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REVIEW

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Decoding mechanisms and protein markers in lung-brain axis

Shiqian Huang[1,2,3†], Yuxi Zhou[1,2,3†], Haipeng Ji[1,2,3†], Tianhao Zhang[1,2,3], Shiya Liu[1,2,3], Lulin Ma[1,2,3], Daling Deng[1,2,3], Yuanyuan Ding[1,2,3], Linlin Han[1,2,3], Shaofang Shu[1,2,3], Yu Wang[1,2,3*] and Xiangdong Chen[1,2,3*]

Abstract

Background The lung-brain axis represents a complex bidirectional communication network that is pivotal in the crosstalk between respiratory and neurological functions. This review summarizes the current understanding of the mechanisms and protein markers that mediate the effects of lung diseases on brain health.

Main findings In this review, we explore the mechanisms linking lung injury to neurocognitive impairments, focusing on neural pathways, immune regulation and inflammatory responses, microorganism pathways, and hypoxemia. Specifically, we highlight the role of the vagus nerve in modulating the central nervous system response to pulmonary stimuli; Additionally, the regulatory function of the immune system is underscored, with evidence suggesting that lung-derived immune mediators can traverse the blood-brain barrier, induce neuroinflammation and cognitive decline; Furthermore, we discuss the potential of lung microbiota to influence brain diseases through microbial translocation and immune activation; Finally, the impact of hypoxemia is examined, with findings indicating that it can exacerbate cerebral injury via oxidative stress and impaired perfusion. Moreover, we analyze how pulmonary conditions, such as pneumonia, ALI/ARDS, and asthma, contribute to neurological dysfunction. Prolonged mechanical ventilation can also contribute to cognitive impairment. Conversely, brain diseases (e.g., stroke, traumatic brain injury) can lead to acute respiratory complications. In addition, protein markers such as TLR4, ACE2, A-SAA, HMGB1, and TREM2 are crucial to the lung-brain axis and correlate with disease severity. We also discuss emerging therapeutic strategies targeting this axis, including immunomodulation and microbiome engineering. Overall, understanding the lung-brain interplay is crucial for developing integrated treatment strategies and improving patient outcomes. Further research is needed to elucidate the molecular mechanisms and foster interdisciplinary collaboration.

Keywords Lung-brain axis, Brain diseases, Lung injury, Mechanisms, Protein markers

†Shiqian Huang MD, Yuxi Zhou MM and Haipeng Ji MD contributed equally to this work.

*Correspondence:
Yu Wang
wangdayuanesthe@163.com
Xiangdong Chen
xdchen@hust.edu.cn

[1]Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1277, Jiefang Avenue, Wuhan 430022, China
[2]Institute of Anesthesia and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
[3]Key Laboratory of Anesthesiology and Resuscitation (Huazhong University of Science and Technology), Ministry of Education, Wuhan, Wuhan 430022, China

Introduction

The interconnectedness of the lungs and brain is vital for maintaining a balance of physiological activities. Respiration is a fundamental communication pathway between the two organs. The lungs, which are key to respiration, not only provide essential nutrients to all organs but also play a role in neural signaling. Studies have revealed that breathing patterns affect neural activity across various brain regions and can alter mental states, with slow breathing promoting relaxation and fast breathing potentially inducing anxiety [1]. Furthermore, pathologically, pulmonary health can have profound implications on neurological function. Lung injuries can exacerbate brain diseases, creating a cycle of dysfunction that complicates treatment outcomes. This relationship is particularly evident in conditions such as stroke, in which lung complications such as pneumonia can worsen neurological outcomes [2]. Impaired lung function is also a critical factor influencing mental health. A prospective cohort study including 280,032 individuals with measured lung function showed that impaired pulmonary function was associated with an increased risk of depression [3]. Moreover, the mechanisms underlying these interactions, including immune responses and neural pathways, are becoming clearer, providing new avenues for therapeutic intervention [4, 5].

The concept of the lung-brain axis represents a crucial area of research that highlights bidirectional communication between the respiratory system and the CNS. This axis is increasingly recognized for its significance in understanding various pathophysiological conditions that affect both the lungs and brain. Understanding the lung-brain axis is crucial for the more effective prevention and treatment of neuro-respiratory disorders, an aspect often overlooked in current symptom-based interventions.

This comprehensive review systematically examines the lung-brain axis through four key sections. First, we elucidate the principal mechanisms of lung-brain communication, including: (1) neural pathways mediated by the vagus nerve and TRPV1 + nociceptors, (2) immune regulation through cytokine networks and microglial activation, (3) microbial pathways encompassing both direct translocation and dysbiosis effects, and (4) hypoxemia-mediated injury cascades. Second, we analyze how specific pulmonary conditions contribute to neurological dysfunction, while also exploring brain-to-lung effects. Third, we evaluate protein biomarkers that bridge pulmonary and neurological pathologies. Finally, we discuss emerging therapeutic strategies targeting this axis, including immunomodulation and microbiome engineering. This organizational framework aims to provide both mechanistic insights and clinical perspectives on lung-brain interactions.

Interplay mechanisms linking lung injury to brain dysfunction: neural, immune, microbial pathways, and hypoxemia

The lung-brain axis represents a complex interplay between the respiratory and neurological systems, underpinned by various physiological and pathological mechanisms [6–8]. This bidirectional communication is mainly facilitated through neural pathways, direct translocation of microbes, immunoregulation, inflammatory responses, microorganism pathways, and hypoxemia. Understanding these interactions is crucial for elucidating how pulmonary conditions influence neurological health.

Interactions of neural pathways

Neural pathways are integral to communication between the respiratory system and the CNS (Fig. 1). The speed of neural pathway activation surpasses that of the circulatory system, enabling swift physiological responses to internal environmental changes such as fluctuations in blood pressure, temperature, and pH, which can stimulate visceral sensory neurons [9]. Recent work has demonstrated that activation of both the parasympathetic and sympathetic nervous systems modulates pathogen-induced immune responses at barrier sites, such as the lungs, skin, and intestine. The vagus nerve plays a pivotal role in the exchange of information between the lungs and brain, with sensory neurons innervating the lung tissue and airways [10]. The vagus nerve terminals, brain integration centers, acetylcholine, and cells expressing α7 nicotinic acetylcholine receptors are central to the pulmonary parasympathetic inflammation reflex, which modulates both lung and brain functions. Stimulation of these components can release acetylcholine or neuropeptides to regulate lung and brain functions [11].

Mechanical ventilation (MV) has been shown to activate the vagus nerve [12], potentially leading to increased inflammation in the hippocampus and postoperative memory impairment in mice [13]. Preventive measures, such as bilateral vagotomy before MV, have demonstrated protective effects against brain injury in mice [14]. Additionally, research has found the peripheral delivery of mesenchymal stromal cells can activate vagus nerve sensory neurons in the lungs. These neurons project to the solitary tract nucleus and further induce the release of serotonin from the dorsal raphe nucleus, indicating a potential role of the "lung vagus nerve brain axis" in treating depression models [15]. Administration of α7 nicotinic acetylcholine receptor (α7nAChR) agonists reduces inflammation and mortality, whereas vagotomy exhibits the opposite effect, demonstrating that activation of the pulmonary parasympathetic nervous system exerts anti-inflammatory effects in Escherichia coli-induced pneumonia [16]. Similarly, the pulmonary

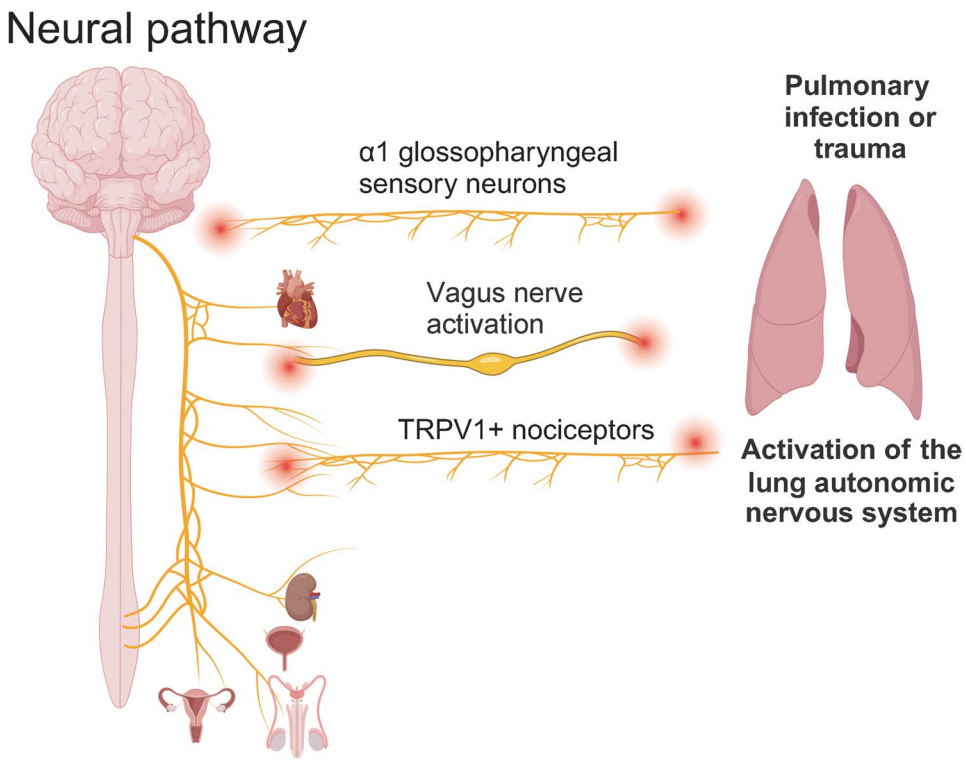

Fig. 1 Neural pathways mediating communication between the brain injury and lung damage. TRPV1: Transient receptor potential vanilloid-1 channel. Created with BioRender.com

sympathetic nervous system also plays a similar role in pneumonia, with sympathectomy amplifying both innate and adaptive inflammatory responses [17]. Furthermore, respiratory distress can activate neural circuits that trigger anxiety and stress responses, highlighting the psychological implications of pulmonary diseases [1].

There is a potential positive feedback loop within the lung-brain axis, which is mediated by neural interactions. Na Ryum Bin et al.'s study identified GABA(A) receptor α1 glossopharyngeal sensory neurons as key players in detecting prostaglandin E2 and eliciting a disease response to respiratory viral infections [18]. Lung TRPV1 + nociceptors detect lipopolysaccharide (LPS) from non-biofilm Pseudomonas aeruginosa (PA) pneumonias via TLR4, with vagal nociceptors in the lung activating acute stress neurocircuits in the hypothalamus precipitating disease-related symptoms such as malaise, fatigue, and anorexia [19]. However, further research is needed to elucidate the neural pathways involved in this process, particularly during the early stages of influenza.

These findings underscore the critical role of neural pathways in detecting environmental changes in the lungs, encoding this information, and facilitating lung-brain communication.

Regulatory role of the immune system and inflammatory responses

The immune system, a sophisticated defense mechanism within living organisms, is a network of interdependent cells, molecules, and organs. Its primary function is to identify and combat invading pathogens, including bacteria, viruses, fungi, and parasites, as well as to neutralize abnormal cells. This intricate system serves as a crucial mediator of communication from the lungs to the brain (Fig. 2A). For example, alterations in the gut microbiota, which are often associated with pulmonary diseases, can further modulate immune responses and contribute to neuroinflammatory processes [20]. This finding highlights the importance of maintaining a balanced immune response to protect both lung and brain health, suggesting that interventions aimed at modulating immune function may have beneficial effects on cognitive outcomes in patients with respiratory disorders.

The lung immune response can have systemic implications, notably affecting the CNS via the circulation of antibodies and complement proteins. Surgery and anesthesia may exacerbate the immune response in the lung-brain axis, leading to a surge in blood tau-PT217 levels, likely through stimulation of its production within the lungs and facilitation of its release from B cells. This immune-mediated process could allow tau-PT217 to breach the brain's defenses, heightening the excitability

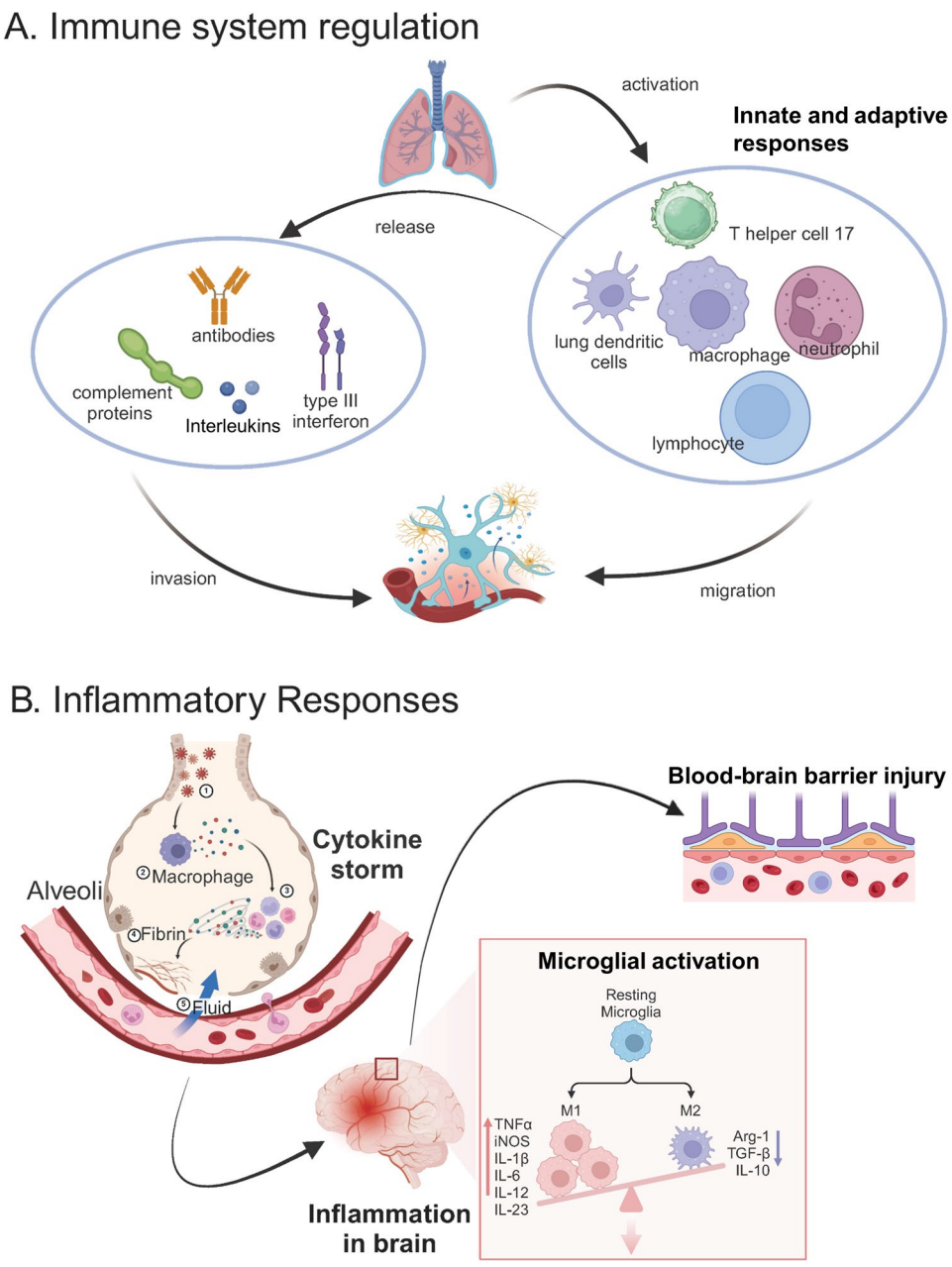

Fig. 2 Immune regulation and inflammatory responses play crucial roles in lung-brain interaction. Created with BioRender.com

of anterior cingulate cortex neurons, and ultimately triggering postoperative delirium-like symptoms in elderly mice [21]. Additionally, antimicrobial peptides produced as part of the immune response may contribute to systemic effects [22]. During viral infections, lung dendritic cells release type III interferon, potentially compromising the integrity of the lung epithelial barrier [23] and contributing to blood-brain barrier (BBB) disruption [24]. The coronavirus disease 2019 (COVID-19) pandemic has underscored the close link between encephalopathy and the intensity of cytokine storms [25]. An animal study highlighted the critical role of immune cell migration to the brain in facilitating immune-to-brain signaling during acute respiratory distress syndrome (ARDS), rather than cytokines alone [26]. In addition, TH17-type inflammation in the lungs of asthmatic patients may significantly influence the pathophysiology of depression and neuroinflammation, impacting long-term brain health [27]. The lungs are also implicated in autoimmune processes within the CNS. Effector T cells transiently reside in the lungs and mature within the local lymphoid structures before migrating to the CNS. There, they interact with antigen-presenting cells, undergo reactivation, and ultimately trigger autoimmune diseases [28].

Inflammation serves as a critical link in the lung-brain axis, influencing both pulmonary and neurological health (Fig. 2B). Inflammatory mediators released in response to lung injury or infection can have profound effects on brain function, potentially leading to cognitive deficits and mood disorders. Brain and lung injuries exhibit similarities in their inflammatory mechanisms, with the upregulation of various proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-18 [29–34]. For example, acute lung injury (ALI) is linked to higher brain cytokine levels, worsening neurological damage and recovery [4, 35] Chronic lung inflammation, as in asthma, is also tied to a higher risk of neurodegenerative diseases [36].

It is worth noting that the immune system plays a crucial role in mediating the interaction between the lungs and the brain, with cytokine networks and neuroinflammation acting as bridges connecting these two systems. Understanding these mechanisms is essential for the development of strategies aimed at preventing and treating brain damage caused by lung diseases.

Cytokine networks in dual immunity

Innate responses The innate immune response constitutes a rapid, nonspecific defense mechanism against pathogens, primarily mediated through pattern recognition receptors (PRRs) that detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [37, 38]. Following pulmonary infection or injury, innate immune cells release an array of cytokines encompassing proinflammatory mediators (TNF-α, IL-1β, IL-6) and regulatory counterparts (IL-10, TGF-β), which exhibit BBB permeability to modulate neurological functions [39]. IL-6 orchestrates diverse physiological processes including inflammatory regulation, antigen-specific immune activation, hematopoietic control, and acute-phase protein synthesis [40]. This evolutionarily conserved cytokine, comprising 212 amino acids with a 28-residue signal peptide, demonstrates structural plasticity that facilitates crosstalk between innate and adaptive immunity. As a canonical innate immune mediator, IL-6 induces microglial TLR4/NF-κB signaling during ventilator-induced lung injury (VILI), triggering frontal cortical apoptosis at tidal volumes of 35 mL/kg—a phenomenon reversible by IL-6 neutralizing antibodies [41]. Transcriptomic analyses of ARDS patients demonstrate SIRS-exacerbated upregulation of inflammasome components, particularly Caspase-1, IL-1β, and IL-18 mRNA levels. These neuroinflammatory cascades propagate across the BBB through cytokine storm mechanisms, potentially exacerbating neurodegenerative processes [42]. Therapeutic interventions targeting IL-18 neutralization or Caspase-1 genetic ablation ameliorate VILI pathology by suppressing microglial pyroptosis [43]. Pharmacological inhibition of Caspase-1 via zinc chelation by doxycycline demonstrates neuroprotective efficacy across preclinical models of stroke [44], multiple sclerosis [45], and Parkinson's disease (PD) [46].

Adaptive responses In contrast to innate immune effectors, cytokines of the adaptive immune system demonstrate specialized regulatory characteristics. The adaptive immune response constitutes an antigen-specific defense mechanism mediated principally by T lymphocytes and B lymphocytes. This system operates through functionally distinct T helper subsets. Th1 derived IFN-γ predominantly orchestrates cell-mediated immunity against intracellular pathogens. Th2 secreted IL-4, IL-5, and IL-13 coordinate humoral responses targeting extracellular pathogens. Th17 produced IL-17 A/IL-17 F mediate mucosal barrier defense and tissue repair, albeit with pathological associations in autoimmune disorders [47, 48]. In Th2-dominant pathologies such as asthma, pulmonary-derived IL-4 induces phosphorylation of Claudin-5 in cerebral microvascular endothelial cells, compromising tight junction integrity and augmenting BBB permeability [49, 50]. Mechanical ventilation-induced IL-17 A elevation facilitates direct CNS infiltration of IL-17 + immune cells. Furthermore, neutrophil-derived IL-17 A stimulates hepatic synthesis of serum amyloid A1 (SAA1), which activates TLR2/NF-κB signaling in ependymal cells and upregulates hippocampal TNF-α expression [51]. Dexamethasone, a cornerstone glucocorticoid in asthma management, suppresses Th2 cytokine polarization (IL-4/IL-5) and attenuates TNF-α-driven neuroinflammation in murine models. This targeted immunomodulation restores synaptic plasticity through BDNF/TrkB pathway activation, effectively rescuing spatial memory deficits in Barnes maze assessments [52]. Such pharmacological dissection highlights the feasibility of selectively modulating adaptive cytokine networks while preserving innate immune surveillance.

Lung injury, neuroinflammation, and brain dysfunction

Lung injury can compromise the BBB and stimulate neuroinflammatory cells such as microglia to release neuroinflammatory factors and trigger neuroinflammation [53].

Systemic cytokine release and BBB disruption Cytokines produced by the lung immune system against invading pathogens can traverse the BBB, triggering neuroinflammation and ultimately resulting in neurological dysfunction [2, 54–57]. Despite the absence of PA loads in the brains of mice with PA pneumonia, there was an increase in pro-inflammatory cytokines, chemokines, adhesion molecules, and recruitment of CD11b + CD45 + cells in the brain [58]. A similar pat-

tern of findings emerged from further exploration of–brain interactions in viral respiratory infections. A study using lung-brain microphysiological systems noted early microvascular brain damage following acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lung infection, even at low viral loads, and a concurrent high level of pro-inflammatory cytokines in the brain [59]. These results imply that both bacterial and viral lung infections are linked to BBB disruption and altered behaviors, which are likely induced by systemic cytokine release rather than direct neural invasion by bacteria or viruses.

Neuroinflammation and microglial activation Neuroinflammation and microglial activation play crucial roles in the interaction between the lung and brain, potentially functioning as the ultimate pathway linking lung diseases to brain dysfunction. Ventilator-induced lung injury (VILI) has the capacity to intensify the systemic inflammatory response [60], leading to the production of inflammatory cytokines such as IL-6 and TNF-α in the lungs [61]. Studies have indicated that VILI not only exacerbates but also initiates brain injury and inflammation [62–64]. Specifically, mice subjected to MV exhibit a decrease in neuronal counts and an increase in the levels of TNF-α, IL-1β, and IL-6 in the hippocampus [65]. Postoperative prolonged MV further exacerbates cognitive decline, partially mediated by glial activation in surgical mouse models [13].

Air pollution is associated with an increased risk and progression of neurodegenerative disorders, including cognitive impairment [66], autism [67], and Alzheimer's disease (AD) [68]. Although the precise mechanisms underlying these associations remain unclear, accumulating evidence suggests that neuroinflammation and microglial activation may serve as common pathways by which air pollution affects various CNS conditions. Exposure to air pollution has been shown to induce microglial activation (indicated by increased IBA1 expression) [69], astrocyte activation (indicated by increased GFAP expression) [70], and the production of 3-NT (a marker of neuroinflammation). Additionally, there is a significant increase in the expression of phosphorylated Tau protein (ser202, thr205) in the cerebellum and olfactory bulb, highlighting the neuroinflammatory processes primarily driven by microglia and astrocytes under conditions of oxidative stress [71]. In response to mixed vehicle emissions, aged mice exhibit diminished pulmonary immune profiles, marked neuroinflammation, and microglial activation [72].

Therefore, understanding the role of neuroinflammation and microglial activation in the lung-brain axis is essential for the development of strategies aimed at preventing and treating brain damage caused by lung diseases.

Microorganism pathway

For many years, it has been commonly believed that the lungs remain uninhabited by bacteria. However, contemporary research debunks this notion. Although the microbial population within the lungs is modest compared to that found in the intestinal mucosa, it is clear that bacteria do indeed reside within the respiratory system. Advances in medical science have shed light on the lung microbiome, challenging the traditional belief that the lungs are a sterile organ [73, 74]. The ongoing fluctuations in the lung microbiota, both in health and during disease, have the potential to profoundly influence the progression of lung conditions. This influence extends beyond the respiratory system, potentially extending its reach to the brain, thereby eliciting a cascade of physiological and pathological changes. Notably, the pulmonary microbiome, characterized by a comparatively lower biomass relative to its gut counterpart, exhibits heightened susceptibility to environmental perturbations. This ecological vulnerability enables disproportionate influence on host homeostasis despite its reduced microbial density. Emerging evidence has established bidirectional crosstalk between CNS autoimmunity and peripheral organ pathophysiology, with the pulmonary system constituting a critical neuroimmune interface. Contemporary research delineates five principal mechanisms through which respiratory microbiota modulate neurological processes: ① microbial translocation across compromised biological barriers; ② epigenetic reprogramming via microbial metabolite-driven modifications; ③ viscerosensory signaling through vagal afferent pathways; ④ hypothalamic-pituitary-adrenal axis-mediated neuroendocrine modulation; and ⑤ priming of peripheral immune cell trafficking to CNS compartments [22]. The last four mechanisms could be considered as indirect pathways resulting from microbiome imbalance (Fig. 3).

The direct translocation of microorganisms

In pulmonary infectious diseases, the direct translocation of microorganisms or microbial products through the alveolar capillary barrier is thought to be a potential mechanism of ALI-related brain damage. The successful entry of microorganisms or their products into the bloodstream can enable them to reach the CNS [22, 75]. In the case of direct translocation, pulmonary microorganisms and their soluble components disrupt the alveolar capillary barrier, subsequently entering the bloodstream and potentially compromising the BBB. Studies indicate that acute severe pneumonia has the potential to result in neurological disorders, a condition linked to the migration of bacteria from the lungs to the brain [76]. In experimental models of severe pneumonia, bacteria similar to those in the lungs have been detected in the brain tissue. Further confirmation through antibiotic treatment

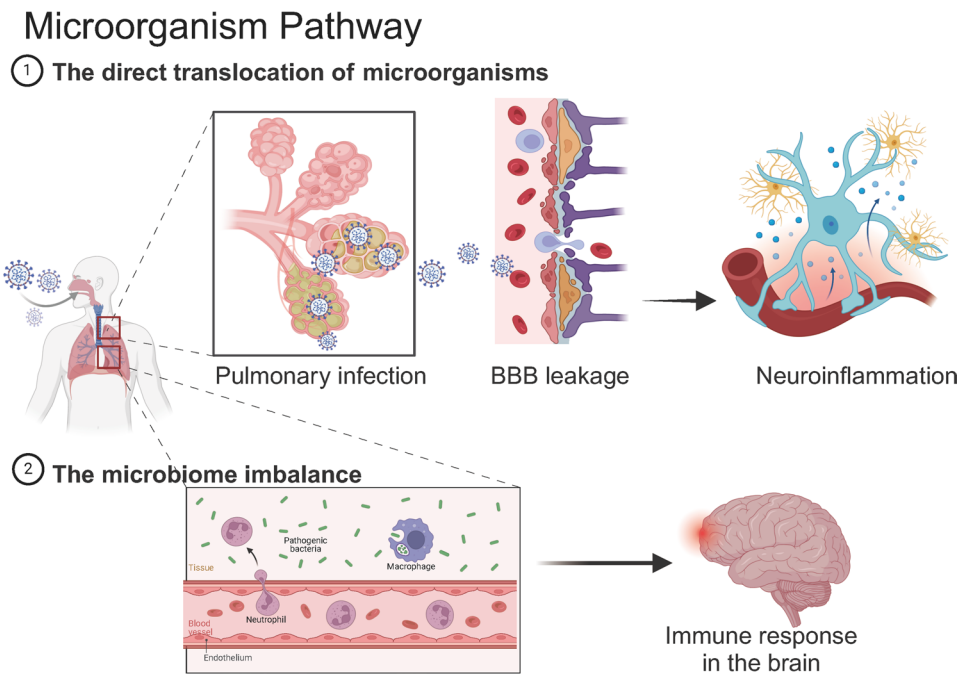

Fig. 3 Microorganism pathway in brain-lung axis. BBB: Blood-brain barrier. Created with BioRender.com

and other experiments indicated that bacteria from the lungs may directly migrate to the brain through compromised barriers, thereby disrupting brain homeostasis. Cryptococcus neoformans, a neurotropic fungal species, employs a "Trojan horse" strategy to traverse cerebral blood vessels within macrophages, thereby contributing to host neurotoxicity [77, 78]. Currently, substantial evidence exists to demonstrate a link between SARS-CoV-2 infection and its associated neurological effects. Several studies have provided evidence of the virus directly invading the brain [79, 80]. The virus may enter peripheral nerve endings and travel retrogradely along the axonal pathways. The presence of the virus in the cranial nerve and CNS nucleus confirms this hypothesis [81].

Indirect pathways mediated by microbiome imbalance

Recent research suggests that beyond the entry of external bacteria or viruses into the lungs, lung microbiota dysbiosis can also precipitate neural damage or dysfunction [82, 83]. Moreover, studies have indicated that the cell wall components of pulmonary bacteria continuously transmit signals to immune cells in the brain, leading to the transformation of resident brain microglia into a state characterized by type I interferon features [84]. Factors such as antibiotics, pollutants, smoking, and lung infections can disrupt the lung microbiota, impacting the brain similarly to gut microbiota alterations. Correspondingly, interventions to support lung microbiota may be beneficial. Leon et al.'s research established a relationship between lung microbiota and brain immune response [82]. This study diverges from previous investigations by emphasizing the mechanistic link between microglial activation within the lung-brain axis and brain disease progression, rather than focusing on T cell transmigration across the BBB or their reactivation processes. Treating rat microbiota with neomycin induced an LPS-rich shift, triggering a shift to favor signaling mediated by the type I interferon pathway. This reduced responsiveness to type II interferon-dominated autoimmune stimulation, decreasing proinflammatory activity, immune cell recruitment, and clinical signs. These findings support a lung-brain axis, where the lung microbiome regulates the CNS immune response and interferes with the development of neuroinflammation, thereby influencing autoimmune disease susceptibility.

A growing body of evidence has established causal links between airway microbial dysbiosis and localized inflammatory pathology in chronic pulmonary disorders, particularly asthma and chronic obstructive pulmonary disease (COPD). Emerging toxicological data reveal that commercially mass-produced carbon quantum dots exhibit dual neurotoxic pathways: direct CNS infiltration via the BBB penetration/olfactory nerve pathways, and indirect neurobehavioral impairments through pulmonary dysbiosis-induced oxidative stress, neuroinflammatory cascades, and neuronal apoptosis [85, 86]. Furthermore, respiratory infection-driven microbial perturbations demonstrate transorgan regulatory effects, notably exacerbating gastrointestinal pathophysiology [87]. Chronic pulmonary infections can lead to systemic inflammation, which in turn alters the composition of the gut microbiota, thereby affecting brain health through

the gut-brain axis [88]. Crucially, the immunomodulatory capacity of pulmonary microbiota in maintaining distal tissue homeostasis remains underexplored, representing a critical knowledge gap. Notably, experimental neuroscience studies employing distal photobiomodulation of the bilateral lungs demonstrated neuroprotective efficacy in repetitive closed-head injury rat models, with concomitant improvements in cognitive performance and reduced tau hyperphosphorylation. Metagenomic profiling post-photobiomodulation revealed significant enrichment of LPS biosynthesis pathways in the lung microbiota, suggesting potential microbiome-mediated neuroprotective mechanisms [89].

Hypoxemia as a driver of Lung-Brain injury

Hypoxemia has been shown to elicit tissue hypoxia and augment the risk of multifaceted organ dysfunction encompassing the brain (Fig. 4). ALI often coexists with hypoxemia and may even lead to respiratory failure, resulting in diminished oxygen and glucose delivery to the brain as well as heightened production of reactive oxygen species [90]. Interestingly, hypoxic stimuli can counteract heightened cerebral blood flow by facilitating vasodilation, thereby maintaining a consistent oxygen supply to the brain [91]. Consequently, the role of hypoxemia as a precipitating factor of brain dysfunction remains uncertain [92]. A clinical study conducted by Mikkelsen et al. on ALI survivors necessitating MV revealed a significant correlation between a mean partial pressure of oxygen of 72 mmHg and prolonged cognitive decline [93]. Hypoxic stimuli activate peripheral chemoreceptors, potentially inducing hyperventilation and subsequent hypercapnia, which may lead to cerebral vasoconstriction and reduced cerebral perfusion [94, 95]. Ischemic brain injury is another prevalent complication observed in patients with ALI, with pathophysiological mechanisms associated with endothelial cell activation, systemic inflammation, coagulation activation, thrombosis, and hypoxia-induced reactive oxygen species [96, 97]. Janz et al. noted that hypoxic brain injury in ARDS patients primarily affects pyramidal neurons in the hippocampal cornu ammonis 1 region [98]. The underlying mechanisms of hippocampal damage due to acute hypoxia include glycolysis, elevated adenosine levels, cardiopulmonary compensatory responses, oxidative stress, and mitochondrial dysfunction [99]. Furthermore, although less common, ALI may be associated with hemorrhagic stroke. Hypoxemia and inflammation can exacerbate endothelial dysfunction and disrupt the BBB, enabling the extravasation of red blood cells and development of diffuse cerebral microbleeds [100], potentially evolving into hemorrhagic stroke [96].

Notably, the mechanisms discussed previously are often not independent. For instance, cerebral damage resulting from pulmonary infection may stem from the direct infiltration of pathogens into neural tissues, in addition to the neurotoxic effects of systemic inflammation triggered by lung injury. Moreover, following lung injury, the neuroendocrine system is modulated, resulting in the release of various neuroregulatory substances,

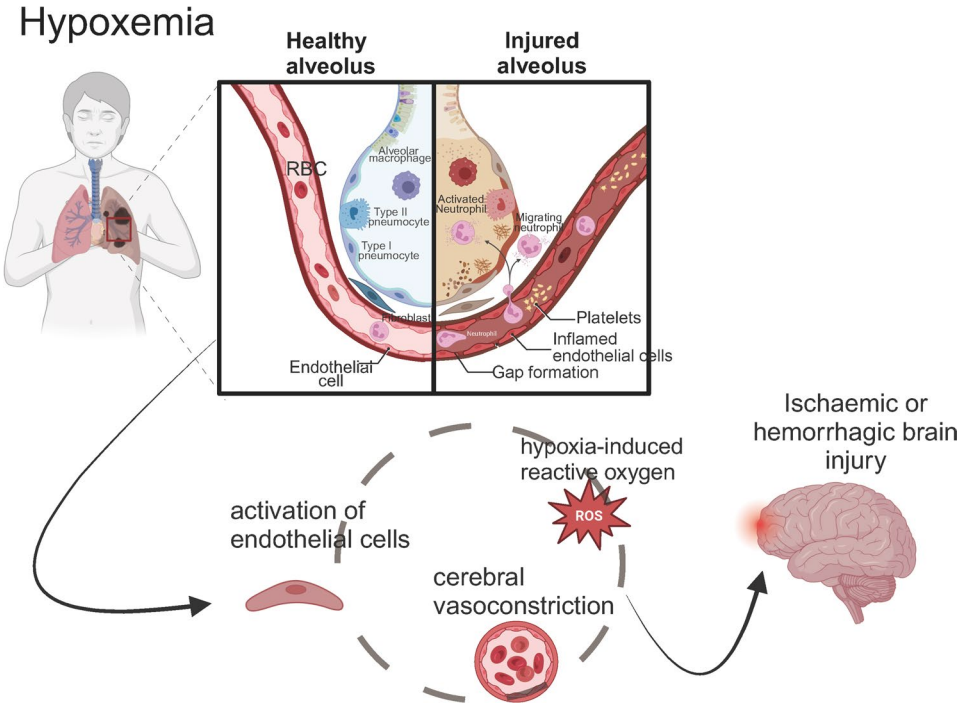

Fig. 4 Hypoxemia in ALI/ARDS can cause brain dysfunction. RBC: Red blood cell; ROS: Reactive oxygen species. Created with BioRender.com

including neuropeptide Y and nerve growth factors [101, 102], and the activation of the hypothalamic-pituitary-adrenal axis [103], which subsequently influences CNS function. Given the limited existing research in this field, a comprehensive exploration of these interactions will not be addressed within the scope of this study. In summary, the lung-brain axis typically involves multiple interacting mechanisms, which further complicate the disease.

The impact of lung injury on brain diseases (Fig. 5)

Pneumonia, ALI/ARDS and brain dysfunction

ALI/ARDS and brain dysfunction

Extrapulmonary complications commonly occur in patients with ALI and ARDS. Among the various organs and systems that may be impacted, the brain emerges as the most susceptible to injury following ALI and ARDS [6]. Survivors of these conditions often exhibit cognitive decline, including memory disturbances, linguistic difficulties, and impairments in cognitive functions [104]. Research suggests that the inflammatory response initiated by ALI can induce neuroinflammation, marked by the activation of glial cells and secretion of proinflammatory cytokines. These cytokines can undermine the integrity of the BBB and contribute to brain dysfunction. For instance, dimethyl fumarate has shown promise in preventing cognitive impairment associated with ALI by reducing inflammation, highlighting the interconnectedness of pulmonary and neurological health [105]. Furthermore, ALI can lead to alterations in cerebral blood flow, exacerbating neurological deficits. Research in neonatal models has demonstrated that autoregulation of cerebral circulation is impaired during ALI, suggesting that the brain's ability to maintain stable blood flow is compromised [106]. This disruption in cerebral hemodynamics can lead to hypoxic-ischemic injury, which is critical for the pathogenesis of cognitive dysfunction following ALI.

Experimental evidence has demonstrated that MV-induced ARDS precipitates hippocampal CA1 neuronal atrophy with concomitant elevation of S-100β, a biomarker indicative of BBB disruption [107]. Notably, both

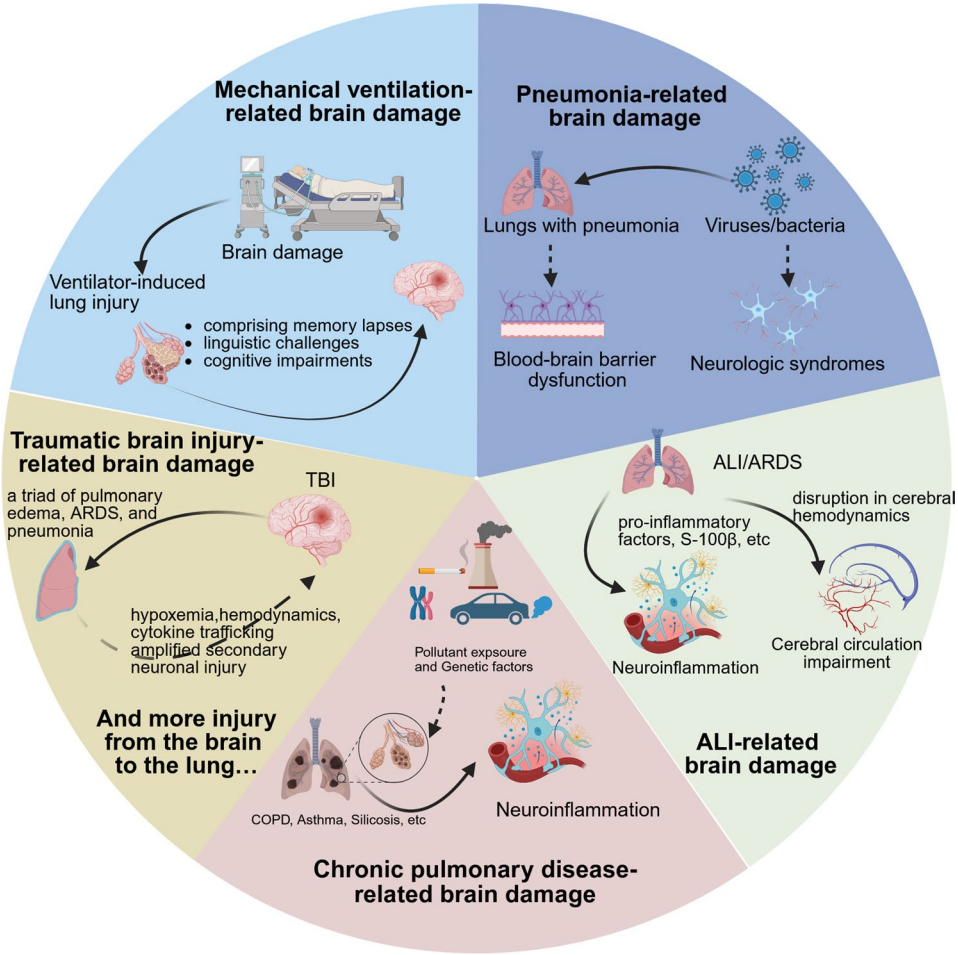

Fig. 5 Bidirectional Impact: Lung Injury on Brain Diseases and Brain on Lung Health. ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome. Created with BioRender.com

ALI and ARDS predispose patients to secondary pulmonary infections, while pulmonary cytokine storms exhibit strong correlations with behaviorally quantified memory deficits. These findings collectively establish ALI/ARDS as multifactorial mediators of cerebral pathology, with pulmonary infection constituting an independent risk amplifier. Although overlapping mechanisms underlie various pulmonary-cerebral comorbidities, this review specifically delineates pulmonary infection-mediated neurological sequelae through dedicated analysis.

Pneumonia and brain dysfunction

Pneumonia caused by pulmonary infection has been shown to significantly affect brain health, primarily through the initiation of inflammatory responses that extend beyond the lungs and affect the CNS. Both the immune and nervous systems have evolved sophisticated, coordinated mechanisms to rapidly detect and respond to environmental stimuli. Emerging epidemiological evidence has revealed a significant association between pneumonia and an elevated risk of cognitive impairment, including dementia spectrum disorders [108]. Notably, pulmonary infections substantially potentiate the susceptibility to multiple sclerosis onset [109]. Experimental studies employing nasal inoculation of Klebsiella pneumoniae or intratracheal LPS administration have established two standardized post-intracerebral hemorrhage pneumonia models. Comparative analyses have demonstrated that Klebsiella pneumoniae-challenged models exhibit exacerbated neurological deficits, aggravated cerebral lesion volumes, and heightened neuroinflammation profiles, mechanistically linking pulmonary infections to poor cerebrovascular outcomes following hemorrhagic stroke [110].

The immune reaction to these infections can lead to systemic inflammation, which in turn triggers neuroinflammatory responses characterized by elevated cytokine levels and activation of microglia in the brain [111]. This inflammatory environment not only contributes to the development of neurological complications but also leads to symptoms such as confusion and altered mental status, which are commonly observed in patients with severe pulmonary infections [112]. Furthermore, bacterial lung infection, whether early or late, increases mortality following traumatic brain injury in male mice [113]. Intratracheal instillation of PA in mice results in significant dysfunction of the BBB, which is evident through the leakage of molecules across cerebral microvessels and decreased expression of cell-cell junction proteins such as VE-cadherin and claudin-5 in the brain [58]. These observations emphasize the complex and potentially harmful consequences of lung infections on brain function.

Neurological complications are prevalent in 30–80% of patients with COVID-19, and the underlying pathogenesis is unclear [114, 115]. Early cerebral microvascular damage has been detected in mice infected with a low viral load of SARS-CoV-2 in their lungs [59]. Respiratory syncytial virus (RSV), a negative single-stranded RNA virus primarily targeting the respiratory system, causes severe acute neurological syndromes in 2% of RSV-positive patients, including confirmed encephalitis, acute encephalopathy, and immune-mediated disorders [116]. Moreover, Epstein-Barr, cytomegalovirus, and varicella-zoster viruses have been implicated in patients with multiple sclerosis [117, 118]. Influenza virus has also been found in patients with PD [119], and three strains of human herpes simplex virus have been detected in the brain samples of patients with AD [120, 121]. These findings suggest that the systemic inflammatory response induced by viral infection may play a role in the development of neurodegenerative disorders.

Chronic lung diseases and cerebral injury

Chronic lung diseases, including chronic obstructive pulmonary disease (COPD) and asthma, exhibit an elevated risk of multiple neurodegenerative disorders, notably dementia and AD [122–124]. Persistent hypoxemia accompanying these conditions can induce neurovascular alterations and neuroinflammation, both integral to neurodegenerative processes. Recent research has emphasized the significance of environmental pollutants, especially PM2.5, with evidence suggesting that exposure may exacerbate pulmonary fibrosis and cognitive decline [125].

Additionally, the concept of brain-lung interplay has been formulated, proposing that systemic inflammation stemming from chronic lung diseases may intensify neuroinflammatory pathways [126]. This interplay perpetuates a vicious cycle in which compromised lung function precipitates brain damage, which further deteriorates lung health. Consequently, elucidating the mechanisms underlying the link between chronic lung disease and neurodegenerative processes is vital for the development of comprehensive treatment approaches.

COPD and brain dysfunction

In particular, COPD has been associated with cerebrovascular disorders, augmenting the likelihood of white matter lesions [127–129]. Population-based cohort studies have identified tobacco smoking as the primary etiological factor for COPD, with longitudinal data demonstrating a significant increase in dementia risk among affected individuals [130]. Under normal physiological conditions, a decreased blood oxygen content triggers an increase in cerebral blood flow to maintain brain oxygenation. However, COPD patients, characterized by chronic

hypoxemia, exhibit reduced perfusion in the periventricular white matter situated in the cerebral artery watershed zone. This could be a plausible mechanism by which COPD predisposes individuals to white matter hyperintensity. Furthermore, studies have demonstrated that patients with COPD face a heightened risk of both ischemic and hemorrhagic strokes [131, 132]. Additionally, alterations in respiratory microflora due to COPD increase the risk of PD and AD [133].

Asthma and brain dysfunction

It is crucial to emphasize that asthma is linked to cognitive and emotional problems, sleep issues, olfactory dysfunction, and other brain-related symptoms, with inflammation and oxidative stress as potential underlying causes [134, 135]. Recent investigations have identified a specific inflammatory pathway connecting asthma-induced airway inflammation with emotion-related neural dysfunction [27]. Asthma-associated TH17-type inflammation has been implicated in the pathophysiology of depression and neuroinflammation, potentially affecting long-term cerebral health. Patients with asthma exhibit elevated levels of neurodegeneration-associated biomarkers, including neurogranin and α-synuclein, which demonstrate robust associations with accelerated cognitive decline [136]. Furthermore, neuroimaging analyses have revealed structural alterations characterized by compromised axonal integrity, diminished myelination, and accelerated neuronal loss in this population [137].

Silicosis and brain dysfunction

Subacute exposure to ozone may lead to communication between lung and brain inflammatory responses [138]. Studies in mice have shown that silica administration leads to alveolar collapse and silicosis, followed by lung inflammation and subsequent upregulation of hippocampal pro-inflammatory cytokines, synaptic damage, accumulation of Aβ peptide, and memory impairment [139].

MV-related brain damage

MV is a life-saving support measure widely used in managing patients during general anesthesia and in critically ill patients [7]. However, many studies have found that prolonged MV may not only lead to VILI but may also cause dysfunction of distant organs, including brain injury manifested as neuropsychological changes or cognitive impairment [62, 63, 65, 140–142]. The public health significance of MV–associated cognitive dysfunction has been amplified in recent times by the high reported prevalence of acute cognitive dysfunction in patients with COVID-19, many of whom receive MV [143, 144]. In addition, the incidence and duration of delirium in mechanically ventilated Intensive Care Unit patients remain high [145]. For extremely preterm infants, MV is a life-saving intervention, yet it is associated with lung and brain injuries [146, 147]. It is noteworthy patients receiving MV are often critically ill, and their primary diseases may already affect cognitive function. Thus, when assessing MV-related cognitive dysfunction, the bias from primary diseases should be excluded. In summary, while MV is crucial for saving lives, its potential impact on cognitive function must not be overlooked. In practice, appropriate rehabilitation and ventilation strategies should be adopted, considering the primary disease and severity, to reduce MV-related brain damage.

Brain affects lung health (Fig. 5)

A robust bidirectional neuro-respiratory axis fundamentally interconnects the pulmonary and CNS. Beyond direct respiratory depression caused by neurological pathologies, cerebral insults precipitate multiorgan sequelae through secondary complications. Post-stroke conditions including immobility-induced hypostatic pneumonia, impaired cough reflexes, neurogenic pulmonary modifications, and stroke-associated immunodepression syndrome collectively predispose to acute respiratory insufficiency [148]. In traumatic brain injury (TBI) populations, pulmonary complications manifest as a triad of neurogenic pulmonary edema, ARDS, and ventilator-associated pneumonia [149]. Clinical epidemiology reveals that TBI-ALI afflicts over 50% of patients with isolated severe TBI, with 30–40% progressing to fulminant ARDS [150]. TBI-ALI establishes a self-perpetuating pathophysiological cycle through: systemic hypoxemia exacerbating cerebral metabolic crisis; disrupted cerebral autoregulation from altered pulmonary hemodynamics; amplified secondary neuronal injury via pro-inflammatory cytokine trafficking. In addition, Su et al. revealed neural circuits linking the lungs and brainstem, demonstrating that allergen-induced airway hyperresponsiveness is mediated by specific nucleus of the solitary tract and the nucleus accumbens. Inhibiting these neurons can significantly blunt the lung's response to allergens and prevent asthma attacks. These findings highlight the potential of targeted neural regulation as a novel therapeutic strategy for asthma management [151]. Mechanistically, this dual-organ failure arises through: pulmonary macrophage activation via extracellular mitochondrial DAMPs [152]; NLRP3 inflammasome-mediated IL-1β/IL-18 maturation and oxidative stress cascades involving NADPH oxidase hyperactivity [153].

Protein markers as integral links involved in lung and neural injury processes

Biomarkers, typically proteins, in biological fluids like blood and urine, indicate specific health states, including disease presence or treatment responses. In the lung-brain axis, certain protein biomarkers are linked to both

lung inflammation and CNS impairments like reduced cognitive function. These markers could help predict lung-brain axis disorders, reveal disease mechanisms, and pinpoint drug targets.

The following section outlines common protein markers in this axis, providing new therapeutic insights. A detailed examination of the distinct roles of these protein markers is presented, as summarized in Table 1. Monitoring these biomarkers could transform diagnostics and treatment for lung and brain conditions. As research validates these markers, their use in clinical practice may improve diagnostics and guide treatment, benefiting patient care. This underscores the importance of ongoing biomarker research in advancing medical approaches to respiratory and neurological health [154].

Toll-like receptor 4 (TLR4)

TLR4, predominantly expressed on the cytoplasmic membrane of hematopoietic stem cells such as macrophages, monocytes, and dendritic cells, functions as a pattern recognition receptor [155]. TLR4 is integral to innate immunity, orchestrating inflammatory responses through the recognition of LPS and bacterial endotoxins [156]. Excessive activation of TLR4 leads to the production of various inflammatory mediators, contributing to conditions like sepsis, endotoxemia, ALI, rheumatoid arthritis, and BBB integrity [157, 158]. Studies have implicated TLR4 in MV-induced lung inflammation [7, 159]. Blocking the NLRP3 inflammasome pathway downstream of TLR4 mitigates LPS-induced ALI [160, 161]. TLR4 also plays a pivotal role in cognitive functions and is involved in neurodegenerative processes [162, 163]. Recent evidence suggests TLR4 as a key regulator of neuronal survival during sterile injury and infection [164, 165], and it is linked to neuroplasticity [166]. Chen Ting et al. found that MV increases hippocampal TLR4 mRNA expression, leading to microglial and astrocytic proliferation and the secretion of pro-inflammatory cytokines [140]. This highlights TLR4's unique role in mediating neuroinflammation following prolonged MV.

Angiotensin converting enzyme 2 (ACE2)

ACE2 is classified as a type I transmembrane metalloproteinase and functions as a carboxypeptidase. The physiological role of ACE2 in human health is complex and not fully understood. It serves as a receptor for SARS-CoV-2 infection and has the capacity to modulate nicotinic acetylcholine receptor function [167], facilitating the virus's entry into host cells, including those of the lung and brain [168–173]. Research by Li et al. revealed a marked upsurge in ACE2 expression 24 h post-SARS-CoV-2 infection, with levels remaining elevated at the 48-hour mark [174]. This indicates that ACE2 is not only pivotal in viral susceptibility but also in the regulation following infection. Additionally, the elevated presence of ACE2 in lung tissue triggers cytotoxicity, neutrophilic inflammation, and immune responses driven by type 2 T helper cells [174]. Conversely, studies have indicated that ACE2 may exert protective effects against lung injury, which could be due to its antioxidant and anti-inflammatory attributes [175–177]. ACE2 can convert angiotensins, with the resulting metabolites possessing vasodilatory properties and other protective effects via Mas receptors, thereby negatively regulating the renin-angiotensin system. In the brain, the enzyme neural phosphatase contributes to the production of Ang-(1–7) and other substrates specific to brain tissue, and its regulatory effects are being investigated as potential therapeutic targets for protecting the brain after stroke [178–180].

Acute-phase serum amyloid A (A-SAA)

A-SAA comprises two primary subtypes, SAA1 and SAA2, which serve as the predominant acute-phase proteins across most vertebrates, encompassing both mice and humans. These proteins are mainly produced in the liver and released into circulation as a response to pro-inflammatory cytokines [181]. In patients with COPD, A-SAA levels are elevated in both blood and lung tissues [182–184], and there is a correlation with O_3 exposure [185, 186]. Furthermore, A-SAA has been shown to elicit IL-6 and IL-17 A-dependent, glucocorticoid-resistant airway neutrophilia [184]. The concentration of A-SAA in the bloodstream has been linked to the counts of neutrophils and Mϕ in bronchoalveolar lavage fluid. The subtypes SAA1.1 and SAA2.1 are capable of traversing the BBB and accumulating within the CNS following O_3 exposure, indicating that SAA may play a pivotal role in mediating the lung-brain axis subsequent to O_3 exposure [187].

High mobility group box-1 protein (HMGB1)

HMGB1 represents a highly conserved nuclear protein that is universally expressed in all nucleated cells and functions as a damage-associated molecular pattern [188]. As a potent mediator of inflammation, it plays a central role in neuroinflammatory processes across various neurological disorders [189, 190]. Exposure to organic dust (OD) prompts the translocation of HMGB1 from the nucleus to the cytoplasm, leading to enhanced cell activation and inflammation, which may initiate, exacerbate, or contribute to the progression of respiratory diseases such as COPD and asthma [191]. Studies have indicated that OD exposure increases the expression of HMGB1, 3-nitrotyrosine, IBA1, GFAP, hyperphosphorylated Tau, and apoptotic cells in the brain, as evidenced by terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick end labeling [71]. O_3, a reactive air pollutant, has been associated with AD risk

Table 1 The role of various protein markers in the lung-brain axis

Protein markers	Models	Species	Key findings	Effect on brain	Reference(s)
TLR4	VILI	Male WT (C57BL) mice; TLR4 KO mice	Both TLR4 KO and TLR4 antagonist treatment can alleviate the neuroinflammation caused by prolonged mechanical ventilation involving lung-brain interaction.	harmful	[140]
ACE2	Intranasal inoculation with SARS-CoV-2	WT (C57BL) mice; UBC-ACE2 mice; Rosa-ACE2 mice	In the UBC-ACE2 line, the SARS-CoV-2 penetrated directly into neurons in the gyrus dentate area and multiple sludges of erythrocytes were observed in the brain tissues.	harmful	[173]
A-SAA	O_3 exposures	Female BALB/c mice; male CD-1 mice	A-SAA in blood correlated with leukocytes, Mfs, and neutrophils in bronchoalveolar lavage from O_3-exposed mice. Both A-SAA isoforms completely crossed the intact BBB, with an increase in A-SAA protein, but not mRNA, in the CNS 24 h after O_3 exposure.	harmful	[**187**]
HMGB1	Organic dust exposures	Male C57BL/6 N mice	Organic dust exposure increased the expression of HMGB1, 3-nitrotyrosine, IBA1, GFAP, hyperphosphorylated Tau, and terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick end labeling (TUNEL)-positive cells in the brain.	harmful	[71]
	O_3 exposures	Male transgenic 5xFAD mice and littermate controls (WT) on a C57Bl/6J background; $HMGB1^{fl/fl}$LysM-cre^{+} and $HMGB1^{fl/fl}$LysM-cre^{-} mice	Short term O_3 exposure in $HMGB1^{fl/fl}$LysM-cre^{-} mice showed a decrease in TREM2 expression in the cortex and midbrain and an increase in NLRP3 in the midbrain.	harmful	[193]
TREM2	O_3 exposures	Male transgenic 5xFAD mice and littermate controls (WT) on a C57Bl/6J background; $HMGB1^{fl/fl}$LysM-cre^{+} and $HMGB1^{fl/fl}$LysM-cre^{-} mice	O_3 exposure resulted in reduced microglial plaque association, impaired upregulation of CNS TREM2 in response to plaque, increased amyloid and neuronal pathology, and dysregulation of the microenvironment around plaques in 5xFAD mice.	protective	[193]
IL-6	VILI	Male or female C57BL/6 mice	VILI induced potentially reversible neuronal injury and inflammation in the frontal cortex and hippocampus, which was mitigated with systemic IL-6 inhibition.	harmful	[**41**]
P2Y1R	VILI	C57BL/6 mice	Lung injury induced by mechanical ventilation exacerbated brain injury in mice by increasing ATP production, activating the P2Y1 receptor, and thus promoting dopamine release.	harmful	[202]

Abbreviation: WT: Wild type; KO: Knock out; VILI: Mechanical ventilation-induced lung injury; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; IBA1: Ionized calcium binding adaptor molecule; GFAP: Glial fibrillary acidic protein; CNS: Central nervous system; TLR4: Toll-like receptor 4; ACE2: Angiotensin converting enzyme 2; A-SAA: Acute-phase serum amyloid A; HMGB1: High mobility group box-1 protein; NLRP3: NOD-, LRR- and pyrin domain-containing 3; TREM2: Triggering receptor expressed on myeloid cells 2; P2Y1R: P2Y1 receptors

and cognitive decline [192]. Experimental mice exposed to O_3 exhibited an augmented pulmonary immune response and elevated levels of circulating HMGB1, which coincided with an increase in amyloid pathology, consistent with the loss of triggering receptor expressed on myeloid cells 2 (TREM2) function [193]. These findings suggest that HMGB1 may serve as a crucial mediator in acute lung-cerebral injury.

Furthermore, inhibiting the activation of the HMGB1 pathway can reduce the pulmonary inflammatory response, downregulate the expression of TLR4 and p-nuclear factor kappa-B, and alleviate $PM_{2.5}$-induced lung injury [194]. In vitro studies using BV2 cells confirmed that $PM_{2.5}$ stimulates hippocampal microglial activation through the modulation of the HMGB1-NLRP3 inflammatory axis [195]. These observations underscore the pivotal role of the HMGB1 inflammatory axis in cognitive and pulmonary impairments, suggesting a potential interplay between the mechanisms underlying lung and brain injuries.

Triggering receptor expressed on myeloid cells 2 (TREM2)

TREM2 is a single-pass transmembrane immune receptor predominantly expressed on microglia and peripheral macrophages in the brain [196]. Despite the incomplete understanding of its functional mechanism, TREM2 has been observed to regulate inflammatory signaling and microglial metabolism, potentially promoting microglial phagocytosis, activation, survival, and proliferation [197]. Consequently, TREM2 is essential for normal immune function and cell viability within the brain. Dysregulation of TREM2 expression may constitute a genetic risk factor for AD [196, 197]. Studies have reported elevated levels of soluble TREM2 (sTREM2) cleavage products in AD patients. A correlation has been established between peripheral sTREM2 levels and those in the cerebrospinal fluid (CSF), as well as between CSF sTREM2 levels and markers indicative of BBB integrity [198]. Another clinical study, involving 89 controls, 135 individuals with mild cognitive impairment, and 79 AD dementia patients, found that sTREM2 was positively associated with pro-inflammatory proteins such as TNF receptor 1 and TNF receptor 2, as well as with anti-inflammatory proteins including TGF-β1, IL-10, and IL-9 [199]. These associations may provide insights into the potential role of sTREM2 in AD pathology, including its impact on BBB integrity, neuroinflammation, and cognitive function. The lung-brain axis hypothesis proposes that the immune response in the lungs and subsequent systemic signals, such as cellular and circulating factors, modulate the health and disease state of the CNS. In support of this hypothesis, Grave and colleagues previously demonstrated that exposure to O_3 elicits a sustained neuroimmune response and amyloid-associated neuropathology, likely due to the elevated circulating factors, including HMGB1, and an enhanced pulmonary immune response [193].

P2Y1 receptors (P2Y1R)

The family of G protein-coupled receptors known as P2Y receptors comprises structures featuring seven hydrophobic transmembrane helixes, accompanied by three intracellular and three extracellular loops. These receptors are crucial mediators in the interplay between neurons and glial cells. Within this subset, P2Y1R has been implicated in potentiating inflammatory processes, notably inflammatory pain [200]. Specifically, P2Y1R functions as a metabolic receptor with a preference for ADP activation, and the inhibition of this receptor through drugs or gene-blocking techniques can offer neuroprotection during ischemic events [201]. Furthermore, Wei and colleagues demonstrated that VILI exacerbates brain damage in mice by augmenting ATP production, stimulating P2Y1R, and facilitating dopamine release within the hippocampus [202].

Although several protein biomarkers associated with lung-brain interactions have been identified, it is essential to note that the causal relationship between these biomarkers and lung-brain diseases requires further validation and research. Protein expression levels may be upregulated to mitigate disease or injury, or its high expression may be a key factor in disease occurrence and progression, warranting further exploration.

Intervention and treatment targets

The established pathophysiological convergence between pulmonary disorders, particularly chronic respiratory diseases, and neurocognitive sequelae, coupled with their clinical comorbidity prevalence, necessitates the implementation of integrated lifecycle disease management strategies. For instance, multiple studies have confirmed the association between COPD and cognitive impairment, underscoring the need to account for potential brain-related effects when treating lung conditions [203]. The exploration of the lung-brain axis offers novel intervention strategies, particularly in the context of the intricate interplay between neurological and respiratory diseases. Interventions that target the lung-brain axis encompass enhancing lung function, modulating inflammatory responses, and employing neuroprotective agents. Research has demonstrated that certain anti-inflammatory drugs can bolster brain function and reduce inflammation by mitigating lung-related inflammatory responses [204]. Furthermore, the regulation of the lung microbiome is emerging as a pivotal research direction, with evidence suggesting that alterations in the lung microbiome can impact the health of the nervous system [75]. Emerging evidence suggests that pulmonary

microbial homeostasis exerts regulatory control over microglial activation states, potentially mediated by the expansion of LPS-producing Proteobacteria taxa within the lung microbiota niche. From a clinical translational perspective, this tightly coupled cross-kingdom interaction presents two therapeutic modulation strategies: localized microbial engineering through probiotic supplementation targeting Bacteroidetes-Firmicutes equilibrium; pathobiont-selective antibiotic regimens to suppress neurotoxic metabolite production [75]. Notably, acute intermittent hypoxia (AIH) has emerged as a novel neurorehabilitative intervention, which enhances neuroplasticity through hypoxia-inducible factor-mediated pathways. Phase II clinical trials in chronic stroke populations have demonstrated both safety and efficacy of AIH protocols, with concomitant improvements in motor cortex reorganization observed via functional MRI [205]. By implementing these interventions, it is anticipated that future treatments will emerge to alleviate neurological symptoms associated with lung diseases.

Recently, as the exploration into the lung-brain axis has progressed, a multitude of research reports focusing on protein marker intervention targets between the lungs and the brain have come to light. IL-6 has been identified as a potential mediator of ventilation-induced brain injury. Previous studies have suggested a role for IL-6 in the development of delirium, and clinical trials are ongoing to evaluate the effectiveness of IL-6 inhibition on pulmonary and systemic outcomes in patients at risk for VILI [206–208]. A clinical trial (NCT02735707) that is currently underway evaluate the safety and efficacy of an anti-IL-6 receptor antibody in patients with COVID-19, which often involves both respiratory and neurological complications. This trial aims to determine whether targeting IL-6 can mitigate both pulmonary and neurological symptoms. Nevertheless, the role of IL-6 in hyperventilation-induced pathology and neuronal damage suggests that anti-IL-6 strategies could be a double-edged sword [209]. Research by Nicklaus et al. revealed that systemic inhibition of IL-6 significantly mitigated neuronal damage in VILI animal models, particularly in the frontal cortex and hippocampus [209]. Despite the potential benefits, anti-IL-6 interventions may result in adverse effects, including an increased risk of infection, hypertension, and hypersensitivity reactions [210, 211]. Moreover, IL-6 deficiency is associated with heightened oxidative stress and neurodegeneration [212]. At the pulmonary level, the neutralization of IL-6 with anti-IL-6 antibodies may worsen protein leakage in mouse models of VILI due to the protective influence of neutrophil-derived IL-6 on alveolar barrier function [213]. While targeting IL-6 could hold promise for critically ill patients, additional mechanistic data is essential for informed decision-making. The expression of TLR4 in microglia and astrocytes contributes to neuroinflammation triggered by VILI. The TLR4 knockout mouse model may alleviate neuroinflammation resulting from lung-brain interactions in mechanically ventilated mice, suggesting TLR4 as a promising new target for the prevention and treatment of MV-associated neuroinflammation [140]. Additionally, ACE2 modulators are being explored in clinical trials (NCT04467931, NCT04401228, NCT04374110) for their potential to reduce pulmonary and neurological complications in COVID-19, highlighting the therapeutic importance of targeting ACE2. Other biomarkers, such as A-SAA, are being studied for their correlation with cognitive decline in conditions like COPD [214], while HMGB1, a key player in inflammation, is being investigated for its role in neuroinflammation and potential as a therapeutic target. Strategies to inhibit the HMGB1-NLRP3 axis have shown promise in reducing inflammation and cognitive deficits induced by PM2.5 exposure during pregnancy [160].

By focusing on the lung-brain axis, treatments can enhance respiratory function while reducing brain damage, often associated with lung conditions. The identification of biomarkers and therapeutic targets like IL-6 and TLR4 indicates that precision medicine strategies may lead to promising outcome. However, these interventions require careful consideration of their potential risks and benefits to ensure patient safety.

Conclusion and perspectives

This review summarizes possible mechanisms and protein markers such as TLR4, ACE2, A-SAA, HMGB1, TREM2, P2Y1R in the lung-brain axis. In conclusion, the exploration of the lung-brain axis has unveiled a significant connection between respiratory health and neurological function, highlighting the bidirectional impact of these systems on each other. This relationship is crucial for understanding how conditions like stroke, neurodegeneration, and psychiatric disorders can be influenced by the state of one's lung. The identification of protein biomarkers within this axis is a promising development for clinical practice, as they may act as indicators for early diagnosis and treatment, potentially leading to more personalized and effective therapies. Continued research is essential to confirm these biomarkers' roles and to develop strategies that can lessen the negative neurological effects of pulmonary issues. Future studies should aim to establish clear causal links between respiratory and neurological conditions through longitudinal research, investigate the molecular mechanisms that connect lung injury to brain disease, and foster interdisciplinary collaboration across fields like immunology, neurology, and pulmonology.

Despite established evidence from basic and clinical research demonstrating intricate functional crosstalk

between the pulmonary and CNS—two vital organ systems interconnected through neuroimmune-endocrine networks—critical knowledge gaps persist regarding their precise regulatory circuits and molecular underpinnings. Systematic interrogation of these mechanisms is imperative to unravel their pathophysiological codependencies. Recent breakthroughs in neuroengineering tools (e.g., optogenetics, multi-channel neuroelectrophysiological recording) have revolutionized our capacity to dissect vagus nerve-mediated lung-brain reflex pathways with spatiotemporal precision. These methodologies enable in vivo decoding of pulmonary afferent signals and their cortical integration patterns. The lung microbiome-CNS axis is gaining scientific traction. Mechanistic studies reveal that pulmonary dysbiosis disrupts BBB integrity via dual pathways. In contrast to the well-characterized gut-brain axis—where microbial metabolites (SCFAs, 5-hydroxytryptophan precursors) orchestrate multiorgan homeostasis via enteroendocrine-immune-neural circuits—the gut-lung-brain tripartite axis remains underexplored.

Building upon the aforementioned research gaps, future efforts must urgently advance lung-brain axis translational medicine through four key directions: Firstly, longitudinal studies to establish causal links between respiratory and neurological conditions. Secondly, advancing mechanistic investigations into pivotal lung-brain mediators, particularly lung-derived exosomes modulating synaptic plasticity, will provide critical insights for designing neuroprotective agents and precision anti-inflammatory regimens. This foundational research must delineate how pulmonary signals are transduced to neural circuits through molecular, cellular, and systemic pathways. Thirdly, implementing evidence-based clinical pathways requires establishing standardized diagnostic matrices incorporating multi-omics biomarkers. A proposed dual-modality approach combining peripheral inflammatory markers (e.g., serum IL-6) with central neurodegeneration indicators (e.g., CSF p-Tau) could enable stratification of high-risk populations for preemptive therapeutic interventions. Finally, the development of computational models mapping microbial-endocrine-immune networks will facilitate discovery of novel therapeutic nodes. Only through deep integration of mechanistic exploration and clinical practice can we unravel the complexities of lung-brain comorbidities and drive innovative disease management in the era of precision medicine. The convergence of these dimensions—mechanistic deconvolution, clinical translation, and systematic biology modeling—constitutes an essential roadmap for tackling lung-brain comorbidities, ultimately catalyzing a paradigm shift in precision medicine for neuro-respiratory disorders.

Author contributions
S.H., Y.Z., and H.J. conducted the literature search, synthesizing the findings, and drafting the initial manuscript. T.Z., S.L., L.M., D.D., and Y.D. contributed to the critical analysis of the literature. L.H., and S.S. assisted with creating the figures and tables presented in the review. Y.W., and X.C. provided guidance on the overall structure and focus of the review. All authors contributed and approved the final version of the manuscript. All authors warrant that the article has not received prior publication and is not under consideration for publication elsewhere.

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Declarations

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Not Applicable.

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