

# Brain-Region-Mediated Neuroimmune Modulation in Sepsis: Research Advances and Therapeutic Prospects

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**Abstract:** Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, lacks effective treatments targeting its pervasive immune dysregulation. Despite growing interest in neuroimmune interactions, there remains a fragmented understanding of how distinct brain regions integrate peripheral immune signals and orchestrate systemic immune responses in sepsis. Emerging evidence highlights the brain as a master regulator of systemic immunity in sepsis through the neuro-immune-endocrine network. This review summarizes recent advances in understanding how distinct brain regions, including the hypothalamus, brainstem, cortex and cerebellum, sense peripheral inflammation and feedback-regulate systemic immune responses via dedicated neural circuits, neurotransmitters, and autonomic outputs. We also highlight the therapeutic potential of neuromodulation techniques designed to target these central circuits and discuss their implications for developing future precision medicine strategies in sepsis management.

**Keywords:** sepsis, neuroimmunity, brain regions, central nervous system

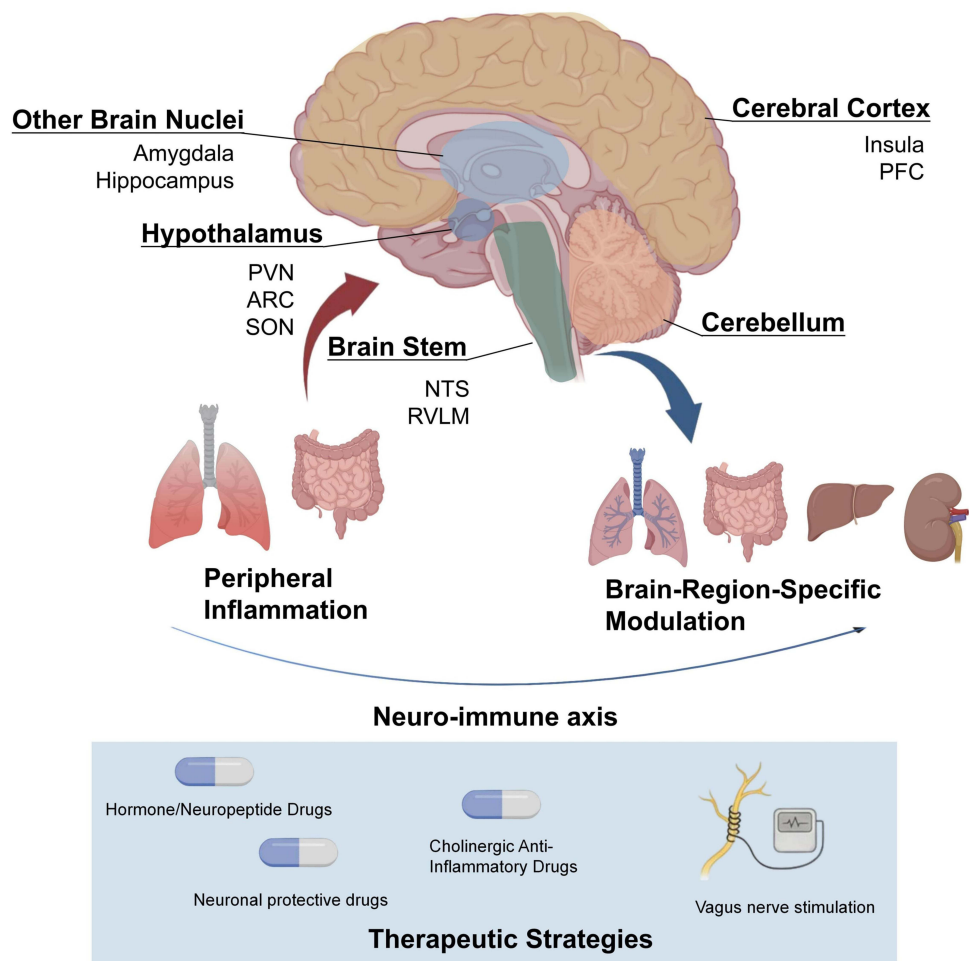
## Introduction

Sepsis is a life-threatening acute organ dysfunction syndrome triggered by an abnormal inflammatory response to infection.<sup>1</sup> Sepsis has become a major challenge in global public health. Its pathophysiological hallmark is an uncontrolled inflammatory response triggered when pathogens breach the host's defense barriers. This manifests as a complex state of simultaneous excessive inflammation and immunosuppression, persisting in a state of imbalance that ultimately leads to organ dysfunction and death.<sup>2</sup>

The central nervous system (CNS), serving as the core regulatory hub of the body, plays a pivotal regulatory role in the pathological process of sepsis through the neuro-immune-endocrine network. Recent studies indicate that vagus nerve stimulation (VNS) significantly reduces systemic inflammatory responses, multi-organ injury, and mortality in murine models of sepsis by activating the vagus nerve-cholinergic anti-inflammatory pathway.<sup>3</sup> This finding suggests a critical regulatory role of neuroimmune mechanisms within the pathophysiology of sepsis.

While the central nervous system (CNS) is increasingly recognized as a key player in sepsis, current literature largely addresses the hypothalamus, brainstem, cortex and cerebellum in isolation. To bridge this gap, this review proposes an integrated framework centered on distinct brain nuclei, synthesizing these discrete pathways into a coherent neuroimmune network. This review will examine key regions including the hypothalamus (paraventricular nucleus, arcuate nucleus, supraoptic nucleus), brainstem (nucleus tractus solitarius, rostral ventrolateral medulla), cerebral cortex (insula, prefrontal cortex), cerebellum, and other brain nuclei (amygdala, hippocampus). In addition, we will explore how to develop neuroimmunotherapy strategies for specific brain areas in sepsis (such as targeted neuroregulation and receptor-specific drug intervention) based on the understanding of the regulatory mechanisms of different brain regions.

## Graphical Abstract

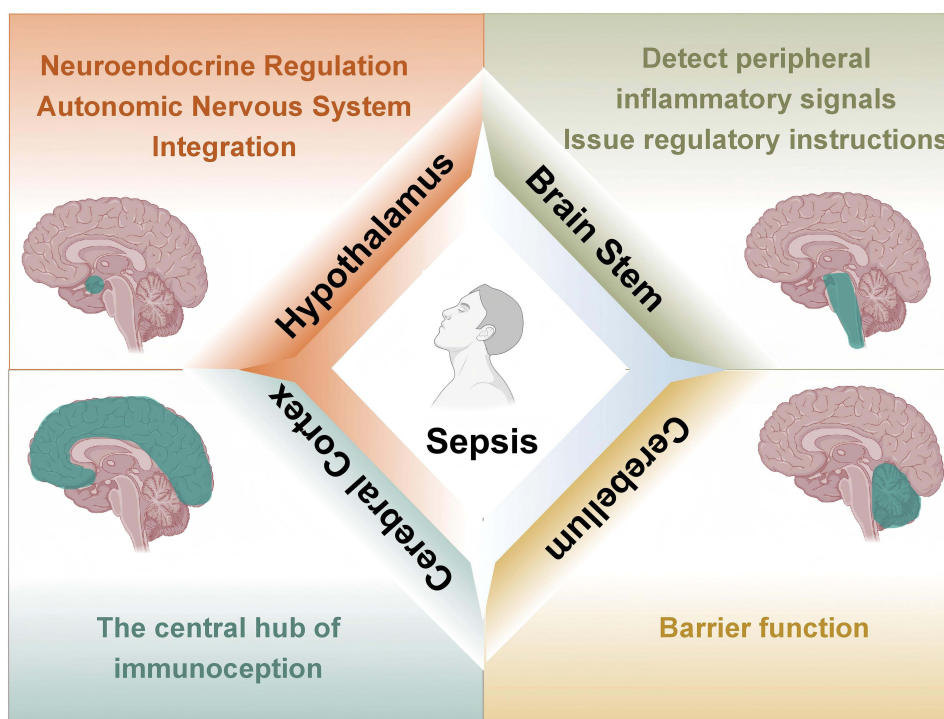


## Methods

We conducted a comprehensive narrative review of the literature on brain-region-mediated neuroimmune modulation in sepsis. A systematic search was performed in PubMed and Web of Science databases from inception to December 2025. The search strategy combined the following key terms: “sepsis”, “neuroimmunity”, “brain region”, “central nervous system”, “hypothalamus”, “brainstem”, “cortex”, “cerebellum” and specific nuclei names. We included preclinical studies, human neuroimaging studies, and clinical trials that investigated the role of specific brain regions or neural circuits in regulating immune responses during sepsis. Studies were excluded if they (1) were not published in English, (2) did not directly address brain-immune crosstalk. The evidence was synthesized to provide a mechanistic overview and to discuss emerging therapeutic strategies.

## Anatomical Localization and Function of Brain Regions Associated with Sepsis

As illustrated in Figure 1, distinct brain regions, by virtue of their specific anatomical positioning, neural circuit connectivity, and functional specialization, play indispensable and diverse roles in the pathophysiology of sepsis, collectively forming a central network within the CNS that regulates systemic immunity.



**Figure 1** Schematic overview of the anatomical locations and proposed functional roles of key brain regions in the neuroimmune axis of sepsis. Created with BioRender.com.

## Hypothalamus

The hypothalamus functions as the central hub for neuroendocrine regulation and the integration of autonomic nervous system functions. The hypothalamic-pituitary axis integrates neural and humoral regulation.<sup>4,5</sup> The hypothalamus is located on the ventral surface of the brain, beneath the thalamus. At least 70 distinct types of neurons exist within the hypothalamic region,<sup>6</sup> including corticotropin-releasing hormone neurons,<sup>7</sup> growth hormone-releasing hormone neurons,<sup>8</sup> oxytocin neurons,<sup>9</sup> and somatostatin neurons,<sup>10</sup> among others. Increased adrenocorticotropic hormone (ACTH) leads to sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis, impairing immune function.<sup>11</sup> The hypothalamic nuclei most closely associated with sepsis include the paraventricular nucleus (PVN), arcuate nucleus (ARC), and supraoptic nucleus (SON).

## Brainstem

Unlike the hypothalamus, which coordinates systemic response through the neuroendocrine axis, the brain stem, as the core relay and integration centre of visceral sensation and autonomous movement instructions, can convert peripheral immune information into a rapid and direct neurological response, thus instantly regulating inflammation and cardiovascular function.

The brainstem contains dense clusters of neural nuclei and nerve tracts, serving as the center for transmission and reflexes.<sup>12</sup> Located in the anterior part of the posterior cranial fossa, it acts as the hub connecting the cerebrum, cerebellum, and spinal cord. The brainstem receives peripheral inflammatory signals,<sup>13</sup> integrates information, and issues regulatory commands through neural and endocrine pathways.<sup>14–16</sup> Among its regions most relevant to sepsis are the nucleus tractus solitarius (NTS) and the rostral ventrolateral medulla (RVLM).

## Cortex

In contrast to the subcortical centers governing autonomic and endocrine outputs, the cerebral cortex provides higher-order regulation of the immune system. Cortical regions process the subjective and cognitive dimensions of sickness,

integrate multisensory signals, and can modulate peripheral inflammation through descending pathways to hypothalamic and brainstem nuclei.

The cerebral cortex, as the higher neural center, exerts precise regulation over the immune system through distinct functional subregions.<sup>17</sup> As the outermost layer of the brain composed of gray matter,<sup>18</sup> different cortical areas influence the inflammatory response and immune status in sepsis via neuroendocrine, autonomic, and neuroimmune pathways.<sup>19–21</sup> Among these, the insular cortex and prefrontal cortex (PFC) are particularly relevant to sepsis.

## Cerebellum

Beyond the classical roles in motor coordination, the cerebellum is increasingly recognized as an immunomodulatory interface in sepsis. Its unique vascular architecture and connectivity allow it to sense circulating inflammatory mediators and influence neuroimmune crosstalk, often manifesting as non-motor neurological complications.

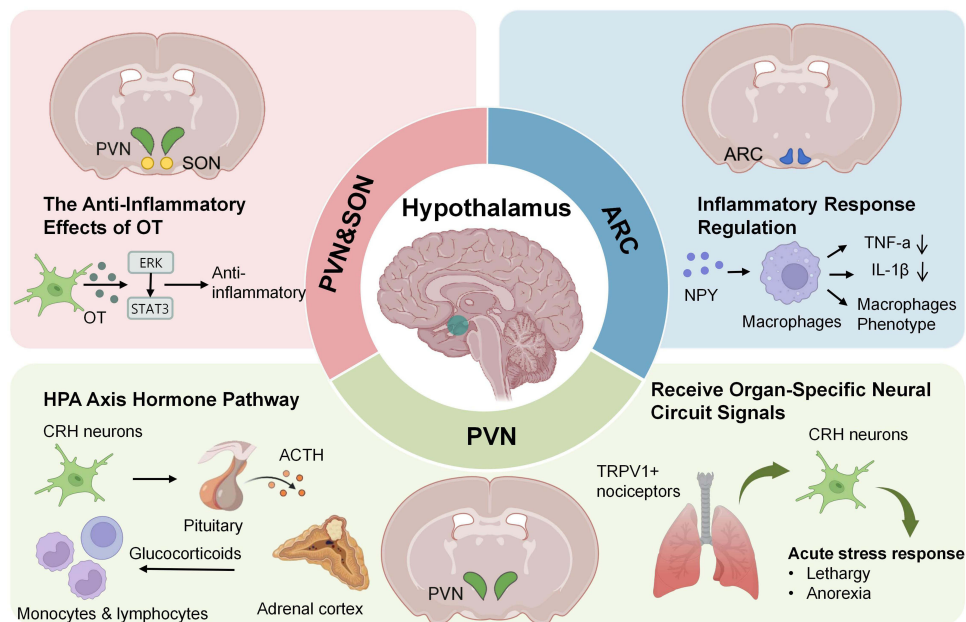
In sepsis, increased permeability of the cerebellar blood-brain barrier (BBB) permits the entry of circulating immune cells into the brain, which triggers or exacerbates glial cell activation.<sup>22,23</sup> Wang J et al found elevated activation levels of microglia and astrocytes in the cerebellum of sepsis model mice. Protein interaction network analysis indicates that interleukin-1 $\beta$  (IL-1 $\beta$ ) is a central factor in sepsis-related brain alterations.<sup>24</sup> As a key immune signaling molecule, IL-1 $\beta$  may induce fever,<sup>25</sup> promote thrombosis,<sup>26</sup> and facilitate inflammatory cell extravasation<sup>27,28</sup> during sepsis. Several drugs have demonstrated potential for treating sepsis-induced cerebellar injury: pregabalin partially ameliorates LPS-induced cerebellar damage in sepsis,<sup>29</sup> while agomelatine prevents LPS-induced brain and cerebellar injury in rats.<sup>30</sup>

## Immunoregulatory Mechanisms of Sepsis Involving Different Brain Nuclei

Figure 2 illustrates how the PVN, ARC, and SON, as core hypothalamic nuclei, play crucial roles in the pathological progression of sepsis through distinct neuroimmune mechanisms.

### PVN

As a key hypothalamic nucleus, the PVN<sup>31</sup> regulates immune and stress responses in sepsis not only through the classical HPA axis but also via direct neural circuitry from peripheral tissues. Corticotropin-releasing hormone (CRH) neurons



**Figure 2** Mechanisms of hypothalamic nuclei in sepsis. The diagram summarizes the pathways mediated by the paraventricular nucleus (PVN), arcuate nucleus (ARC), and supraoptic nucleus (SON). Created with BioRender.com.

**Abbreviations:** ACTH, Adrenocorticotropic Hormone; ARC, Arcuate Nucleus; CRH, Corticotropin-Releasing Hormone; ERK, Extracellular Regulated Protein Kinases; HPA, Hypothalamic-Pituitary-Adrenal; IL-1 $\beta$ , Interleukin-1 $\beta$ ; NPY, Neuropeptide Y; OT, Oxytocin; PVN, Paraventricular Nucleus; SON, Supraoptic Nucleus; STAT3, Signal Transducer and Activator of Transcription 3; TNF- $\alpha$ , Tumor Necrosis Factor- $\alpha$ ; TRPV1, Transient Receptor Potential Vanilloid1.

constitute the primary component of the parvocellular neurons in the PVN.<sup>32</sup> These neurons regulate the body's stress response and immune response by promoting the secretion of ACTH<sup>33</sup> and cortisol.<sup>34</sup> Clinical evidence indicates that plasma ACTH levels are often suppressed in patients with sepsis and are inversely correlated with disease severity.<sup>35</sup> ACTH reaches the adrenal cortex via the bloodstream, stimulating it to release mineralocorticoids and glucocorticoids (GC).<sup>36</sup> In the early stages of sepsis, plasma levels of ACTH and cortisol increase rapidly,<sup>37</sup> accompanied by disruption of the body's hormonal secretion rhythms<sup>38</sup> and the onset of immune dysregulation.<sup>39</sup> This suggests that CRH may be involved in the development of sepsis, and the mechanism by which CRH mediates sepsis remains to be explored.

Poller et al demonstrated that acute stress activates PVN neurons. Specifically, chemogenetic activation of PVN-CRH neurons not only elevated peripheral corticosterone levels but also significantly reduced circulating monocytes and lymphocytes. Notably, further animal experiments demonstrated that while this acute stress response confers protective effects in autoimmune disease models, it exacerbates the severity of SARS-CoV-2 and influenza virus infections.<sup>40</sup> These findings in preclinical models elucidate the potential bidirectional regulatory function of PVN-CRH neurons across different immune contexts.

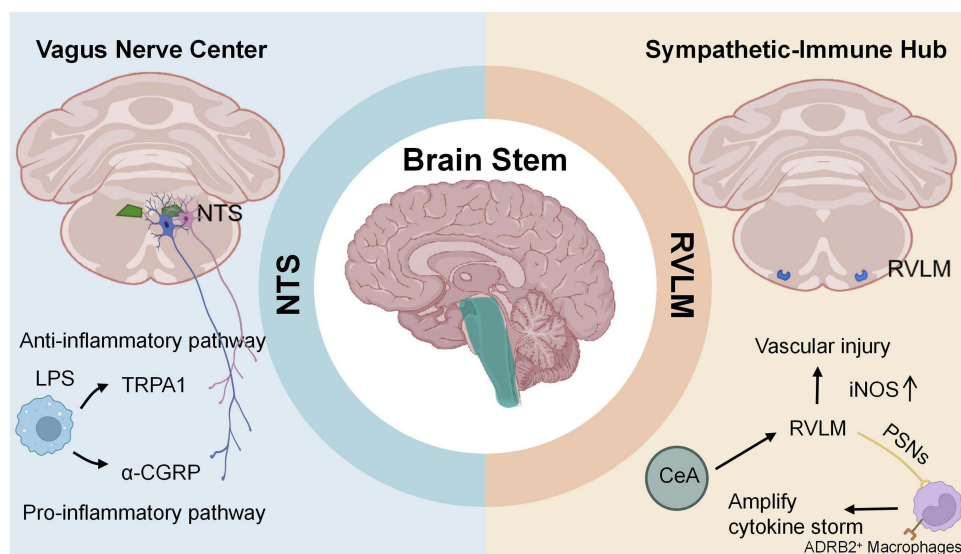
The PVN not only participates in sepsis immunity by secreting hormones through neurons but also directly regulates immunity by receiving signals from specific neural circuits. Research by Granton E et al elucidates the central role of the PVN of the hypothalamus in pulmonary infection: in a lipopolysaccharide (LPS)-induced pneumonia model, activation of TRPV1+ nociceptors in the lungs stimulates PVN CRH neurons through a specific neural circuit, triggering a classic acute stress response characterized by disease behaviors such as lethargy and anorexia, as well as thermoregulation dysregulation. The study specifically revealed that biofilm pathogens capable of producing extracellular polymeric substances (EPS) enhance pathogenicity by evading activation of this lung-brain neural pathway.<sup>41</sup> This discovery may provide a new perspective for understanding the mechanisms of neuro-immune interactions in infectious diseases. Notably, the effects of PVN-CRH activation appear highly context-dependent; while it may confer protection in autoimmune settings, it can exacerbate outcomes in viral infections, underscoring the need to delineate its precise role across diverse sepsis etiologies before considering targeted interventions.

## ARC

The ARC primarily contains neuropeptide Y (NPY) neurons, which participate in regulating appetite, energy metabolism, and bone metabolism. NPY is stored and released together with norepinephrine (NE).<sup>42</sup> In sepsis, NPY expression increases,<sup>43</sup> which is closely associated with the release of inflammatory mediators such as tumor necrosis factor alpha (TNF- $\alpha$ ) and IL-1 $\beta$ .<sup>44</sup> During the inflammatory phase, NPY promotes macrophage production of TNF- $\alpha$  by activating Y1 receptors (Y1R) while simultaneously inhibiting IL-1 $\beta$  release, thereby helping to regulate the inflammatory response and prevent tissue damage caused by excessive inflammation.<sup>45</sup> NPY can also suppress interleukin-12 (IL-12) and TNF- $\alpha$  production in macrophages by activating Y1R, thereby converting macrophages to an M2 anti-inflammatory phenotype and reducing pro-inflammatory factor release.<sup>46</sup> The precise mechanisms governing ARC-mediated bidirectional cytokine regulation remain unclear. Further investigation is required to determine whether NPY signaling shifts dynamically during the transition from the hyperinflammatory to the immunosuppressive phase of sepsis.

## SON

Oxytocin (OT) secreted by magnocellular neurons in the SON and PVN exerts anti-inflammatory effects through multiple mechanisms: On one hand, oxytocin directly inhibits the release of proinflammatory cytokines and modulates immune responses via the hypothalamic-pituitary-portal system.<sup>47</sup> On the other hand, it reduces levels of inflammatory mediators such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$  by suppressing the shift of macrophages from a resting state to a proinflammatory phenotype, thereby mitigating organ damage caused by sepsis.<sup>48</sup> In the pathophysiology of sepsis-associated encephalopathy (SAE), oxytocin activates the oxytocin receptor (OXTR), thereby modulating the ERK/STAT3 signaling pathway. This effectively suppresses abnormal activation of microglia and neuroinflammation, thus protecting synaptic plasticity in the hippocampus and improving cognitive dysfunction.<sup>49</sup> It is noteworthy that despite basic research having clearly demonstrated oxytocin's significant organ-protective efficacy, its translation into clinical applications still



**Figure 3** Mechanisms of brainstem nuclei in sepsis. The diagram highlights the roles of the nucleus tractus solitarius (NTS) and the rostral ventrolateral medulla (RVLM). Created with BioRender.com.

**Abbreviations:**  $\alpha$ -CGRP, alpha-Calcitonin Gene - Related Peptide; ADRB2,  $\beta$ 2-adrenergic receptors; CeA, Central Amygdala; iNOS, Inducible Nitric Oxide Synthase; LPS, Lipopolysaccharide; NTS, Nucleus Tractus Solitarius; PSNs, Pulmonary Sympathetic Nerves; RVLM, Rostral Ventrolateral Medulla; TRPA1, Transient Receptor Potential Channel A1.

requires careful and comprehensive evaluation. Particularly in perinatal patients, strict and dynamic monitoring of fluid balance must be conducted during clinical administration to avoid adverse reactions.

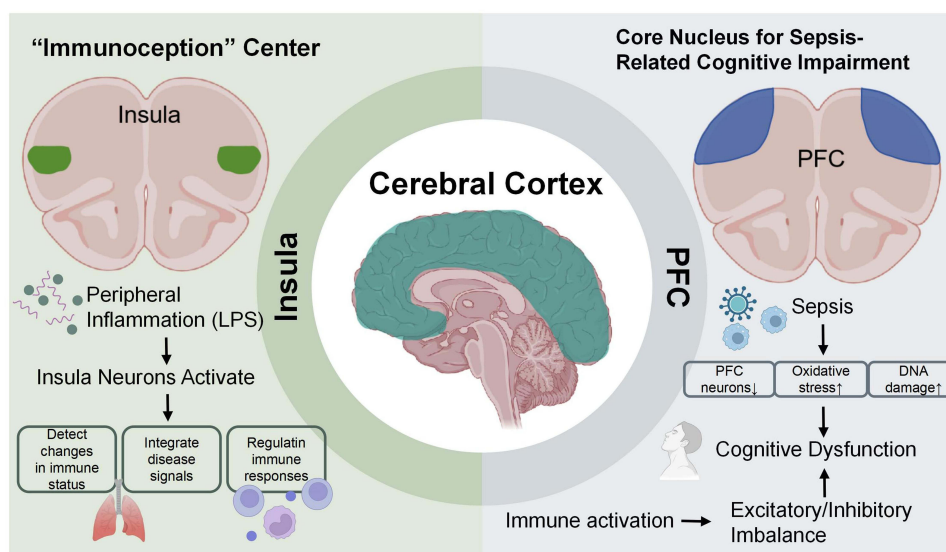
The NTS and RVLM, as core nuclei regulating sepsis in the brainstem, play pivotal roles in systemic inflammation and organ injury by integrating the vagus nerve anti-inflammatory reflex and mediating sympathetic nervous system excitation, respectively, as depicted in Figure 3.

## NTS

The NTS serves as the primary projection target and integration center for the central axons of the vagus nerve.<sup>50</sup> Following intraperitoneal injection of LPS in mice, cytokines activate distinct vagal sensory neuron populations to transmit inflammatory status to the brain. These signals travel along two distinct pathways: one carries anti-inflammatory signals by activating the transient receptor potential channel A1 (TRPA1) and acts on NTS neurons to enhance the anti-inflammatory response. Conversely, another pathway responds to proinflammatory signals by activating calcitonin gene-related peptide alpha ( $\alpha$ -CGRP) and contributes to reducing proinflammatory responses. Both pathways activate distinct populations of vagal ganglion neurons, ultimately converging in the NTS.<sup>51</sup> In sepsis, the number of activated microglia in the NTS increases, and elevated levels of interleukin-1 $\beta$  induce hypotension and tachycardia, ultimately leading to vascular injury.<sup>52</sup> In a cecal ligation and puncture (CLP) model, activation of central adenosine A1 receptors (A1AR) in the NTS promotes cholinergic antagonism of cardiac and neuroinflammatory responses associated with sepsis and related cardiomyopathies and neuropathologies.<sup>53</sup>

## RVLM

The RVLM is a key nucleus in sepsis-associated pneumonia and vascular injury.<sup>54</sup> Numerous studies indicate that the upregulation of inducible nitric oxide synthase (iNOS) in the RVLM during sepsis is a key contributor to vascular injury.<sup>55,56</sup> Dexmedetomidine may improve sepsis by inhibiting sympathetic activation,<sup>57</sup> whereas morphine exacerbates sepsis-induced cardiovascular and autonomic dysfunction through  $\mu$ -opioid receptor-mediated mechanisms, while also amplifying central inflammatory, chemotactic, and oxidative signaling.<sup>58</sup> Research by Li W et al has revealed the critical regulatory role of the RVLM in pneumonia-associated cytokine storms. Specifically, their work demonstrates that GABAergic neurons in the central amygdala (CeA) activate  $\beta$ 2-adrenergic receptors (ADRB2) on interstitial macrophages (Mac2) via the CeA-RVLM-pulmonary sympathetic nerves (PSNs) pathway, thereby amplifying the cytokine



**Figure 4** Mechanisms of cerebral cortex nuclei in sepsis, focusing on the insula and prefrontal cortex (PFC). Created with BioRender.com.  
**Abbreviations:** LPS, Lipopolysaccharide; PFC, Prefrontal Cortex.

storm.<sup>59</sup> Targeted inhibition of this pathway has been shown to improve prognosis in animal models, suggesting a potential therapeutic strategy for pneumonia. However, the significance of this pathway in human polymicrobial sepsis remains to be established, and therapeutic targeting of the RVLM requires balancing its dual role in driving harmful inflammation and maintaining essential sympathetic vascular tone.

As summarized in [Figure 4](#), the insula acts as the hub of “immunoception”, and the prefrontal cortex (PFC) is the primary target for cognitive impairment, reflecting their critical roles within the cerebral cortex during sepsis.

### Insula

As the central hub of “immunoception”, the insula participates in regulating neuroinflammation and systemic immune homeostasis during sepsis by detecting changes in immune status, integrating disease signals, and modulating peripheral immune responses. Asya Rolls et al found that neurons distributed in the mouse insula activate during inflammatory states, thereby regulating peripheral immune responses.<sup>60</sup> MRI scans of the brains of sepsis patients reveal hyperactivation of the insular cortex. During LPS-induced inflammatory responses, the insula participates in the perception and integration of disease symptoms such as physical discomfort.<sup>61</sup> Although direct studies on the role of the insula in neuroimmunoregulation during sepsis are currently limited, existing neuroimmunological research and neuroinflammatory mechanisms associated with sepsis suggest that the insula may influence the immune response to sepsis by regulating “immunoreception” and neuroinflammatory pathways. It remains unclear whether insular activity primarily serves as an afferent function for inflammation perception in sepsis or also directly participates in efferent commands for immune regulation. Future research should integrate functional neuroimaging with immune profiling analysis to elucidate this critical mechanism in clinical patients.

### PFC

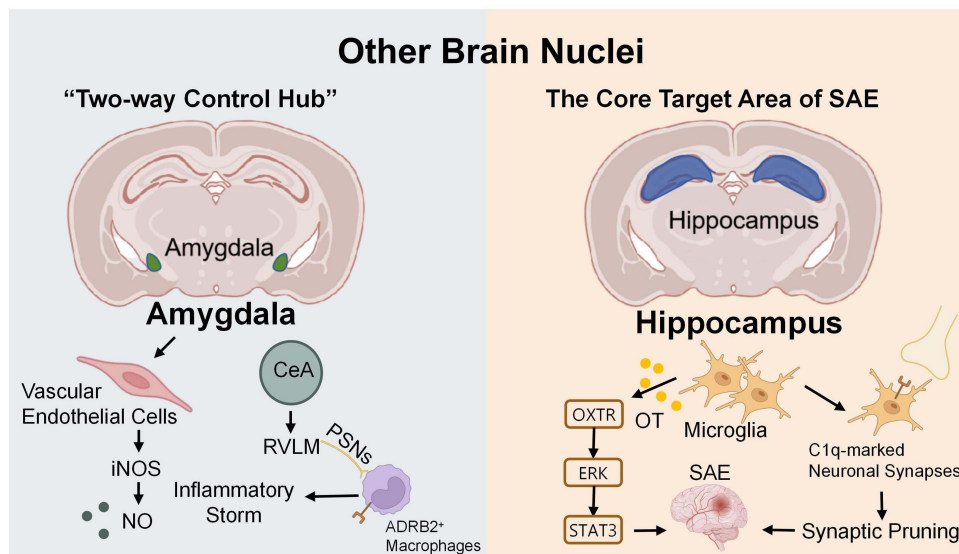
The PFC experiences a disruption in excitatory/inhibitory balance due to neuroinflammation during sepsis, leading to cognitive dysfunction. Research indicates that sepsis can lead to a reduction in the number of PFC neurons, increased oxidative stress, and oxidative DNA damage.<sup>62</sup> Additionally, sepsis causes a significant increase in proinflammatory factors (such as TNF- $\alpha$  and IL-1 $\beta$ ) in the PFC, which are key contributors to neuroinflammation and cognitive impairment.<sup>63</sup> Research by Mittli et al indicates that systemic immune challenges affect the function of PFC neurons through multiple molecular and cellular mechanisms, including increased intrinsic excitability of pyramidal cells, while inhibitory interneurons show no significant changes. Additionally, immune activation affects the synaptic networks of the PFC, leading to increased excitatory synaptic currents and decreased inhibitory synaptic currents, thereby triggering an

excitatory/inhibitory imbalance in the PFC. This imbalance may correlate with the activation of microglia, subsequently further exacerbating neuroinflammation.<sup>64</sup> Multiple drugs and therapies have been shown to modulate the neuroimmune response in the PFC. For example, pleiotrophin (PTN) has been demonstrated to regulate glial cell-mediated neuroinflammation;<sup>65</sup> Berberine inhibits NLRP3 inflammasome-mediated neuroinflammation in mice.<sup>66</sup> While these findings illuminate potential mechanisms of cognitive dysfunction, it remains unclear whether the observed excitatory/inhibitory imbalance is a cause or a consequence of sustained neuroinflammation. Moreover, the efficacy of preclinical interventions in reversing long-term cognitive deficits in human sepsis survivors represents a major translational gap that future clinical trials need to address.

In addition to the nuclei within the aforementioned brain regions, the amygdala and hippocampus are also two key nuclei in the neuroimmunoregulation of sepsis. Their functions as the “two-way control hub” for neuroinflammation and the primary target site for cognitive impairment are shown in Figure 5.

## Amygdala

The amygdala, as a core brain region for emotional regulation and stress responses, serves as a bidirectional regulatory hub in the neuroimmune dysregulation triggered by sepsis. It is activated by sepsis-related immune signals while simultaneously modulating peripheral and central immune responses through neural pathways, ultimately influencing the progression and prognosis of sepsis. In septic shock, there is minimal activation of microglia and glial expression of TNF- $\alpha$  within the amygdala, while vascular endothelial cells exhibit a significant increase in inducible nitric oxide synthase (iNOS) expression.<sup>67</sup> Subsequent studies have revealed that nitric oxide (NO) produced by iNOS in the amygdala participates in the central nervous system’s central response to immune stimuli during sepsis.<sup>68</sup> The amygdala also plays a key role in driving peripheral inflammatory responses through neural circuits. As detailed in the RVLM section above, inhibitory GABAergic neurons in the central amygdala (CeA) can initiate a CeA→RVLM→pulmonary sympathetic nerve pathway that ultimately exacerbates lung inflammation via adrenergic signaling to macrophages.<sup>59</sup> This highlights the amygdala’s role as a higher-order regulator capable of amplifying peripheral cytokine storms through well-defined brainstem and sympathetic efferents.



**Figure 5** Mechanisms of the amygdala and hippocampus in sepsis. Created with BioRender.com.

**Abbreviations:** ADRB2,  $\beta$ 2-adrenergic receptors; CeA, Central Amygdala; ERK, Extracellular Regulated Protein Kinases; iNOS, Inducible Nitric Oxide Synthase; NO, Nitric Oxide; OT, Oxytocin; OXTR, Oxytocin Activates The Oxytocin Receptor; PSNs, Pulmonary Sympathetic Nerves; RVLM, Rostral Ventrolateral Medulla; SAE, Sepsis-Associated Encephalopathy; STAT3, Signal Transducer and Activator of Transcription 3.

## Hippocampus

The hippocampus is the core target region of SAE.<sup>69</sup> SAE is one of the most common and severe complications of sepsis,<sup>70</sup> while neuroinflammation represents the most critical pathological basis for SAE-related cognitive impairment.<sup>71</sup> Microglia play a crucial role in the development and progression of neuroinflammation.<sup>72</sup> Oxytocin in microglia exerts anti-inflammatory and neuroprotective effects, improving SAE outcomes through the OXTR-ERK-STAT3 signaling pathway.<sup>49</sup> Microglia can also phagocytose C1q-marked neuronal synapses. Intrahippocampal injection of C1q-blocking antibodies reduces synaptic pruning following the acute phase of sepsis-associated encephalopathy, thereby preventing the development of neurocognitive deficits.<sup>73</sup>

## Neuroimmunotherapeutic Strategies Targeting Different Brain Regions in Sepsis

Various drugs have been demonstrated to effectively intervene in the pathological progression of sepsis by targeting neuroimmune regulatory mechanisms in different brain regions (Table 1).

### Hormone/Neuropeptide Drugs

The hypothalamus profoundly influences the imbalance between systemic inflammatory response syndrome (SIRS)<sup>85</sup> and compensatory anti-inflammatory response syndrome (CARS)<sup>86</sup> in sepsis by regulating the HPA axis and multiple neuroendocrine pathways. Under septic stress, the PVN releases CRH.<sup>68</sup> Subsequently, the HPA axis cascade reaction is initiated: CRH stimulates the pituitary gland to secrete ACTH, ultimately triggering the adrenal glands to release GC. According to the 2024 updated SCCM guidelines on GC application in sepsis, short-term administration can suppress Nuclear Factor Kappa-B (NF- $\kappa$ B) and reduce the release of proinflammatory factors (TNF- $\alpha$ , IL-6), but long-term excessive activation may lead to immunosuppression. Individualized treatment should be selected based on the stage of sepsis to achieve precise intervention.<sup>74</sup>

**Table 1** Mechanisms of Neuroimmunomodulatory Drugs in Sepsis and Associated Brain Nuclei

Category	Drug	Mechanism	Relevant Brain Regions and Nuclei	References
<b>Hormone/ Neuro-peptide Drugs</b>	Glucocorticoids (GC)	Inhibit NF- $\kappa$ B and reduce the release of pro-inflammatory factors (TNF- $\alpha$ , IL-6)	Paraventricular nucleus (PVN)	[36,74]
	Oxytocin (OT)	Reduce organ damage caused by sepsis through anti-inflammatory effects	Supraoptic nucleus (SON) and paraventricular nucleus (PVN)	[47,48,75]
	CGRP receptor antagonists	Suppressing CGRP-induced neurogenic inflammation by inhibiting immune cell infiltration into tissues	Trigeminal Nucleus (TN)	[76,77]
	Neuropeptide Y (NPY)	Activation of Y1R suppresses IL-12 and TNF- $\alpha$ production in macrophages	Arcuate Nucleus (ARC)	[45]
<b>Cholinergic anti-inflammatory drugs</b>	GTS-21	Inhibiting the synthesis and release of TNF- $\alpha$ in the early stages of sepsis to mitigate the systemic inflammatory response	Nucleus tractus solitarius (NTS)	[78–80]
	Galantamine			[81,82]
<b>Neuronal protective drugs</b>	Magnesium ferrocyanide	Suppressing microglial activation and neuronal copper toxicity	Widely distributed across various brain nuclei	[83]
	Pioglitazone (PG)	Activation of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) attenuates microglial activation.		[84]

**Abbreviations:** ARC, Arcuate Nucleus; CGRP, Calcitonin Gene-Related Peptide; GC, Glucocorticoids; IL-12, Interleukin-12; IL-6, Interleukin-6; NF- $\kappa$ B, Nuclear Factor Kappa-B; NPY, Neuropeptide Y; NTS, Nucleus Tractus Solitarius; OT, Oxytocin; PG, Pioglitazone; PPAR $\gamma$ , Peroxisome Proliferator-Activated Receptor  $\gamma$ ; PVN, Paraventricular Nucleus; SON, Supraoptic nucleus; TN, Trigeminal Nucleus; TNF- $\alpha$ , Tumor Necrosis Factor- $\alpha$ ; Y1R, Neuropeptide Y1 Receptor.

Oxytocin secreted by magnocellular neurons in the SON and PVN mitigates sepsis-induced organ damage through anti-inflammatory effects.<sup>47,48,75</sup> The trigeminal nucleus (TN) releases calcitonin gene-related peptide (CGRP), which promotes a massive infiltration of immune cells into tissues, thereby inducing neurogenic inflammation.<sup>76</sup> CGRP receptor antagonists (such as erenumab) can suppress neurogenic inflammation.<sup>77</sup> ARC-mediated secretion of NPY suppresses IL-12 and TNF- $\alpha$  production in macrophages by activating Y1R, thereby converting macrophages to an M2 anti-inflammatory phenotype and reducing proinflammatory factor release.<sup>49</sup> These preclinical findings suggest a potential basis and intervention targets for personalized precision treatment of sepsis.

### Cholinergic Anti-Inflammatory Drugs

The cholinergic anti-inflammatory pathway forms a critical neuroimmune circuit in sepsis. In this reflex arc, peripheral inflammation is detected by vagal afferent fibers, which transmit signals to the NTS in the brainstem.<sup>87</sup> The NTS serves as the integration center; upon activation, it stimulates vagal efferent fibers to release acetylcholine. Acetylcholine then acts on  $\alpha 7$  nicotinic acetylcholine receptors ( $\alpha 7$ nAChR) in peripheral tissues, inhibiting the synthesis and release of pro-inflammatory cytokines such as TNF- $\alpha$  and thereby mitigating the systemic inflammatory response.<sup>88–91</sup> Conversely, excessive sympathetic nervous system activation can inhibit this cholinergic pathway, exacerbating inflammatory dysregulation and organ dysfunction.<sup>92</sup> Targeting this axis,  $\alpha 7$ nAChR agonists such as GTS-21<sup>78–80</sup> and galantamine<sup>81,82</sup> have demonstrated protective effects in sepsis models, highlighting the therapeutic potential of modulating this “neuroimmune hub”.

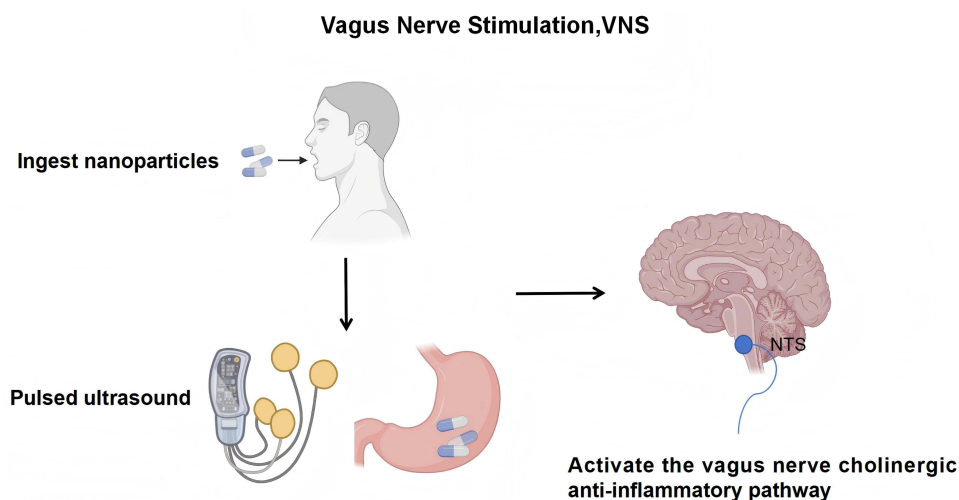
### Neuroprotective Agents

Microglia and astrocytes are widely distributed across various brain regions of the central nervous system, playing crucial roles in maintaining brain homeostasis and neuroimmune function.<sup>93,94</sup> In sepsis, microglia and astrocytes undergo a phenotypic shift from an anti-inflammatory M2 state to a pro-inflammatory M1 phenotype, leading to neuronal damage.<sup>95</sup> In rodent models, magnesium ferrocyanide has been shown to alleviate sepsis-associated encephalopathy by inhibiting microglial activation and neuronal copper toxicity.<sup>83</sup> Pioglitazone (PG) activates peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), attenuates microglial activation, enhances the survival of dopaminergic neurons in the nigrostriatal system, and exerts neuroprotective effects against sepsis-induced brain injury.<sup>84</sup> These findings suggest potential directions for clinical treatment, and targeting the regulation of glial cell polarization represents a promising avenue for future investigation.

### Vagus Nerve Stimulation

The core pathology of sepsis is the coexistence of an uncontrolled systemic inflammatory response and immunosuppression.<sup>96</sup> Traditional anti-inflammatory drug strategies are often accompanied by immunosuppression or organ toxicity due to their broad mechanism of action. In recent years, advances in the “neuro-immune” network research have enabled the regulation of the body’s innate immune system through precise neural stimulation.

The afferent fibers of the vagus nerve originate from visceral organs and project to the NTS in the medulla oblongata, where they contribute to innate defense against inflammation through the cholinergic anti-inflammatory pathway (CAIP).<sup>97</sup> Both pharmacological and electrical stimulation of the vagus nerve to activate the CAIP have demonstrated significant efficacy in mitigating cytokine storms.<sup>98,99</sup> Vagus nerve stimulation (VNS) can provide more precise and targeted stimulation.<sup>100–102</sup> A novel integrated strategy combining oral administration with ultrasound has been proposed and validated in the latest research: After ingesting capsaicin-coated piezoelectric nanoparticles, a portable low-intensity pulsed ultrasound device generates microcurrents in situ within the gastric wall, noninvasively activating the vagus nerve-cholinergic anti-inflammatory pathway. This approach significantly reduces systemic inflammation, organ damage, and mortality in septic mice, offering a safe and accessible new solution for bedside or home-based neuroimmunomodulation,<sup>3</sup> as illustrated in Figure 6. Mughrabi et al implanted miniature “electrochemical probes” into the spleens of live mice: Real-time monitoring of NE release via fast-scan cyclic voltammetry (FSCV) provides instantaneous feedback on vagus nerve, greater splanchnic nerve, or splenic nerve stimulation intensity within seconds. This response negatively correlates with subsequent TNF- $\alpha$  suppression effects. By integrating splenic voltammetric



**Figure 6** Diagram of a non-invasive vagus nerve stimulation strategy for sepsis. Created with BioRender.com.  
**Abbreviations:** NTS, Nucleus Tractus Solitarius; VNS, Vagus Nerve Stimulation.

electrodes with implantable stimulators, this approach delivers an immediate, quantitative “physiological benchmark” for neuroimmunoregulation.<sup>103</sup>

Clinical studies have demonstrated that VNS can significantly improve the sepsis-induced coagulopathy (SIC) score at 24 hours in patients with sepsis-induced coagulopathy (SIC).<sup>104</sup> The world’s first neuroimmunomodulatory device approved for immune disorders-SetPoint Medical’s vagus nerve stimulation device-has received official approval from the US Food and Drug Administration (FDA) for treating rheumatoid arthritis (FDA Premarket Approval P240039),<sup>105</sup> marking the transition of neuroimmunomodulation from experimental research to clinical application. The translation of invasive VNS to septic patients requires navigating complex ethical and practical landscapes, including conducting rigorous risk-benefit analyses for critically ill patients, navigating the complexities of informed consent in this vulnerable population, and ensuring long-term safety and efficacy.

## Clinical Implications and Translational Significance of Neuroimmunity in Sepsis

The clinical relevance of neuroimmune crosstalk is profound within the intensive care setting. Sepsis-associated encephalopathy (SAE), characterised by delirium and cognitive disorders, is a prominent clinical manifestation of neuroinflammation with direct prognostic significance.<sup>106</sup> Similarly, although Sepsis-induced ARDS is fundamentally derived from peripheral inflammation and endothelial damage,<sup>107</sup> its pathophysiology may be significantly modulated by sympathetic-vagus nerve imbalances involving key brain stem nuclei (such as RVLN and NTS). Furthermore, this central autonomic dysregulation extends to the cardiovascular system, manifesting as sepsis-induced cardiac dysfunction (SICD). Here, aberrant sympathetic outflow and the consequent catecholamine surge can induce cardiomyocyte toxicity and myocardial depression, highlighting a pathological brain-heart axis driven by neuroimmune disturbances.<sup>108</sup>

Importantly, these central neuroimmune pathways exert profound influence over the peripheral vasculature. Endothelial injury,<sup>109</sup> immunothrombosis,<sup>110</sup> and microcirculatory dysfunction<sup>111</sup> are well-established determinants of organ failure in sepsis, with sepsis-induced acute kidney injury serving as a prime example, driven by inflammatory and oxidative stress pathways as well as dysregulated innate immune signaling.<sup>112,113</sup> Each of these processes is susceptible to modulation by neurogenic signals, as shown by improvements in oxygenation and microcirculatory parameters with iloprost treatment in COVID-19-related ARDS, which provides an important translational bridge highlighting the interplay between central neuroimmune regulation and peripheral endothelial function.<sup>114</sup>

Therefore, sepsis should be conceptualized as a syndrome encompassing central regulatory dysfunction, endothelial injury, and peripheral organ damage. This comprehensive view emphasises the therapeutic potential of neuromodulatory strategies aimed at rebalancing autonomic output. For example, VNS can not only reduce systemic inflammation, but also

reduce secondary microcirculation disorders, serving as an adjunct to conventional organ support therapy in the treatment of sepsis. However, it is critical to acknowledge the models from which these mechanisms are derived. Such models often utilize homogeneous populations under controlled conditions, which may not fully capture the immense heterogeneity in etiology, comorbidities, and treatment responses seen in human sepsis. Notably, current mechanistic understanding relies heavily on preclinical models. Direct clinical evidence linking brain regional activity to immune outcomes in sepsis remains sparse. Therefore, future research must integrate multi-modal methods, such as advanced neuroimaging, continuous autonomic monitoring and deep immune phenotypes, to verify these pathways, reveal potential substitution or competition mechanisms, and finally determine clinically feasible phenotypes. Integrating perspectives and addressing challenges from neurological critical care is crucial to transforming these promising mechanisms into effective treatment. This gap underscores the significant translational journey required to move from promising experimental neuromodulation to safe, effective, and widely applicable clinical therapies.

## Conclusion

The central nervous system (CNS) serves as the core hub of the immune regulatory network in sepsis, dynamically coordinating systemic inflammatory and immune responses through multi-regional and multi-level pathways. In recent years, therapeutic strategies based on neuroimmune mechanisms have achieved significant breakthroughs. From drug design targeting specific receptors (such as  $\alpha 7nAChR$ , CGRP, and NPY) to non-invasive neuromodulation technologies, these approaches have demonstrated promising translational potential.

To realize this potential, the field must now address key translational challenges. At a fundamental level, major scientific questions remain unanswered, particularly regarding how to achieve precise spatiotemporal control over complex neuroimmune circuits to ensure pathway specificity without systemic side effects. Moreover, successful translation requires overcoming patient heterogeneity (driven by genetics, comorbidities, and sepsis etiology) to enable personalized targeting, as well as defining the optimal timing for intervention across the dynamic stages of sepsis. Finally, rigorously evaluating the safety profiles of neuromodulatory devices and validating predictive biomarkers remain indispensable for guiding clinical therapy.

Collectively, these insights pave the way toward a precision medicine approach in sepsis, centered on aligning brain-region-specific interventions with individualized neuroimmune signatures. Translating this paradigm into clinical practice will require defining clinically actionable phenotypes based on autonomic function, central inflammatory markers, or other biomarker profiles. Future research would benefit from focusing on identifying specific patient subgroups, such as those with autonomic dysregulation, high risk of SAE, or distinct biomarker profiles, which could indicate greater responsiveness to neuroimmune-targeted therapies. Clinical evaluation of neuromodulatory approaches like vagus nerve stimulation should advance through structured study phases, progressing from mechanistic validation to controlled trials in sepsis cohorts. Furthermore, the development of integrated biomarker strategies, including neuroendocrine, autonomic, and inflammatory signatures, will be important for guiding patient selection and monitoring treatment responses in a more individualized manner. With the advancement of research methodologies and technological platforms, neuroimmunomodulatory strategies hold significant translational promise and could contribute to more targeted approaches in the clinical treatment of sepsis.

## Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

## Author Contributions

Xuechun Zhou: Writing-review & editing, Writing – original draft, Investigation. Ying Tang: Writing-review & editing, Investigation. Hui Chen: Writing – original draft, Investigation. Wei Huang: Supervision, Writing – Review & Editing, Funding Acquisition. Haibo Qiu: Supervision, Project Administration, Writing – Review & Editing, Funding Acquisition. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by National Science and Technology Major Project (2022YFC2304600), the Noncommunicable Chronic Diseases-National Science and Technology Major Project (2023ZD0506500), Jiangsu Province Science and Technology Plan Project “Provincial Frontier Technology R&D Program” (BF2024054), National Natural Science Foundation of China (No. 82202390), Jiangsu Provincial Double-Innovation Doctor Program (JSSCBS20220106) and the Fundamental Research Funds for the Central Universities and Zhishan Scholars Programs of Southeast University (2242023R40034).

## Disclosure

The authors report no conflicts of interest in this work.

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