticity [16]. Furthermore, astrocytes can use brain-derived neurotrophic factor (BDNF) to orchestrate neuronal network oscillations [16] and mediate adult hippocampal neurogenesis [22]. In addition to acting alone, microglia and astrocytes can also cooperate to act by interacting with each other. IL-1$\alpha$, TNF and C1q released by activated microglia, for example, can induce the generation of neurotoxic reactive astrocytes [23]. The latter triggers the death of neurons and oligodendrocytes by saturated lipids [24].

As previously stated, microglia and astrocytes can influence the function of neurons. In turn, they also recognize and respond to neuron-derived signals. Activated neurons are able to modify the morphology and function of microglia via ATP [25]. They can also induce focal and rapid depolarizations in peripheral astrocyte processes, which impact the capacity of astrocytes to clear glutamate [26]. Another study also illustrated that the axonal terminals of neurons in the hypothalamic paraventricular nucleus might directly activate oxytocin receptor-expressing astrocytes in the lateral central amygdala by secreting oxytocin [27].

Taken together, glial cells, such as microglia and astrocytes, communicate with neurons bidirectionally in the CNS. These communications are of crucial importance for the proper functioning of the brain. How-

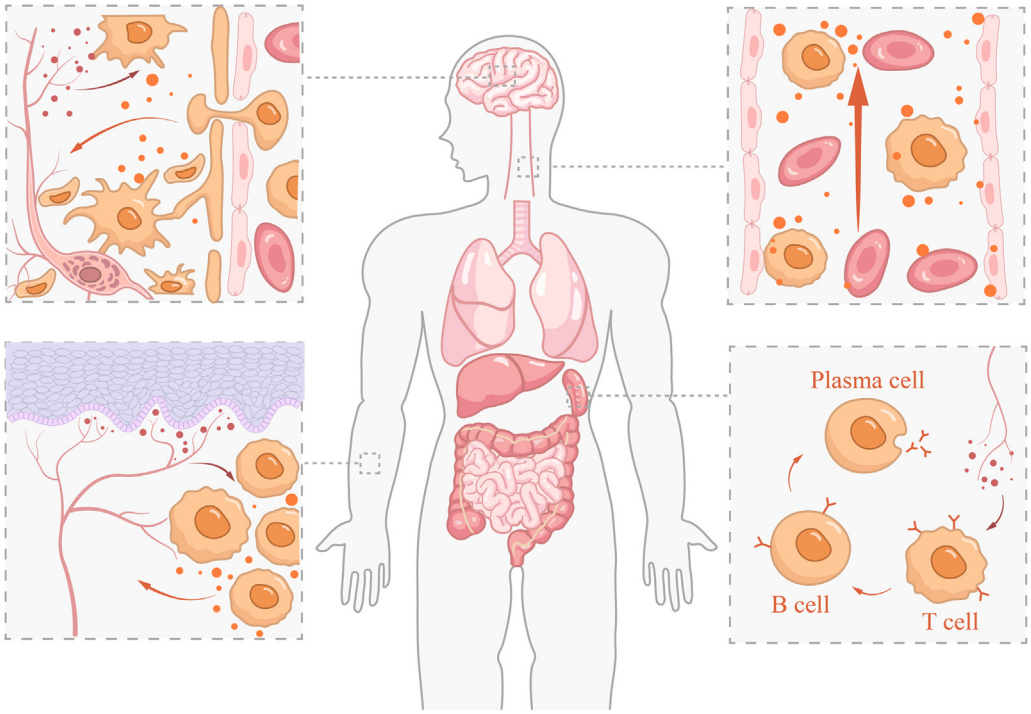


**Fig. 1. Local and intersystem neuroimmune interactions.** Neurons and immune cells bidirectionally communicate with each other in local tissues. For example, in the skin, immune cells release immune mediators to interact with corresponding receptors expressed on the axon terminals of neurons. Neurons, in turn, affect the functions of immune cells through several molecules. In the brain, neurons also have bidirectional dialogues with microglia and astrocytes. Moreover, neurons and immune cells between the CNS and local peripheral tissues are also capable of interacting with each other. It has been shown that corticotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus and central amygdala can modulate the generation of plasma cells via splenic nerves. Peripheral immune cells, in turn, can directly infiltrate the CNS and affect neurons. On the other hand, they also secrete immune mediators, which can enter the CNS by circulating blood, to perform their functions. The existence of several axes, including the liver-brain axis, lung-brain axis, gut-brain axis, bone marrow-brain axis (not shown) and brain-spleen axis, also supports the existence of intersystem neuroimmune interactions.

ever, our knowledge of how glial cells function in the CNS, especially their interactions with neurons, is still in its infancy. Many unknowns remain to be investigated.

## 3. Neuroimmune interactions between peripheral tissues and the CNS

Neuroimmune interactions are present not only in local sites but also between peripheral tissues and the CNS. These intersystem neuroimmune interactions are also bidirectional.

### *3.1. Interactions between peripheral neurons and central immune responses*

In neuropathological pain, the process of pain is mediated by local neuroimmune interactions at the site of peripheral nerve injury, which can also induce similar neuroimmune communications in the CNS [9]. It is unknown if these communications can be regarded as the replaying of local neuroimmune interactions in the CNS, and if so, how the interactions in local peripheral tissue are transformed into communications in the CNS. Signals from peripheral tissues can be relayed to the brain by neurons in the PNS. Therefore, peripheral neurons are likely to act as carriers of these interactions. In the case of peripheral nerve injury, it seems that injured afferent sensory neurons release chemokines, ATP and other molecules in their innervation sites in the CNS, followed by the activation of microglia, which then activate astrocytes and induce the infiltration of peripheral immune cells via a variety of immune mediators [9]. This suggests that immune signals in peripheral tissues can be converted into immune signals in the CNS by afferent neurons, i.e., “immune signals-neural signals-immune signals”. In this process, immune responses in peripheral tissues activate neurons (i.e., immune signals are transformed into neural signals). Through neural transmission, these signals are relayed to the CNS, where the activated neurons release related factors to replay immune responses (i.e., neural signals are transformed into immune signals). This may imply that neural signals can be converted into immune signals and vice versa.

In addition to causing the infiltration of peripheral immune cells through immune mediators, activated peripheral neurons can directly open a path for peripheral immune cells to reach the CNS, providing another way to induce central immune responses, thus creating a vicious cycle. For instance, the activation of sensory neurons in soleus muscles led to alterations in dorsal blood vessels in the fifth lumbar cord through sympathetic nerves, which opened a gateway for transferred pathogenic $CD4^+$ T cells to migrate into the CNS, contributing to the development of experimental autoimmune encephalomyelitis (EAE) [28]. This pathway for peripheral immune cells to enter the CNS needs the help of peripheral nerves and local vessels. Moreover, central neurons may also be involved in this process. This idea has been supported by a study showing that pain induction by ligating the middle branch of the trigeminal nerves activated sensory neurons, and the signals were then relayed to anterior cingulate cortex (ACC) and in turn descended via sympathetic nerves, which mediated the accumulation of MHC class $II^+$ $CD11b^+$ cells in the ventral vessels of the fifth lumbar cord and further recruited multifarious immune cells, including pathogenic $CD4^+$ T cells, resulting in the relapse of EAE [29].

Taken together, the activation of peripheral neurons appears to be able to affect central immune responses. This raises the question of whether central immune responses can in turn influence peripheral neurons. Central immune responses may, in theory, alter the activity of neurons in the CNS, which then relay the signals to peripheral neurons and modulate them via efferent nerves. In addition, it is still poorly under-

stood whether the effects of peripheral neurons on central immune responses can be achieved directly through their secretions crossing the blood-brain barrier and functioning in the CNS. Further studies are warranted to fully elucidate these processes.

### 3.2. Interactions between peripheral immune responses and central neurons

It is becoming increasingly clear that peripheral immune responses can impact neurons in the CNS, further resulting in behavioral changes. For example, chronic inflammation in the liver can generate behavioral changes, including sickness behaviors, by causing central neural changes via TNF$\alpha$, IL-1$\beta$ and IL-6 [30] (Fig. 1). In the disease of multiple sclerosis, autoreactive T cells can migrate into the bone marrow and mobilize myelopoiesis, resulting in dramatically augmented production and output of neutrophils and monocytes, which penetrate the CNS and escalate central inflammation and demyelination [31]. Moreover, defects in the immune system can also disturb the functions of the brain. Research has demonstrated that T-cell-deficient mice develop cognitive disorders, which are ameliorated by transferring mature T lymphocytes (Kipnis, 2016.).

Central neurons, in turn, are also capable of modulating peripheral immune responses. Activating dopaminergic neurons in the ventral tegmental area (VTA) strengthens innate and adaptive immune responses through the sympathetic nervous system [32]. In addition, ablation of suprachiasmatic nuclei (SCN) interrupts circadian oscillations in enteric group 3 innate lymphoid cells (ILC3s), which disturbs homeostasis in the intestine [33]. Furthermore, corticotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus (PVN) and central amygdala (CeA) are able to release norepinephrine in the spleen via splenic nerves, which interacts with its receptor in choline acetyl transferase-expressing T cells, resulting in the secretion of acetylcholine to act on B cells and promote the generation of plasma cells [34] (Fig. 1). Through this pathway, these neurons can modulate adaptive immunity inside the body to some extent in some cases [34]. Additionally, corticotropin-releasing hormone neurons in the PVN also control the bone marrow homing of lymphocytes and monocytes from secondary lymphoid organs and blood during acute stress [35]. And the motor cortex and motor centers in the medulla mobilize neutrophils to egress from the bone marrow to peripheral tissues under the same condition [35].

Taken together, the studies mentioned above imply that the brain possesses the capacity to regulate peripheral immune responses. This ability is not executed by one single brain area only. It may be a diffuse system consisting of numerous brain areas in the CNS that collaborate with each other to orchestrate peripheral immune responses. Here, we refer to this system as the central diffuse immunomodulatory system, and the neurons that influence immunological responses in this system are referred to as immunomodulatory neurons. This raises the question of which brain areas in the CNS make up this system. Schiller et al. summarized that the hypothalamus, brainstem, insular cortex, primary somatosensory cortex, amygdala, hippocampus and ventral tegmental area are involved in the regulation of peripheral immune responses [1]. All of these areas may be members of the central diffuse immunomodulatory system (Fig. 2). The suprachiasmatic nuclei, hypothalamic paraventricular nucleus, motor cortex and medulla, as previously discussed, may also be involved in this system (Fig. 2). However, these are not the only brain areas involved, and there may be still more undiscovered nuclei. Furthermore, the CNS contains intricate connections between these brain areas. The role that their connections play in regulating peripheral immune responses is also unclear, as is the question of whether there is a core to the central diffuse immunomodulatory system or if its components are hierarchical. To determine the core or how the hierarchy is structured, as well as the factors that determine the formations of the core or hierarchy, it requires additional explorations to decipher and clarify the central diffuse immunomodulatory system.

The existence of the central diffuse immunomodulatory system gives the brain the strength to modulate peripheral immune responses effectively. This leads to the question of why the brain evolved this ability. Schiller et al. suggested that the brain can integrate all kinds of information inside or outside the body to orchestrate physiological processes and immune responses and thus synchronize them, which enables optimization and effectiveness of immune responses [1]. The brain can also predict upcoming potential threats and prime the immune system in advance [1]. Moreover, the brain responds swiftly to stimuli, which makes it feasible to initiate and terminate immune responses in a short time [1] (Fig. 2). These suggest that the central diffuse immunomodulatory system is of indispensable significance to the organism.

Some brain areas in the CNS are capable of regulating peripheral immune responses, which also raises the question of whether there exist brain areas in the CNS that can encode information about peripheral immune responses. It has been proposed that the immune system may serve as a “sixth sense” of the body responsible for perceiving the factors that the body cannot detect by hearing, seeing, smelling, tasting or touching [36,37]. It seems that, in a sense, the immune system is also a sensory system but different from others in that its duty is to monitor and perceive the internal environment. However, the organism is not conscious of what the immune system senses. If this is true, the information that the immune system perceives, in theory, should be able to be encoded and stored in the brain. One seminal study indicated that after recovery from colitis or peritonitis, activating insular cortical neurons that were active during inflammation could, to some extent, recapitulate the original inflammatory state specifically in the colon or peritoneum [38]. This suggests the possibility that neurons in the insular cortex are capable of encoding and storing information about peripheral immune responses, which could be retrieved later [38]. Moreover, the phenomenon of learned immune responses, which is observed when, after pairing a conditioned stimulus with an unconditioned stimulus that can elicit a certain immune response, applying a conditioned stimulus alone can also induce an immune response that does not appear previously [1,36,39], also suggests that some areas in the brain can detect and encode peripheral immune responses. Ample evidence supports that insular cortex is involved in learned immune responses [36]. Taken together, these studies suggest that neuronal ensembles in the insular cortex may play an important role in the processes of the CNS responding to peripheral immune responses (Fig. 2). Therefore, whether insular cortex is the brain center that encodes and stores peripheral immune response-related information, and whether this phenomenon can be regarded as immune-related memory are important questions to examine. To distinguish it from traditional immunological memory (Farber et al., 2016.), we define this phenomenon as neuro-immunological memory. This kind of memory can be perceived but not recognized by the organism. We also designate the neurons participating in this kind of memory as immunological engrams. We are simply conceptualizing this phenomenon here, and further evidence is needed to verify it. In the study by Koren et al., only activating neurons in insular cortex that were active during peripheral inflammation did not completely mimic the original immune responses [38], suggesting that immune-related information is multidimensional and that its brain representations are complex. Information about peripheral immune responses is not entirely acquired by one nucleus in the CNS, rather different brain areas are responsible for one or more of its dimensions. Therefore, the activation of neurons in one of these brain areas repeats only one aspect of immune responses. In addition, if this neuro-immunological memory truly exists, how the brain perceives the change in immune responses and obtains related information is also mysterious.

The aforementioned neuro-immunological memory in the research of Koren et al. may be a negative condition. It is possible that if the organism encounters the stimuli in the internal or external environment that can activate immunological engrams for these memories, comparable inflammation may appear. This may be the underlying mechanism of psychosomatic diseases [38]. The evolutionary benefit to an organism to

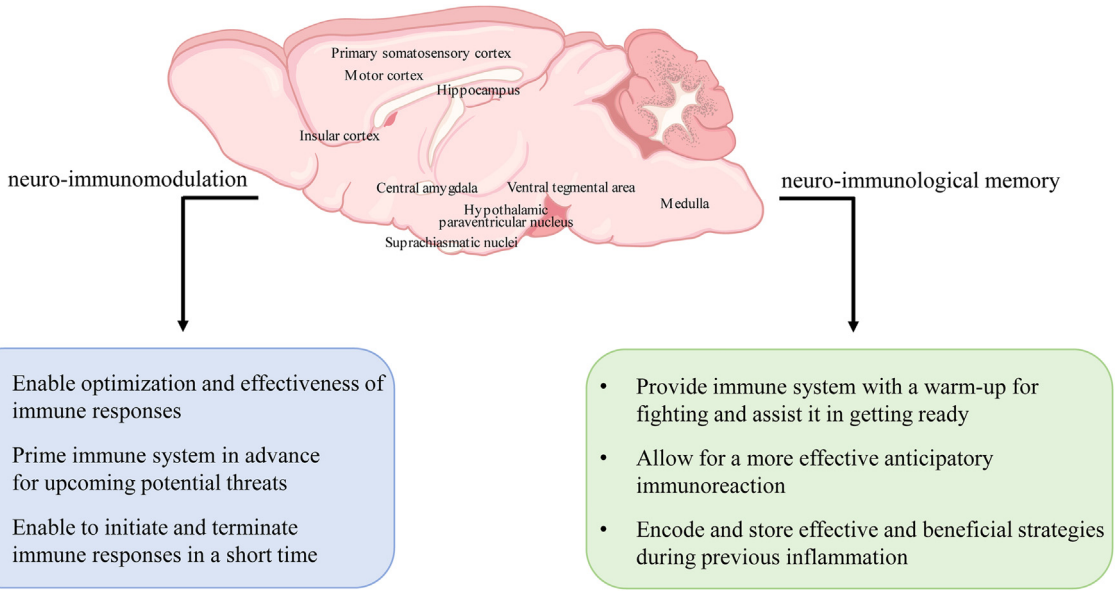


**Fig. 2. The central diffuse immunomodulatory system and neuro-immunological memory.** It has been reported that several brain areas in the CNS, including the primary somatosensory cortex, motor cortex, insular cortex, hippocampus, central amygdala, hypothalamic paraventricular nucleus, suprachiasmatic nuclei, ventral tegmental area and medulla, are involved in the regulation of immune responses, which together may constitute the central diffuse immunomodulatory system. The existence of this system endows the organism with the ability to optimize immune responses, prime the immune system in advance for upcoming potential threats, and make it possible to initiate and terminate immune responses in a brief time. Among these brain areas, insular cortex also encodes and stores information about peripheral immune responses, which may form neuro-immunological memory. This kind of memory may help the immune system become ready to fight against diseases by providing it with a warm-up and allow for a more effective anticipatory immunoreaction when stimuli recur. Additionally, positive neuro-immunological memory may encode and store the effective and beneficial strategies used during previous immune responses, while negative neuro-immunological memory may be the underlying mechanism of psychosomatic diseases.

evolve a system that seems to harm itself is not immediately clear. It may be an early warning for upcoming threats. When confronted with situations that may cause previous inflammation, the organism can retrieve these memories to simulate a possible but relatively mild inflammatory state, providing the immune system with a warm-up for fighting and assisting it in getting ready. Another possibility is that the brain, at the same time, also records its own response during these experiences, allowing for a more effective anticipatory immunoreaction when stimuli recur [38]. On the other hand, there may exist another type of positive neuro-immunological memory that has yet to be uncovered. This kind of memory encodes and stores the effective and beneficial strategies that the organism uses during previous inflammation. Therefore, when a comparable inflammatory response recurs, these strategies can be used to guide immune cells to rapidly restore homeostasis (Fig. 2). Another concern is how we can use noninvasive methods to eliminate or strengthen neuro-immunological memory. Using the methods that are applied to manipulate memory in neuroscience research as a reference may help us to achieve this goal.

In summary, neurons and immune cells have bidirectional sophisticated interactions between peripheral tissues and the CNS. These interactions depend on the connections between them. Although it has been demonstrated that several organs can communicate with the brain through specific axes, such as the liver-brain axis [30], lung-brain axis [40], gut-brain axis [15,41], bone marrow-brain axis [31] and brain-spleen axis [34] (Fig. 1), the detailed immune-related connections between these peripheral tissues and the CNS are still elusive. Moreover, the questions of whether other organs or tissues are also able to interact with the brain and whether one brain area in the CNS is responsible for one peripheral organ or tissue remain to be answered. Therefore, it is essential to depict an atlas of connections in neuroimmune interactions between peripheral tissues and the CNS. The atlas should include the immune mediators, innervation, infiltrating pathways for immune cells among other information. This atlas will provide us with a platform to better comprehend and effectively modulate these intricate processes, as well as providing a basis on which more useful potential therapeutic strategies for neuroimmune-related disorders will be developed.

## 4. The roles of neuroimmune interactions in neurodegenerative diseases

As mentioned above, neuroimmune interactions play a pivotal role in maintaining homeostasis. Imbalances in these interactions will trigger the initiation and development of many disorders. Mounting evidence indicates that the activation of innate immunity and chronic neuroinflammation can be observed in multiple neurodegenerative diseases [12]. A genome-wide association study also showed that several risk genes of AD and related dementias are associated with the immune system (Bellenguez et al., 2022.), among which *TREM2, CD33, CR1* and other genes are expressed exclusively in microglia [21]. Some risk genes of PD, including *BST1, SYT11* and *GRN*, are also closely related to the immune system (Tansey et al., 2022.). The activation of microglia, astrocytes, peripheral lymphocytes and macrophages has also been observed among ALS patients [14]. Moreover, dysregulation of several immunological checkpoints or pathways in microglia, such as the Trem2, Cx3cr1-fractalkine sensing and progranulin pathways, increases the risk for neurodegeneration [13]. To summarize, these studies point to the idea that the immune system, as well as its interactions with the nervous system, plays a vitally important role in the process of neurodegenerative diseases. Here, we focus on AD, PD and ALS, the three most common neurodegenerative disorders, to illustrate the roles of neuroimmune interactions in neurodegeneration.

### *4.1. Local neuroimmune interactions and neurodegenerative diseases*

#### *4.1.1. Alterations in peripheral immune responses*

During the process of AD, the populations of peripheral monocytes and their gene expression change [42]. For example, the expression of

proinflammatory genes for IL-6, IL-1$\beta$, NLRP3, TNF, IL-18 and others was decreased in the prodromal stage but significantly increased in the advanced disease stage [42]. In addition, the number and inhibitory function of myeloid-derived suppressor cells (MDSCs) are augmented in the prodromal stage of AD but reduced in the later stage [42]. In PD, peripheral monocytes are pathologically hyperactive and possess a proinflammatory predisposition (Grozdanov et al., 2014.). It was demonstrated that a lower quantity of lymphocytes in circulating blood was linked to an increased risk for PD (Jensen et al., 2021.). Naive $CD4^+$ and $CD8^+$ T cells as well as naive B cells in peripheral blood are reduced among early-stage PD patients, while the number of central memory $CD4^+$ T cells, IL-17-producing $CD4^+$ Th17 cells, IL-4-producing $CD4^+$ Th2 cells, IFN-$\gamma$-producing $CD8^+$ T cells and TNF-$\alpha$-producing $CD19^+$ B cells are increased (Yan et al., 2021.). In addition, immature transitional B cells and follicular T cells are also reduced and produce a proinflammatory profile among PD patients (Li et al., 2022.). At the same time, the interactions between follicular helper T cells and B cells are aberrant (Li et al., 2022.). Similar to AD and PD, the subtype distribution, gene expression signature and function of peripheral monocytes also change in patients with ALS [43]. For instance, $CD16^-$ monocytes are decreased among ALS patients [44]. In addition, circulating neutrophils are augmented [44]. It has been shown that a higher neutrophil count in peripheral blood was significantly relevant to shorter survival among ALS patients (Murdock et al., 2021.), and the ratio of neutrophils to $CD16^-$ monocytes, which was dramatically increased in ALS, was closely associated with the progression of the disease [44]. Moreover, the inhibitory function of regulatory T lymphocytes in peripheral blood is also abnormal in ALS patients (Beers et al., 2017.).

Taken together, these studies imply that there are tremendous alterations in the peripheral immune system in the progression of these neurodegenerative diseases. How do these changes interact with the nervous system to take effect in these disorders? Existing studies suggest that they may participate in this process by influencing intersystem neuroimmune interactions, such as by the means of infiltrating the CNS or secreting immune mediators to cross the blood-brain barrier and function in the CNS, which can give rise to neurotoxicity as well as neuroinflammation [45]. For example, in AD, neutrophils can enter the brain via LFA-1 integrin attachment [46] and cause toxicity directly to neurons by releasing IL-17 and neutrophil extracellular traps (NETs) [45,47]. And in ALS, elevated proinflammatory cytokines and chemokines in the periphery, such as TNF-$\alpha$, IL-1$\beta$ and IL-6, which may be the results of dysregulation of the peripheral immune system, can alter the function of resident cells and exacerbate neuroinflammation in the brain after they enter the CNS [48]. However, the question of how the changes of peripheral immune responses alter local peripheral neuroimmune interactions to affect the progression of neurodegeneration is still unclear. These changes are likely to be the bases of the alterations of local peripheral neuroimmune interactions in these diseases. This still needs further research to take deep insight into.

As mentioned above, the number, type and function of immune cells and immune mediators in peripheral tissues change markedly during the progression of neurodegenerative diseases, which leads to prominent alterations in peripheral immune responses. These alterations may promote the development of the diseases and hence exacerbate the symptoms. Sommer et al. demonstrated that in vitro, T cells mediated the death of midbrain neurons derived from human induced pluripotent stem cells (hiPSCs) from PD patients via the IL-17-IL-17R signaling pathway [49]. On the other hand, these alterations can also stifle or slow down the progression of diseases, thereby alleviating symptoms. Furthermore, there exist certain resemblances but also differences in the alterations of peripheral immune responses among different neurodegenerative diseases, such as the changes in peripheral monocytes noted above. Whether these similarities are the root causes of the similar symptoms and whether these distinctions, to some extent, determine the specificity of the diseases remains unclear. To further clarify the relationship between the alterations of peripheral immune responses and neurodegenerative diseases, it is essential to systematically detail the changes in immune cells, immune mediators and other components in peripheral tissues in different neurodegenerative disorders and make comparisons among them. Furthermore, despite extensive research into the alterations of peripheral immune responses in several neurodegenerative diseases, a full understanding of how these changes take effect in peripheral tissues to mediate the disorders is still lacking. Nevertheless, targeting these alterations is still able to delay or alleviate the symptoms of neurodegenerative diseases. For example, peripheral administration of IL-33 ameliorated AD-like pathology and rescued cognitive deficits in APP/PS1 mice (Fu et al., 2016.).

#### *4.1.2. Alterations in central immune responses*

Both astrogliosis and microgliosis have been observed in the brains of AD, PD and ALS patients [12]. In addition, neurotoxic reactive astrocytes, which can induce the death of neurons in the CNS, were found in the hippocampus and prefrontal cortex of AD patients, the substantia nigra of PD patients and the motor cortex of ALS patients [23]. These findings imply that changes in central immune responses mediated by microglia and astrocytes also have a role in the development of neurodegenerative diseases. In this section, we will focus on AD to examine the effect of central immune response-related changes on the progression of neurodegenerative disorders.

A previous study indicated that microglia could constitute a barrier around amyloid plaques to restrict the expansion and toxicity of the plaques [50]. Similarly, activated phagocytic microglia were also able to prevent the seeding of A$\beta$ [51]. These findings suggest that microglia can prevent neurons from being damaged by toxic factors and thus play a protective role in the process of AD. In contrast, another study demonstrated that microglia could aid in the propagation of A$\beta$ [52]. And A$\beta$ accumulation in the brain may lead to the release of complement C1q from neurons, which can activate its corresponding receptor, C1qR, on microglia and result in synaptic pruning and phagocytosis by microglia, giving rise to neuronal toxicity and death [46]. Moreover, in response to A$\beta$, microglia can also secrete cysteine protease cathepsin B to cause apoptosis of neurons [53]. The activation of NF-$\kappa$B signaling pathway in microglia has also been shown to facilitate the seeding and dissemination of tau (Wang et al., 2022.). Tau, in turn, can activate NF-$\kappa$B signaling pathway in microglia (Wang et al., 2022.), possibly resulting in a vicious cycle. Additionally, in an AD mouse model, aberrant glycolysis in microglia might raise the level of lactate-dependent histone modification, further leading to increased expression of glycolytic genes and exacerbation of microglial dysfunction, which drives the pathology of AD [54]. Interrupting this positive feedback loop could ameliorate neuroinflammation and reverse the cognitive decline in AD [54]. According to these studies, microglia can amplify neuroinflammation as well as the destructive effects of toxic factors and kill neurons via releasing proteases, and thus appear to be detrimental in AD. The results concerning the role of microglia in AD are contradictory in different studies and the real role of microglia in AD remains unclear. The hypothesis that there are two peaks of microglial activation in the course of AD is gaining traction [42,55]. The early activation of microglia may be protective, whereas later activation may be proinflammatory and destructive [42,55]. Therefore, in the research stated above, microglia may be in different phases, resulting in opposite effects. If so, it is important to understand what factors mediate the activation of microglia at different stages and the mechanisms that underpin these factors. Furthermore, another study indicated that microglia surrounding the amyloid plaques were primarily derived from the bone marrow [56]. Microglia of this type were able to eliminate amyloid deposits [56]. This may imply that microglia playing a protective role in the progression of AD are foreign to the brain rather than resident microglia. If so, it will be important to know if microglia activated at different stages of AD come from distinct origins. Providing a comprehensive and detailed description of the changes, subtypes and origins of microglia in the trajectory of AD will assist in better comprehending the roles of microglia in the initi-

ation and development of AD and identifying more effective potential therapeutic targets.

Astrocytes are also involved in the process of AD. It was demonstrated that the expression of $\alpha$2-$Na^+/K^+$ ATPase was increased in astrocytes in the brains of AD patients [57]. Inhibiting this ATPase suppresses neuroinflammation and the accumulation of tau pathology [57]. Additionally, when exposed to A$\beta$, astrocytes might release complement component C3, which binds to the G-protein-linked receptor C3aR expressed on neurons, contributing to the changes of dendritic morphology and network dysfunction [58]. And inhibition of this complement component may ameliorate cognitive decline and reverse the loss of synapses in AD (Vainchtein and Molofsky, 2020.). Moreover, in AD, dysregulated astrocytes are likely to exert excitotoxic effects on neurons owing to the accumulation of glutamate [58]. In addition, reducing the expression of apoE3 and apoE4 in astrocytes was able to reduce the deposition of amyloid plaques and the activation of microglia around the plaques [59], which implies that astrocytes can harm neurons indirectly and exacerbate the symptoms of AD via the release of apoE3 and apoE4. Taken together, these studies suggest that astrocytes also have a significant importance in the initiation and development of AD and that they can cooperate with microglia to coordinate this process. However, the precise content and the underlying mechanisms of the interactions between astrocytes and microglia in the progression of AD remain unclear and require further investigation.

### 4.2. Intersystem neuroimmune interactions and neurodegenerative diseases

As discussed above, alterations in peripheral and central immune responses have an impact on neurodegenerative diseases. Due to the close communications between local peripheral tissues and the CNS, the interactions between them also play a pivotal role in neurodegeneration. In this section, we summarize recent research about PD and ALS to support the idea that interactions between peripheral tissues and the CNS have a marked impact on the development of neurodegenerative disorders.

Overexpression of $\alpha$-synuclein in the midbrain, which can be secreted by exocytosis from neurons [12], has been reported to cause T cell infiltration [60], which may be the result of T cells recognizing $\alpha$-synuclein-derived peptides (Sulzer et al., 2017.). And evidence has revealed that the activation of these infiltrating T cells can give rise to the death of dopaminergic neurons. As an example, activated $CD8^+$ T cells can directly attack $\alpha$-synuclein-expressing dopaminergic neurons [61]. In addition, intestinal infection in $Pink1^{-/-}$ mice may lead to the generation of cytotoxic mitochondria-specific $CD8^+$ T cells [62]. These T cells were also able to infiltrate the CNS and cause the death of dopaminergic neurons, which may mediate PD-like motor impairment [62]. In addition to acting on neurons directly, peripheral immune cells infiltrating the brain can also interact with resident immune cells in the CNS. Astrocytes, for example, can function as antigen-presenting cells in the brains of PD patients, activating infiltrating $CD4^+$ T cells [63]. And these activated $CD4^+$ T cells can be polarized to T helper cells and cause the death of dopaminergic neurons through the pathway of IL-17-IL-17R or via the interplay between lymphocyte function-associated antigen 1 (LFA1) and intercellular adhesion molecule 1 (ICAM1) [61]. They are also able to be polarized to type 1 T helper cells, activating and recruiting other immune cells to attack dopaminergic neurons via the robust secretion of proinflammatory cytokines, such as interferon-$\gamma$ (IFN-$\gamma$) [61]. Moreover, they are capable of promoting the production of plasma cells from B cells to release specific autoantibodies to damage dopaminergic neurons [61]. Targeting these peripheral immune cells infiltrating the CNS in pathological conditions may ameliorate the symptoms of neurodegeneration to some extent. Depletion of T cells has been shown to reverse the loss of dopaminergic neurons caused by overexpression of $\alpha$-synuclein [60], which supports this theory. However, it is important to keep in mind that not all peripheral immune cells that migrate into the CNS are destructive and noxious. It has been shown that natural killer (NK) cells are capable of invading the CNS and clearing $\alpha$-synuclein, and systemic depletion of NK cells might aggravate related symptoms in PD mice [64]. Therefore, eliminating all the peripheral immune cells that infiltrate the brain is not the best approach. We should instead identify the roles of these immune cells in the diseases in detail, and then take measures to weaken or strengthen their functions according to their effects.

Similar to PD, peripheral immune cells migrate into the CNS in ALS. It has been shown that cytotoxic $CD8^+$ T cells can infiltrate the CNS to mediate the death of spinal motor neurons in an ALS mouse model [65]. These activated T cells can produce IFN-$\gamma$ to elicit and maintain the expression of major histocompatibility complex (MHC)-I on motor neurons and finally exert their cytotoxic effects on neurons via Fas and granzyme pathways [65]. Moreover, NK cells were observed in both the motor cortex and spinal cord of ALS patients and mice [66]. However, in contrast to PD, NK cells infiltrating the CNS in ALS were able to directly cause the death of motor neurons in a NKG2-dependent manner [66] or via the release of toxic factors, such as perforin [67]. They can also suppress the recruitment of regulatory T cells via IFN-$\gamma$ and instruct microglia to shift into a proinflammatory phenotype, exacerbating the disease [66]. In contrast, peripheral monocytes might preserve motor neurons after invading the CNS [43].

Altogether, the roles of neuroimmune interactions between peripheral tissues and the CNS in neurodegenerative diseases, such as PD and ALS, are mediated by peripheral immune cells directly or indirectly acting on central neurons after they infiltrate the CNS. Different peripheral immune cells invading the CNS may have similar or opposite effects in the same neurodegenerative illness. In addition, the same kind of immune cells that migrate into the CNS may also play similar or contrary roles in different neurodegenerative disorders, such as cytotoxic $CD8^+$ T cells and NK cells in PD and ALS [62,64-66]. This may be due to the distinct signals detected by peripheral immune cells in the diseases. However, it is still unclear how these signals command immune cells to perform their functions similarly or differently. Moreover, it is unclear what the signals are that entice peripheral immune cells to invade the CNS in the same or different neurodegenerative diseases. The mechanisms by which these immune cells penetrate the CNS and whether there is a distinction remain to be investigated. In addition, neurodegenerative diseases usually have a long course and multiple stages. Whether there is a difference in the peripheral immune cells that invade the CNS at different stages or whether there is an order or a schedule for their migration are also open questions. Additionally, whether another form of interactions exists for peripheral immune cells to affect central neurons in neurodegeneration that is independent of invading the CNS and releasing immune mediators is unknown.

In summary, neuroimmune interactions have an important role in the progression of neurodegenerative diseases. Dysregulation of local or intersystem neuroimmune interactions may exacerbate these disorders. Therefore, therapeutically targeting these mechanisms to rebalance the nervous system and the immune system may delay and ameliorate neurodegeneration to some extent. However, whether the immune system or the nervous system is responsible for this dysregulation is unclear. Are the alterations in the immune system the initiation of this dysregulation, which then disturb the nervous system and result in neurodegenerative diseases? Or do pathological changes first arise in the nervous system, followed by a maladjusted immune system, which further worsens the disorders, leading to a virous cycle? Therefore, the relationship between the nervous system and the immune system, as well as the sequential order of the changes, still requires more information.

In addition, there exist some similar and distinct processes of neuroimmune interactions in the progression of neurodegenerative diseases. Here, we focus on microglia to make comparisons in terms of neuroimmune interactions among AD, PD and ALS. In the process of these neurodegenerative disorders, many intracellular or extracellular materials that directly or indirectly derived from neurons, such as A$\beta$ in AD [12,13], $\alpha$-synuclein in PD [12,61] and mutant superoxide dismutase 1 (mSOD1) in ALS [12,13], can activate microglia via bind-

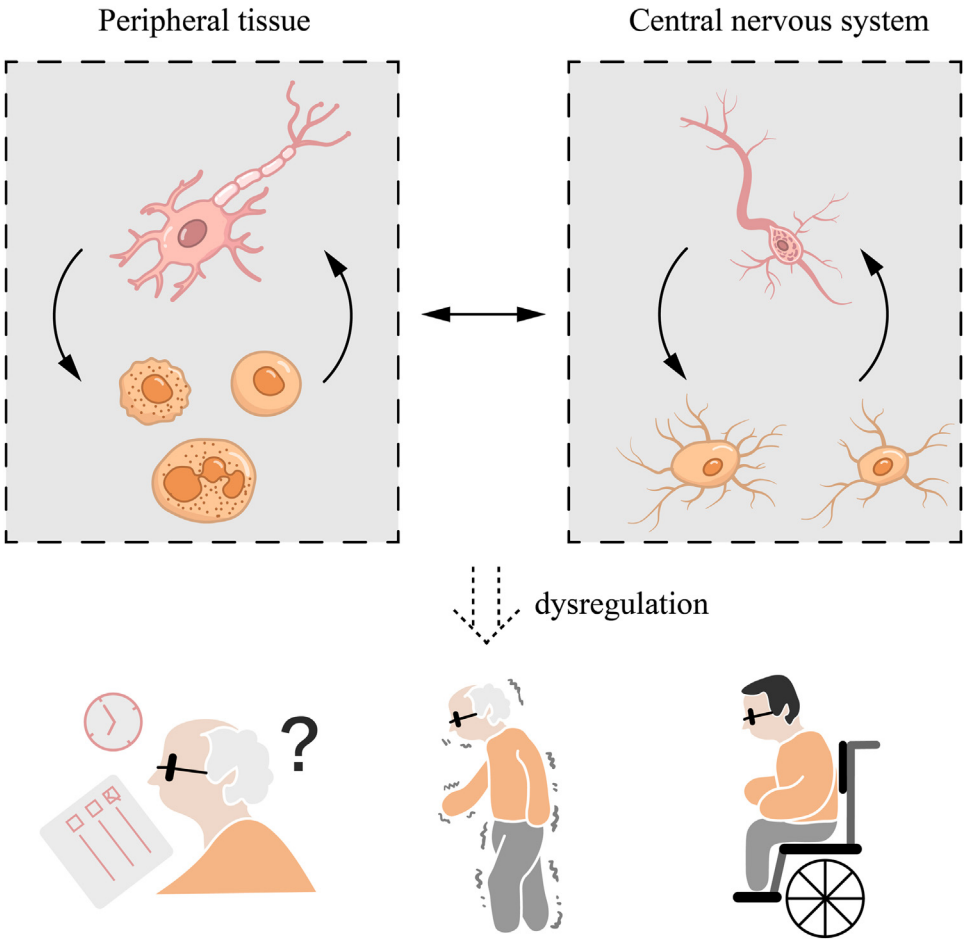


**Fig. 3. Dysregulation of neuroimmune interactions contributes to the initiation and development of neurodegenerative diseases.** Neurons and immune cells possess bidirectional, sophisticated and delicate communication with each other. This interplay exists not only in local tissues but also between the peripheral and central systems. Dysfunction of these interactions is involved in the initiation and development of several neurodegenerative disorders, including AD, PD and ALS.

ing to pattern recognition receptors expressed on microglia, including TLR2, TLR4 and TLR6 [12]. At first, the activated microglia can help to clear these substances to prevent neurons from injury, but finally they exert toxic effects on neurons owing to overload and chronic activation [13,48,67,68], resulting in neurodegeneration. In this condition, these activated microglia are able to damage and kill neurons through direct or indirect methods [13]. They can directly degrade neurons by phagocytosis [61] or cause excitotoxic neuronal death via releasing glutamate as well as overexpressing iNOS [13]. Additionally, they can release proinflammatory cytokines to amplify local neuroinflammation [61] and reduce the production of neuroprotective factors, including brain-derived neurotrophic factor (BDNF) as well as insulin-like growth factor (IGF) [13], giving rise to the death of neurons indirectly. Via secreting cytokines, such as IL-1$\alpha$ and TNF, they can also promote the conversion of neuroprotective astrocytes to neurotoxic astrocytes [45,61,67] which can cause neuronal demise through reduced trophic support and release of neurotoxic factors [68]. These processes are the same in these three diseases, and there also exist some differences. In AD and PD, dysregulated microglia can spread toxic materials they cannot digest to healthy neurons [13,61], which, in our knowledge, is still not reported in ALS. For instance, in AD, microglia can spread tau aggregates in a non-synaptic transmission pathway [68] and carry A$\beta$ to unaffected brain tissue [52]. Similarly, in PD, microglia can facilitate the propagation of toxic forms of $\alpha$-synuclein to healthy dopaminergic neurons [61,69]. Moreover, unlike that in AD and ALS, activated microglia in PD are capable of inducing the expression of MHC class I molecules on dopaminergic neurons [70] and functioning as antigen-presenting cells to present dopaminergic neuronal antigens to T cells, leading to the activation of these cells and the arrival of immune attack to dopaminergic neurons [45,61]. Additionally, activated microglia can induce ferroptosis of dopaminergic neurons through disrupting iron homeostasis and increasing oxidative stress in PD [71], whereas in AD, they mediate the apoptosis of neurons via secreting proteases [53]. Why do different neurodegenerative diseases have these similar processes? Are they the common foundations of the initiation or development of neurodegeneration? And whether the distinctions determine the specificity of the diseases? All these questions are still poorly understood. And besides microglia, such similarities and distinctions also exist in other cells. Therefore, it is essential and necessary to depict and compare the systemic changes of the immune system and the alterations of neuroimmune interactions in various neurodegenerative diseases. These findings will help us gain new insights into the role of neuroimmune interactions in neurodegeneration and develop more effective disease-specific therapies.

Although we just emphasize the effects of neuroimmune interactions on neurological disorders in this review, especially neurodegenerative diseases, it should be noticed that they also function in other illnesses, including immune disorders. It has been shown that neuroimmune interactions have a pivotal role in pathophysiology of allergic inflammation, such as asthma [7]. It seems that noradrenaline derived from sympathetic nerves and acetylcholine derived from parasympathetic nerves are able to suppress group 2 innate lymphoid cell (ILC2)-mediated type 2 airway inflammation, resulting in alleviating the symptoms of asthma

**Table 1**
**How to distinguish between immunomodulation-related and neuro-immunological memory-related brain areas.**

| Manipulation | Effects on the first immune response? | Similar immune responses after recovery? | Role? |
|---|---|---|---|
| activation or inhibition of specific brain area | yes | no | neuro-immunomodulation |
| | no | yes | neuro-immunological memory |
| | yes | yes | both |
| | no | no | neither |

[7]. Moreover, in the development of rheumatoid arthritis, sympathetic nerves might mediate the differentiation of naive $CD4^+$ T cells into Th1 cells, which accumulate within the synovial fluid and secrete IFN-$\gamma$ to promote the inflammatory process [6]. Additionally, neuroimmune communications also appear to affect the initiation, maintenance and aggravation of psoriasis (Ayasse et al., 2020.), as well as the development and relapse of EAE [28,29]. All these studies suggest that neuroimmune interplay is also crucial in the progression of immune diseases. Given the general existence of the immune system and the nervous system inside the body, their interactions may also play a vitally important role in other disorders not directly related to these two systems. Deeper insights into this aspect and its details still warrant further research.

## 5. Conclusion and perspectives

In this review, we discuss the local and intersystem neuroimmune interactions inside the body. These communications are critical for maintaining homeostasis, the dysfunction of which can lead to the initiation and development of many disorders, such as neurodegenerative diseases, including AD, PD and ALS (Fig. 3). Targeting these interactions and restoring the balance between the nervous system and the immune system will be a more effective and preferential way to prevent and ameliorate associated disorders.

The structure known as synapse is responsible for signal transmission between neurons. Similar structures can also be found between different immune cells, which are called immunological synapses (Dustin, 2014.). These findings prompt us to wonder whether a similar formation also exists between neurons and immune cells in the process of neuroimmune interactions. It has been indicated that glial cells can closely contact neuronal processes or form tripartite synapses [12,16]. However, it remains unclear whether a similar structure can form between neurons and peripheral immune cells, such as T cells and monocytes. Owing to the relatively high motility of peripheral immune cells, it may be challenging for this structure to be constituted. Another possibility is that when neurons and peripheral immune cells communicate with each other, they form this structure quickly, and this structure exists for only a brief time before dissipating. With current technologies, it is difficult to capture such a structure. The morphology of this interaction site if it exists and the detailed processes of its formation and extinction are also important issues.

Earlier in this review, we conceptualize the central diffuse immunomodulatory system and neuro-immunological memory. The existence of neuro-immunological memory seems to assist the organism in better modulating immune responses. From this perspective, the related brain areas may also have the capacity for immunomodulation at the same time. For example, insular cortex has been demonstrated to be involved in both the modulation and encoding of immune responses [1,36,38]. Whether there are distinct neurons in this location that execute these different functions and how can we identify and categorize them remain open questions. Moreover, in order to distinguish between immunomodulation-related and neuro-immunological memory-related brain areas, we need to consider the effect of activating or inhibiting specific brain areas on the first immune response and whether its reactivation can induce similar immune responses after recovery. In other words, if the brain area is associated with neuro-immunomodulation only, its activation or inhibition may influence the first immune response, and the reactivation of the neuronal ensemble in this brain area, which is active during the initial immune response, should not be able to induce a similar immune response after recovery. If reversed, the brain area may be responsible for neuro-immunological memory (Table 1). In addition, it is important to understand how these two functional systems change during the progression of neurodegenerative diseases, causing alterations in immune responses and the dysregulation of neuroimmune interactions. For instance, in neurodegenerative diseases, peripheral immune responses could be the outcome of pathogenic alterations or central immune responses of the central diffuse immunomodulatory system. If this is the case, the central diffuse immunomodulatory system and neuro-immunological memory may also take part in neuroimmune-related disorders. Thus, it is important to investigate what roles they play and how they are altered in related diseases.

Aging has been recognized as one of the major risk factors for neurodegenerative diseases [14]. Immunosenescence and inflammaging are two age-related immune system alterations that often occur as people age (Tansey et al., 2022.). This raises the question of whether neuroimmune interactions change during aging. One study found that T cells invaded the subventricular zone neurogenic niche in aged mice, where they released IFN-$\gamma$ to suppress the proliferation of neural stem cells [72]. This suggests that neuroimmune communications may deteriorate with age, which may also be associated with the initiation and development of neurodegenerative diseases. Both microglia isolated from adult mice and peripheral monocytes derived from elderly individuals were found to exhibit phagocytosis deficits of $\alpha$-synuclein (Bliederhaeuser et al., 2016.). Accordingly, it seems that aging may trigger dysfunctions in neuroimmune interactions, increasing the risk for the onset of neurodegenerative disorders. However, more evidence is still needed to validate this hypothesis.

The delicate and sophisticated interplay between the nervous system and the immune system has uncovered new avenues for treating related diseases. To alleviate neurological disorders, we can target the immune system. Similarly, we can treat immune-related diseases by manipulating the nervous system. In addition, we are also able to achieve this indirectly via other systems. One study found that pulmonary microbial communities altered the immune reactivity of microglia in the brain via lipopolysaccharide, therefore affecting the development of autoimmune disease in the CNS [40]. Moreover, intestinal mucosa-associated fungi induced type 17 immunity through T helper cells to increase the level of IL-17A systemically, which interacted with its receptor on neurons and then affected the social behaviors of mice [41]. These studies suggest that other systems and their components are also able to influence the nervous system. This function is carried out, in part, by modulating the immune system. Therefore, targeting other potential related components to treat neurological diseases may be a reasonable option, yet

the underlying mechanism still partly depends on neuroimmune interactions.

When targeting neuroimmune interactions to treat neuroimmune-related diseases, some key signaling pathways, which may be the common language for both the immune system and the nervous system, should be valued. Transforming growth factor-$\beta$ (TGF-$\beta$), for example, plays an integral role in modulating both the innate and adaptive immunity [73,74], and also has multiple functions in the CNS [73,75]. TGF-$\beta$ is a potent regulator of T cell proliferation, survival and homing [74], as well as B cell proliferation, differentiation and activation [76]. It is also able to control the development and functions of NK cells, macrophages, and dendritic cells, among other innate cells [76]. Meanwhile, TGF-$\beta$ can regulate the initial formation of the nervous system, patterning of the CNS, axon guidance, neuronal migration, microglial development, cerebral cortex angiogenesis, neurogenesis and synaptogenesis [73,75,77]. Similarly, the complement cascade, a major component of the innate immune system, specialized to recognize and eliminate invading pathogens and dead or modified self-cells [78,79], is also essential for brain development and function, as it regulates neurogenesis, neuronal migration and synaptic refinement [78]. These common signaling pathways function both in the nervous system and the immune system. Therefore, caution must be taken when targeting these pathways to modulate one of the systems. Their effects on the other system should not be ignored, or it will backfire. Given the importance of these signaling pathways in the nervous system, their roles in neurodegenerative diseases should not be underestimated. Ample evidence has shown that the alterations of these signaling pathways function in the etiology and progression of neurodegeneration. The level of TGF-$\beta$ is significantly elevated in AD and PD cases [73,80], as well as the plasma concentration of TGF-$\beta$1 in ALS patients [75]. In AD patients, TGF-$\beta$ signaling pathway is deficient, which may contribute to A$\beta$ accumulation, tau pathology and neurofibrillary tangle formation (Caraci et al., 2011.). In PD, TGF-$\beta$ plays an important role in the differentiation, maintenance and synaptic function of dopaminergic neurons [80], and the injection of TGF-$\beta$ can decrease the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced degeneration of dopaminergic neurons in substantia nigra [73]. With respect to ALS, TGF-$\beta$ pathway loses its neuroprotective effects and enhances excitotoxicity induced by glutamate at the pre-symptomatic stage, and gives rise to microglia activation as well as neuromuscular junction dismantling at the symptomatic stage [75]. Similarly, the expression of complement components is significantly increased in various neurodegenerative disorders, including AD, PD and ALS [73,78,79]. And they are likely to be functionally implicated in the pathogenesis of these diseases through regulation of inflammation and phagocytosis [73,79]. Blocking complement cascades effectively limits the influences of neurodegeneration-associated pathology [73]. Therefore, these common signaling pathways in neuroimmune interactions may be promising therapeutic targets for neurodegenerative diseases, which will be a major research focus moving forward.

Despite the fact that progress has been made on the treatments for neurodegenerative diseases by targeting neuroimmune interactions, it is still difficult to employ this strategy because the best time to weaken or strengthen these communications remains unclear, owing to the dual roles of immune responses in disease progression. In AD and ALS, it has been demonstrated that early immune responses are neuroprotective, while late immune responses are neurotoxic [42,44,55]. Therefore, determining the timepoint at which protective immune responses transform into destructive responses has become a great challenge for treatment. Determining this timepoint will guide the application of suitable modulatory strategies for neuroimmune interactions at an appropriate time.

To overcome this obstacle, finding specific biomarkers for neuroimmune interactions during neurodegeneration is critical. For example, in AD, it has been found that the concentration of alpha-2 macroglobulin in the blood, a major component of the innate immune system, is correlated with the concentration of markers of neuronal injury, tau and phosphorylated tau in cerebrospinal fluid (CSF) in preclinical AD patients (Varma et al., 2017.). Furthermore, soluble TREM2 (sTREM2), CX3 chemokine ligand 1 (CX3CL1) and progranulin (PGRN) can also reflect changes in microglial functions in AD (Zhang et al., 2021.). The alterations of these biomarkers, to some degree, can be regarded as surrogate indicators for the changes in neuroimmune interactions. However, the existing biomarkers come from a variety of cells in vivo, and some of them are associated with diseases but not the process of neuroimmune interactions. Therefore, there is still a need for biomarkers that can accurately reflect the alterations of neuroimmune interplay in neurodegenerative diseases. In addition, it is also necessary to delineate the dynamic changes of these biomarkers in disease progression.

In conclusion, the interplay between the nervous system and the immune system is intricate and delicate and plays a pivotal role in many disorders, especially neurodegenerative diseases (Fig. 3). To further discover neuroimmune interactions, more in-depth collaborative interdisciplinary research and novel state-of-the-art technologies are urgently needed. In addition, more research paradigms must be established and improved. Existing research has laid the groundwork, but there is still a long way to go.

## Declaration of competing interest

The authors declare that they have no conflicts of interest in this work.

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**Bai-Rong Chen** is a Ph.D. candidate at Peking University, with a primary focus on the mechanisms of sleep regulation. Specifically, he is interested in understanding the roles of metabolism and glial cells in this process. Additionally, he is intrigued by the relationship between sleep and pain, as well as neuroimmune interactions.

**Yun Wang** (BRID: 08901.00.97998) is the associate dean of the School of Basic Medical Sciences, Peking University, the president of Chinese Association for Physiological Sciences, deputy director of the Steering Committee of Basic Medical Sciences Education, Ministry of Education, China. She devoted research in Neurobiology, achieving a series of research findings on pain, neurodevelopment, and psychiatric disorders. She published more than 70 articles in peer-reviewed journals and obtained 6 patents in China. She was awarded the distinguished Young Scholars of NSFC, Hsiang-Tung Chang Young Scientist Award in Neuroscience and Wuzhou Women Science & Technology Award of China Medical Women's Association.