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Review Article

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The Impact of Pulmonary Disorders on Neurological Health (Lung-Brain Axis)

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
AD, Alzheimer's disease; ApoE4, apolipoprotein E epsilon 4; ARDS, acute respiratory distress syndrome; Aβ, amyloid beta; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CNS,

ABSTRACT

The brain and lungs, vital organs in the body, play essential roles in maintaining overall well-being and survival. These organs interact through complex and sophisticated bi-directional pathways known as the 'lung–brain axis', facilitated by their close proximity and neural connections. Numerous studies have underscored the mediation of the lung-brain axis by inflammatory responses and hypoxia-induced damage, which are pivotal to the progression of both pulmonary and neurological diseases. This review aims to delve into how pulmonary diseases, including acute/chronic airway diseases and pulmonary conditions, can instigate neurological disorders such as stroke, Alzheimer's disease, and Parkinson's disease. Additionally, we highlight the emerging research on the lung microbiome which, drawing parallels between the gut and lungs in terms of microbiome contents, may play a significant role in modulating brain health. Ultimately, this review paves the way for exciting avenues of future research and therapeutics in addressing respiratory and neurological diseases.

Keywords: Lungs; Inflammation; Brain; Lung-brain axis; Pulmonary diseases; Neurodegenerative disease

INTRODUCTION

The lungs are responsible for blood oxygenation by removing carbon dioxide (CO_2) and adding oxygen (O_2) through respiration (1). Oxygen-rich blood travels from the lungs via the pulmonary veins and enters the left side of the heart, driving blood circulation throughout the body, including the brain (2). The brain is an organ with a high demand for O_2 and glucose to support metabolic processes and maintain proper functioning (3). Efficient oxygenated blood transport is crucial for several brain functions that regulate peripheral tissues, including the lungs and heart (4). Overall, the proximity and complex network of blood vessels among the lungs, heart, and brain facilitate the efficient transport of oxygenated blood, contributing to proper body homeostasis.

The lungs and brain play orchestrated roles in regulating CO_2, a by-product of cellular metabolism (5). Elevated CO_2 levels disrupt normal processes and cause life-threatening

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central nervous system; CO2, carbon dioxide; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DEPTOR, DEP Domain Containing MTOR Interacting Protein; ET-1, endothelin-1; GABA, γ-aminobutyric acid; HDM, house dust mites; IPF, idiopathic pulmonary fibrosis; MRI, magnetic resonance imaging; O2, oxygen; PA, Pseudomonas aeruginosa; PAH, pulmonary arterial hypertension; PAI-1, plasminogen activator inhibitor-1; PD, Parkinson's disease; PF, pulmonary fibrosis; PH, pulmonary hypertension; PSNS, parasympathetic nervous system; SCFA, short-chain fatty acids; SNS, sympathetic nervous system; TBI, traumatic brain injury.

Author Contributions

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health problems. Pulmonary disorders, such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis, are associated with elevated CO_2 levels (6,7). The body relies on a system called acid-base regulation to maintain a stable pH balance (2). The brain plays a crucial role in acid-base regulation by monitoring CO_2 levels in the blood through specialized pH-sensitive chemoreceptors and stimulating respiration (8). The respiratory centers in the brain stimulate an increase in the rate and depth of breathing, leading to increased air exchanged in the lungs to return CO_2 levels to normal (9).

Immunological interactions between the lungs and brain play pivotal roles in multiple diseases and contribute to the disease process (10). In pathologic conditions such as asthma, pneumonia, and COPD, lung inflammation and the consequent cytokine production (e.g., IL, TNF-α, TGF-β) may cause brain inflammation and blood-brain barrier (BBB) disruption, illustrating intricate functioning of the lung-brain axis (11,12). Additionally, immune cells activated in diseased lungs can migrate to the brain parenchyma, causing nerve damage, thereby highlighting the intricate crosstalk between these organs at the cellular level (13,14).

The lung contains substantial amounts of microbiome (15,16). Recent advanced microbiome studies have revealed that the resemblance between the lung and gut microbiome suggests potential similarities between the gut-brain and lung-brain axes (17). Considering the significant effects of the gut microbiome on brain functions indirectly through the activated immune cells or directly through the metabolites, the impact of the lung microbiome on the brain is highly anticipated. In this review, we reviewed studies that present the connection of the lung and brain through the microbiome, directly or indirectly. Alterations in microbiome contents could induce inflammation by breaking the homeostatic conditions of the lung (18). Conversely, the inflammatory condition can alter the microbiome milieu, which could increase the production of metabolites that can irritate the brain (16).

All these cells and substances enable interorgan communication and linking neurodegenerative diseases due to chronic lung inflammation (19). Understanding the crosstalk between the lungs and brain opens new avenues for therapeutic interventions that simultaneously target both organs, providing a promising approach for treating various respiratory and neurological conditions. Here we discuss the co-occurrence of pulmonary inflammation and brain dysfunction and elucidate the molecular mechanisms that mediate this lung-brain axis.

ASSOCIATION OF BRAIN DISEASES WITH LUNG DISEASES

The association between lung diseases and brain disorders frequently hinges on inflammatory pathways, as demonstrated by key studies in conditions like COPD and asthma. While the brain maintains a degree of immune privilege, it remains vulnerable to systemic inflammatory responses incited by lung inflammation due to environmental exposures (20).

Acute lung inflammation triggers the recruitment of immune cells, such as neutrophils and eosinophils, which activate lung macrophages (21). These cells potentially lead to further immune responses by producing additional immune cells from the bone marrow through airway granulocyte colony-stimulating factor secretion induced by IL-17 and TNF-α (22). The influx of immune cells into the bloodstream can lead to widespread inflammation throughout the body and render the brain more susceptible to inflammation (**Fig. 1**) (23). For instance,

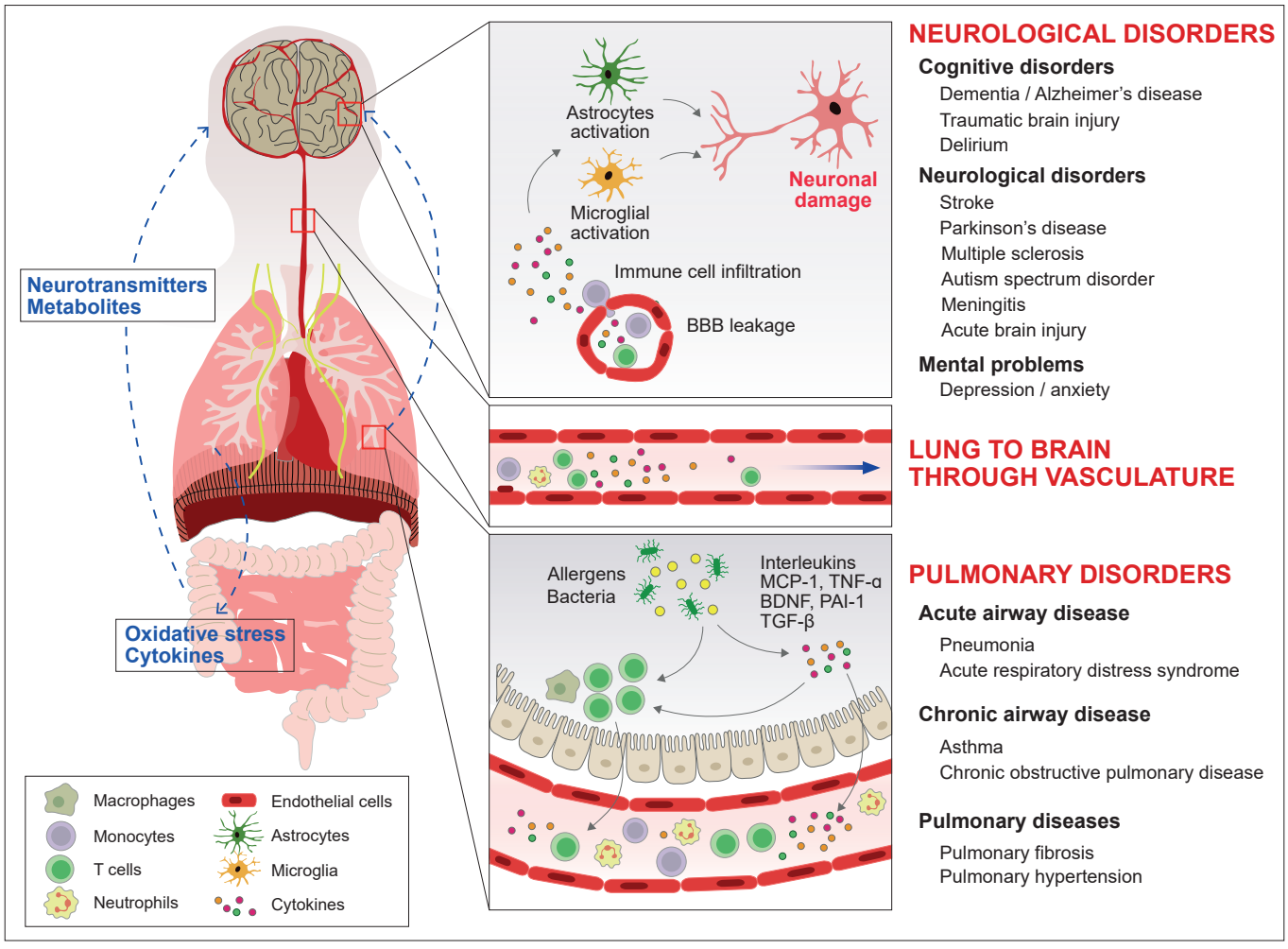

Figure 1. Schematic representation of the lung-brain axis highlighting the intricate relationship between inflammatory lung conditions and various neurological dysfunctions, including mental health disorders. Secreted cytokines and activated immune cells traverse from the lungs to influence the immune milieu within the brain.

the likelihood of stroke development in patients with asthma correlates with the population of these immune cells in the blood, indicating that acute lung inflammation can lead to brain damage (24). Chronic inflammatory lung conditions can impair cognitive functions, a phenomenon underscored by the observed correlation between diminished arterial oxygen levels—a direct consequence of compromised lung function—and cognitive decline (25).

Lung diseases are more likely to co-occur with neurological disorders (**Table 1**) (26-68). Despite a limited understanding of the precise mechanisms and cytokines responsible for these associations, patients with lung diseases exhibiting specific cytokine profiles have been observed to develop neurological disorders, possibly because of the pathogenesis of the lung–brain axis. As lung diseases primarily affect O_2 uptake, a hypoxic condition is considered a potential cause of neurological disorders. Furthermore, the production of proinflammatory cytokines, which varies based on the type of lung disease, can induce systemic inflammation, directly or indirectly affecting brain function or disrupting brain homeostasis. In subsequent sections, we will discuss various lung diseases, including both acute and chronic respiratory conditions, and their relevance to neurological disorders. We will explore their clinical

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Table 1. Table showing the association between various lung diseases and brain disorders

Lung disease	Mechanism/Pathway	Cooccurrence of the neurological disorders in human	References
Common	Hypoxia	Delirium, dementia, Alzheimer's disease, stroke, acute brain injury, hemorrhagic stroke, hypoxic ischemic brain injury, cognitive impairment, epilepsy	(27-32,40-52)
	Systemic inflammation which can cause neuroinflammation	Delirium, dementia, Alzheimer's disease, stroke, acute brain injury, hemorrhagic stroke, hypoxic ischemic brain injury, epilepsy, cognitive impairment, depression and anxiety	(27-30,35,40,41,44-52)
Pneumonia	Disruption of the blood-brain barrier	Delirium, dementia, Alzheimer's disease, stroke	(26-28,40,41,53)
	Secondary or direct infections weaken the immune system through Pneumonia	Delirium	(26,27,53,54)
	Bacterial infectious agent-induced infection	Meningitis	(55)
Acute respiratory distress syndrome	Disruption of the blood-brain barrier	Acute brain injury, hemorrhagic stroke, hypoxic ischemic brain injury, cognitive impairment	(29,56-59)
	Cerebral vascular dysfunction and blood flow changes	Cerebral edema, hemorrhagic stroke, Alzheimer's disease, delirium, stroke, hypoxic ischemic brain injury	(60-62)
	Cytokine storm	Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis	(63)
Asthma	Vascular edema and changes in blood flow to the brain	Cognitive impairment, stroke	(31,32,34,42,43,64)
	Altered synaptic connections	Autism spectrum disorder, cognitive impairment, dementia, Alzheimer's disease	(32-34)
	Release of stress hormones and activation of brain regions involved in the stress response	Stroke	(64)
Chronic obstructive pulmonary disease	Chronic oxidative stress-induced brain structure change	Cognitive impairment, depression and anxietyy, dementia	(35,46-49,65)
Pulmonary fibrosis	Genetic association	Alzheimer's disease	(36)
Pulmonary hypertension	Disruption of the blood-brain barrier	Depression and anxiety, stroke, Alzheimer's disease	(37-39,66-68)

relevance to neurological disorders, followed by a discussion of pre-clinical trials and mouse model studies that offer valuable insights into this intriguing relationship.

Acute airway diseases

Pneumonia

Pneumonia, an inflammatory disease that occurs in the lung air sacs, is caused by infections from bacteria, viruses, fungi, or protozoa. The symptoms of pneumonia include breathing difficulties, cough, chest pain, fever, and fatigue (26). Pneumonia can range in severity from mild to severe and can be particularly dangerous for those who have weakened immune systems, such as infants, young children, and older adults (26).

Pneumonia has been linked to an increased risk of cognitive impairments, including dementia (26). A clinical study has shown a significant association between pneumonia hospitalization and varying degrees of cognitive decline (no decline, minimal decline, and severe decline), highlighting the potential for pneumonia to precipitate neurological disorders (27). Patients with pneumonia who are hospitalized had rates of 22.8% and 10% for minimal and severe rapid cognitive decline, respectively. In contrast, patients with pneumonia who are not hospitalized experienced rates of 19.3% and 4.6% for minimal and severe declines, respectively. In some cases, pneumonia can be caused by ventilation performed to treat central nervous system (CNS) diseases such as acute traumatic brain injury (TBI) or meningitis, leading to secondary cognitive impairment (69,70). A clinical study analyzing patients with bacterial pneumonia revealed diverse impacts on the development of distinct types of dementia, such as Alzheimer's disease (AD), vascular dementia, and unspecified dementia, depending on the types of bacteria (28). In this report, *Haemophilus* had a 3.8-fold higher hazard ratio for AD and *Staphylococcus* had a 5.4-fold higher hazard ratio for vascular dementia in the pneumonia group compared with the non-pneumonia group (28).

In mouse models, airway inoculation of *Pseudomonas aeruginosa* (PA), which is known to induce pneumonia, significantly reduced the field excitatory postsynaptic potential and long-term potentiation of hippocampal neurons (71). These phenomena were blocked by Tau depletion, indicating that the learning and memory impairment induced by PA occurs through Tau production. Another study revealed that variation in the reduction of hippocampal dendrites depends on the administration route of endothelium-derived amyloid caused by PA (72). In this study, compared with other injection routes such as intracerebroventricular and intraperitoneal injection, intratracheal administration of endothelium-derived amyloid showed the most pronounced impact on reducing dendrite spines. These findings emphasize the significant effect of bacterial infection through the airway route on cognitive impairment (72). A study recently demonstrated that PA-induced pulmonary infection also triggers anxiety-like behavior by disrupting the BBB in mice (73). Intratracheal instillation of PA-induced BBB leakage within 24 h leads to increased inflammatory cytokines and immune cell influx into the CNS, thereby resulting in the onset of behavioral disorders. These results are consistent with those of a previous clinical report demonstrating that PA infection induced by intraventricular catheter is associated with nosocomial post-surgical meningitis (74).

One recent study showed that the lungs, as well as the airway, could directly serve as a pathway for bacteria to reach the brain (75). The intratracheal administration of LPS significantly increased the production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α in the lungs with bacterial invasion of the CNS and showed anxiety, spatial memory impairment, and cognitive impairment. Interestingly, a concurrent increase in inflammatory cytokines was observed in the brain hippocampal tissue simultaneously, along with increased microgliosis and astrogliosis, accompanied by amyloid beta (Aβ) accumulation. These phenomena were observed due to decreased BBB integrity caused by lung infection and were reversed by Rapamycin, a mTOR inhibitor (75). While the exact mechanisms remain unclear, the data collectively hint at a strong association between bacterial-induced pneumonia and CNS inflammation-induced neurological disorders.

Acute respiratory distress syndrome (ARDS)

ARDS is a condition characterized by lung inflammation that damages the alveoli and surrounding capillaries, leading to fluid leakage into the alveolar spaces (76). ARDS can be caused by various factors, including infections (such as influenza, bacteria, and coronaviruses), smoke inhalation, vomiting, or injury, and medical procedures (such as surgery) (77). Fluid accumulation in the lungs results in severe respiratory distress, leading to decreased blood oxygenation (76).

Patients with ARDS record a mortality rate of up to 40%, and over 80% of survivors experience secondary neurological disorders—such as cognitive and emotional impairments (78,79), post-traumatic stress disorder (80), depression, and anxiety (81,82)—and acute brain injuries—such as hemorrhagic stroke, ischemic stroke, and cerebral edema (83). The impact and potential hazards associated with ARDS extend beyond the duration of hospitalization. ARDS can exert lasting effects that transcend the acute phase of the illness, manifesting in cognitive impairment and psychiatric disorders (83). A comprehensive study examining ARDS survivors discharged for 1 year revealed that 78% of survivors continued to experience cognitive impairments. However, an overall improvement in health conditions, including mental health and aspects of emotional functioning, was observed after discharge compared with during the hospitalization period (84). In a longitudinal study spanning 5 years, half of the patients with ARDS exhibited persistent psychological distress (85). The duration

of delirium—a common occurrence in patients with ARDS (86)—during the hospital stay emerged as a potent risk factor for long-term cognitive impairment (30).

The inflammasome pathways are strongly associated with ARDS (87). In patients with ARDS, inflammasome-related mRNA such as Caspase-1, IL-1β, and IL-18 were elevated, which was exacerbated by systemic inflammatory response syndrome which might result in neurodegenerative diseases (88). The ventilator-induced injury was alleviated by IL-18 neutralization or genetic depletion of *Il-18* or *Caspase-1* (87). Tetracyclines, a class of antibiotic medication, have been used to alleviate several neurological disorders, including stroke (89), multiple sclerosis (90), and Parkinson's disease (PD) (91), by suppressing caspase-1 activation (92). In a murine ARDS model, inhibiting inflammasome-caspase-1 signaling using tetracycline results in a marked decrease in IL-1β and IL-18 production by alveolar leukocytes (92).

A study using pigs as an alternative mammalian model found that induction of ARDS during mechanical ventilation resulted in perceptible shrinkage of the hippocampal CA1 neurons compared to the hypoxemia-alone group (93). This phenomenon was accompanied by a significant increase in the diagnostic marker of brain injury, S-100 protein (93). Another study using pigs with acute lung injuries showed that increased cytokine production in the lungs of pigs is coupled with memory deficits in continuous behavioral tests (94). These findings demonstrate that inflammation of the lungs leads to cognitive impairment through hippocampal damage as well as increased cytokine production, underscoring the potential of lung injury to induce lasting damage to the brain. However, a comprehensive understanding of the full extent and long-term implications of ARDS-induced brain damage requires further investigation.

Chronic airway disease

Asthma

Asthma is one of the most prevalent respiratory diseases, with >260 million reported cases worldwide in 2019, according to the Global Burden of Disease (95). This chronic respiratory condition is marked by airway inflammation induced by allergens, irritants, and infections, leading to symptoms such as narrowed airways, shortness of breath, and persistent coughing (96). Patients with asthma have been shown to exhibit elevated levels of biomarkers such as neurogranin and α-synuclein, which are strongly associated with cognitive decline (31,32). Furthermore, they have demonstrated reduced axonal integrity, myelination, and neuronal loss, as evidenced by diffusion magnetic resonance imaging (MRI) (33). Although these studies did not rule out the possible influence of medications prescribed for asthma treatment on cognitive function, the findings demonstrate a significant association between asthma and neurological disorders.

House dust mites (HDM) are a major source of allergens that cause chronic airway inflammation including asthma (97,98). Mice treated with HDM displayed upregulation of proinflammatory cytokines and chemoattractant factors in the lungs, which are accompanied by cognitive impairment, depression-like behavior, and synaptic alterations in the cortex and hippocampus (34,99). Notably, the increased cytokines were observed only in the lungs but not in the brain despite the occurrence of a neurological disorder induced by HDM administration (34). These results indicate the possible influence of another factor in the lung-brain axis that surpasses immune cell transmission, necessitating further investigation. Moreover, the treatment of dexamethasone, a commonly used medication for asthma, not only rescued cognitive impairment but also inhibited the expression of cytokines, including IL-4, IL-5, and TNF-α in the asthma mouse model (34,100).

Brain-derived neurotrophic factor (BDNF) is one of the neurotrophin family. It plays a crucial role in regulating various aspects of neurons, including their growth, survival, and synaptic plasticity, affecting physiological and pathological brain functions (101,102). Although reduced BDNF levels have been associated with neurological disorders such as AD, chronic stress, and aging (102,103), its expression is paradoxically raised in airway inflammation such as asthma (104,105) and COPD (35). Mice administered with mixed allergen reproduced asthma phenotypes, and inhibition of BDNF activity or smooth muscle cell-specific BDNF deletion alleviated mixed allergen-induced hyper-responsiveness, airway inflammation, and immune cell infiltration (106). In a chronic asthma mouse model, elevated BDNF expression via airway epithelial cells promotes increased eosinophil survival, contributing to airway inflammation and elevated proinflammatory cytokine expression (107). The precise role of lung-derived BDNF in brain dysfunction—whether exacerbating pathogenesis or offering protection—remains to be elucidated, particularly as it may change during different disease stages or combinations. Further research is essential to understand BDNF's function in the lung-brain axis for a range of pathological conditions.

COPD

COPD is a progressive and chronic respiratory disease characterized by persistent airflow limitation and lung inflammation. Long-term exposure to irritants such as cigarette smoke, occupational exposure, air pollution, and genetic predisposition can contribute to COPD progression (108). COPD is strongly associated with neurodegenerative diseases (such as AD and PD) as they share some risk factors.

The pathogenesis of COPD and cerebral small vessel disease shares similar risk factors such as aging and smoking (109). MRI of cerebral small vessels has revealed small infarctions, lacunae, white matter hyperintensities, enlarged perivascular space, cerebral microbleeds, and brain atrophy in patients with COPD (109). Patients with COPD have a gradual decrease in scores on cognitive tests measuring executive function, attention, and delayed memory and a significant reduction in gray matter density in the prefrontal cortex, limbic system structures, and thalamus (110).

The occurrence of COPD has been reported to be associated with genetic factors linked to neurodegenerative diseases, including apolipoprotein E epsilon 4 (ApoE4) and plasminogen activator inhibitor-1 (PAI-1). ApoE4 is a strong risk factor for late-onset AD, and its neuronal activity is involved in amyloid-β plaque and pTau accumulation in the CNS (111). Mice with ApoE4 deletion in neurons showed significant reduction of AD-induced neurodegeneration, including tauopathy, neuroinflammation, and myelin deficit (112). A study showed that smoking, the most common cause of COPD, elevated the risk of dementia (113). The presence of the ApoE4 allele among patients who smoke showed an increased likelihood of developing dementia and AD, indicating a close association between smoking and AD progression (113). PAI-1 is a major risk factor for stroke. PAI-1 inhibits fibrinolysis, which contributes to ischemic stroke by blocking blood flow in the brain (114). Patients with COPD have a high risk of stroke, especially after exacerbation (115), and exhibit high levels of PAI-1 (116). Although physiological PAI-1 expression in the brain parenchyma of astrocytes can reduce neuronal cell death in stroke, PAI-1 overexpression increases the infarct volume in thrombosis models (114).

Studies that directly test the cognitive functions of mice with COPD are absent. However, the cognitive and memory deficits observed in the mouse model for cerebral small vessel disease

and the risk factors shared with COPD strongly indicate the need for research on cognitive tests in COPD mice.

Pulmonary diseases

Pulmonary fibrosis (PF)

PF is a condition characterized by the progressive scarring, stiffening, and thickening of lung tissues (117). The specific cause often remains elusive. However, prolonged exposure to environmental toxins, infections, and autoimmune conditions are recognized as potential contributors to PF development (117). Several signal transduction pathways, including TGF-β, WNT, and connective tissue growth factor, are linked to fibrosis pathophysiology, and these pathways converge to govern the stimulation and maintenance of the myofibroblast phenotype in patients with idiopathic PF (118). Among these signaling pathways, TGF-β signaling is the most targeted pathway in clinical trials (119,120).

Several studies have indicated a possible link between PF and neurological disorders such as AD, PD, and overall cognitive decline (36,121,122). Moreover, recent genome-wide association studies, which have omitted the imaging results of patients with neurological disorders, have discovered risk variants for idiopathic pulmonary fibrosis (IPF). These variants, located on chromosomes 8 and 17, have a strong correlation with brain structure changes as detected by phenotypes based on imaging. In particular, the expression of the DEP Domain Containing MTOR Interacting Protein (DEPTOR) gene variant on chromosome 8, a known inhibitor of mTOR signaling, has been linked to cortical thinning in the anterior cingulate cortex (123). However, the exact mechanisms through which DEPTOR variants contribute to IPF and the potential influence of lung function on these brain changes remain unclear and warrant further investigation.

Pirfenidone is a drug approved by the United States Food and Drug Administration for IPF, which targets the TGF-β signaling by reducing the expression of ligands and receptors (124). Pirfenidone not only improves declined lung function but also recovers brain injury and functional deficit following TBI. Oral pirfenidone administration ameliorated inflammation, neurodegeneration, and clinical parameters in TBI-induced rats, and these effects may be attributed to its broad anti-inflammatory properties (125). In contrast, another study showed that the TGF-β/Smad2/3 pathway is beneficial for AD pathology. In some studies, TGF-β1 was found to clear Aβ, the main contributor to AD, by activating microglia while reducing inflammation-mediated radical species (126,127). WNT signaling, specifically the canonical pathway that leads to the accumulation of β-catenin—which is known to induce impairment of epithelial cells by promoting senescence and increasing fibrotic markers is noteworthy (128). In IPF, there is a noted increase in the mRNA levels of Wnt1, 7b, and 10b in lung tissue, coinciding with a heightened accumulation of β-catenin protein (129). Additionally, WNT5A is found to be upregulated in bronchoalveolar lavage fluid extracellular vesicles (130). Conversely, other studies revealed that activation of Wnt/β-catenin signaling has been observed to be advantageous in restoring neuronal function and the integrity of the BBB in AD and PD (131,132).

These discrepancies surrounding the TGF-β and WNT signaling pathways highlight the complex effects on neuropathology. Further research is necessary to fully comprehend its role in neurological effects and its function as a linker in the lung-brain axis.

Pulmonary hypertension (PH)

Several factors, including diseases and environmental elements such as pulmonary artery

clotting, smoking, and asbestos exposure, can cause PH and increase the risk of developing PH (133). The symptoms of PH include shortness of breath, fatigue, and an increase in neuropsychiatric symptoms such as cognitive dysfunction, autonomic deficits, depression, and anxiety (37,38). According to the World Health Organization, PH is classified into 5 groups based on its cause: pulmonary arterial hypertension (PAH), left-sided heart disease, lung disease and/or hypoxia, and pulmonary artery obstructions of the lungs (134).

The relationship between PH progression and various neurological symptoms is associated with a reduction in the volume of brain regions. A recent study using high-resolution MRI revealed that the gray matter in patients with PH significantly decreased with tissue damage (135). As the reduction in gray matter is the hallmark of brain tissue damage, the diminished brain areas observed in patients with PH directly affect cognitive, autonomic, and mood functions. Moreover, the effects of PH on neurological function may be due to low O_2 levels and impaired gas exchange. Cerebral oxygenation and CO_2 reactivity are impaired in patients with PH and worsen with exercise (136). Therefore, considering the anatomical and pathophysiological alterations in the lungs and brain, continuous positive airway pressure or long-term O_2 therapy could be encouraged (137).

Endothelin-1 (ET-1) has been recognized to be crucial in PH development and progression (138). In the lung tissue of patients with PH, a significant increase was observed in the mRNA and protein levels of ET-1, which was concomitantly observed with medial thickness of the pulmonary artery and intimal fibrosis (138). Subsequent studies have revealed that ET-1 is expressed in the endothelium, smooth muscle, fibroblast, and macrophages due to cytokines, hypoxia, and hormones (139). Therefore, pharmacological intervention against ET-1 and ET-1 receptor interaction, especially bosentan therapy, has been used to overcome PAH pathogenesis (140,141). In the CNS, ET-1 can aggravate neuropathological conditions by increasing BBB permeability and glial activation, leading to leukocyte infiltration into the brain parenchyma (39). For instance, in a PH-induced rat model using Sugen5416 or monocrotaline, damaged white matter with microvascular alteration was observed (142), and hypothalamic inflammation with enhanced sympathetic drive was reported (143). Understanding the biological mechanisms by which PH may lead to neurological disorders remains incomplete, warranting further research to explore the effects of PAH-induced hypoxia, cognitive decline, and cytokine elevation, with an emphasis on targeting ET-1.

Impact of lung microbiome on the brain

The human body is not solely composed of human cells but is harbored with 10 to 100 trillions of microbiota (144). Several organs, such as the gut, lungs, mouth, and skin, have microbiota and the microbiome. The amount of microbiome presents in the most well-studied organ, the gut, is assumed to be approximately 10^{14} (145). Several studies have investigated the close relationship between the gut microbiome and CNS. For instance, the gut microbiome can lead to several neurological disorders, such as multiple sclerosis, AD, autism spectrum disorder, and PD (146-148). Furthermore, the microbiome can even influence human behavior, including social behavior and emotions, by producing metabolites and peptides. The correlation between gut metabolites or hormones and the CNS is extensively described in a previous review (149).

Unlike the gut, the lungs have long been regarded as sterile organs until it was reported by Hilty in 2010 using culture-independent techniques (150). Consequently, direct studies on the quantities of the lung microbiome are lacking. Nevertheless, this amount can be

estimated from previous mouse studies by multiplying the weight-fold difference between mice and humans. The lungs obtained from mice in the specific pathogen-free condition have >10^7 cells/g, and the weight of the mice lung is approximately 0.1–0.15 g, whereas that of the human lung is 0.7–1.3 kg (151). Thus, the estimated microbiome in the human lungs is approximately 10^{11} cells under naïve conditions (152).

The lung microbiota composition is a diverse community of microorganisms such as bacteria, viruses, and fungi (15,16). Hilty reported well on the composition of bacteria in the airways. The authors found that the bacterial composition in the left upper lobe of the lung, detected via 16S rRNA polymerase chain reaction, is distinctive from the nasal and throat microbiota, with a higher abundance of *Haemophilus* species (150). The abundant bacteria phyla are *Firmicutes* and *Bacteroidetes,* similar to the gut microbiome (17). Despite the low microbiome content in the lungs, several studies have shown that microbiome dysbiosis in the lungs could contribute to the development of lung diseases such as lung cancer or PF as well as lung inflammatory diseases (153-155). Recently, Hosang *et al.* found a strong association between lung microbiome changes and CNS inflammation (156). The authors demonstrated that alterations in the lung microbiome can influence the susceptibility to autoimmune diseases of the CNS (156). Considering the meta-analysis data showing that antibiotics-induced gut dysbiosis can affect brain function and psychiatric conditions (157), investigating the correlation between neurological conditions and the microbiome in the lungs becomes a subject worthy of future exploration.

Lung microbiome research related to brain diseases such as AD and PD is lacking. In the gut, proinflammatory bacteria such as *Fusobacterium nucleatum*, *Prevotella intermediam*, and *Bacteroidetes* are prominently detected (158,159). In contrast some bacteria such as *Firmicutes* and *Bifidobacterium* are less frequently detected in older people or patients with AD (159,160). Considering the meta-analysis data showing that antibiotics-induced gut dysbiosis can affect brain function and psychiatric conditions (157), it would be worth investigating the potential lung-brain axis as an extension of the well-studied gut-brain axis.

DISCUSSION

Neurodegenerative diseases are increasingly recognized as a significant global health concern. Multiple factors, such as genetics, external pathogens, and infections, can induce these diseases, leading to secondary damage to neurons and the manifestation of debilitating symptoms over time. Considering the interconnected nature of the CNS with various organs, inflammatory conditions originating in peripheral tissues are often closely associated with neurodegenerative diseases. Consequently, research into these interconnections, often referred to as “axes,” holds promise in treating neurodegenerative diseases. The concept of interorgan communication, including the gut-brain and lung-brain axes, has gained significant attention in the biology field. This review highlights current insights into the lung-brain axis, with a focus on how lung inflammation can lead to brain disorders.

The lung and gut are organs that interface with the external environment and possess innate and adaptive immune systems. Based on single-cell ribonucleic acid sequencing, human lungs comprise 38% immune cells, encompassing B cells (0.8%), plasma cells (0.3%), CD4 T cells (3.6%), CD8 T cells (5.0%), NK cells (2.9%), various dendritic cell types (ranging from 0.1% to 1.6%), alveolar macrophages (11.7%), different monocyte subtypes (ranging

from 1.5% to 4.8%), and mast cells (1.1%) (161). Similarly, the adult human intestine harbors 9% B cells, 2.9% CD4 T cells, 2.3% CD8 T cells, 0.5% NK cells, 0.7% dendritic cells, 1.6% macrophages, 0.3% monocytes, and 0.1% mast cells (162). In comparison to the gut, the lung exhibits a higher proportion of CD8 T cells and a lower abundance of B cells, with a heightened myeloid cell population. Although immune cell populations differ between the lung and gut, both organs share similarities in immune responses. They feature mucosal immune systems that combat external pathogens (163). They can develop tertiary lymphoid organs in response to chronic inflammation, identified as Peyer's patches in the gut and bronchial-associated lymphoid tissues in the lungs (164). Moreover, the lung and gut produce immunoglobulin A via B cells (165) and harbor resident memory B cells, which are advantageous for long-term protection and swift responses to familiar Ags (166). The resemblance between the immune systems of the lung and gut indicates that a study of the lung-brain axis can draw upon concepts and unveil mechanisms from the gut-brain axis.

Lung microbiome dysbiosis occurs within inflammatory conditions. Analysis of coronavirus disease 2019 (COVID-19) patients' microbiome has revealed that potential pathogens, such as *Acinetobacter baumannii* and *Candida* spp., are more prevalent than in patients with non-COVID-19 pneumonia (167). In lung cancer research, specific microbiomes have been proposed as biomarkers for predicting metastasis (168). The oropharyngeal, lung, and gut microbiome, via the esophagus and trachea, can spread to other organs, and metabolites from the microbiome, along with activated immune cells and secreted cytokines, can affect other organs (169). Currently, there is no direct evidence that lung microbiota affect brain function as gut microbiota do; for instance, *Bacteroides*, *Parabacteroides*, and *Escherichia* species in the gut produce γ-aminobutyric acid (GABA), which is crucial for brain development and cognitive functions (170,171). The similarities between the lung and gut microbiome strongly show that investigating the lung-brain axis through the lung microbiota could be productive.

The brain plays a pivotal role in regulating various organ systems, including the gastrointestinal tract and lungs, by sending efferent signals. The autonomic nervous system, comprising the sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS) branches, along with the phrenic nerve, is integral to this regulation (**Fig. 2**) (172). The SNS and PSNS modulate the lungs' smooth muscle and bronchiole activity, facilitating breathing (173,174). The phrenic nerve specifically controls the diaphragm, generating the negative pressure required for inhalation. Moreover, the Bötzinger complex within the ventral respiratory group acts as a respiratory pacemaker, coordinating the respiratory pattern to adapt to the body's metabolic demands and varying conditions (175,176). Therefore, the brain's regulation of respiration is crucial for oxygenation and carbon dioxide removal, which is key to maintaining homeostasis. This regulatory process also influences the immune response, as changes in breathing can affect blood flow and the interaction between immune cells and the blood vessel endothelium. Neurological disorders and brain injuries can alter these processes and lead to an increased release of cytokines and catecholamines, which subsequently cause lung inflammation (177). The interconnectedness of lung and brain disease is highly complex due to their simultaneous interaction with each other, and further research should consider this with care.

Several studies indicate the effects of anti-inflammatory drugs used to treat lung inflammation on neurological diseases. Anti-inflammatory drugs, such as dexamethasone (178), tetracycline (92), and nonsteroidal anti-inflammatory drugs like ibuprofen, naproxen, and aspirin (179), reduce the risk of neurological disorders in patients with respiratory disease. The detailed mechanism remains unclear; however, this indicates the potential

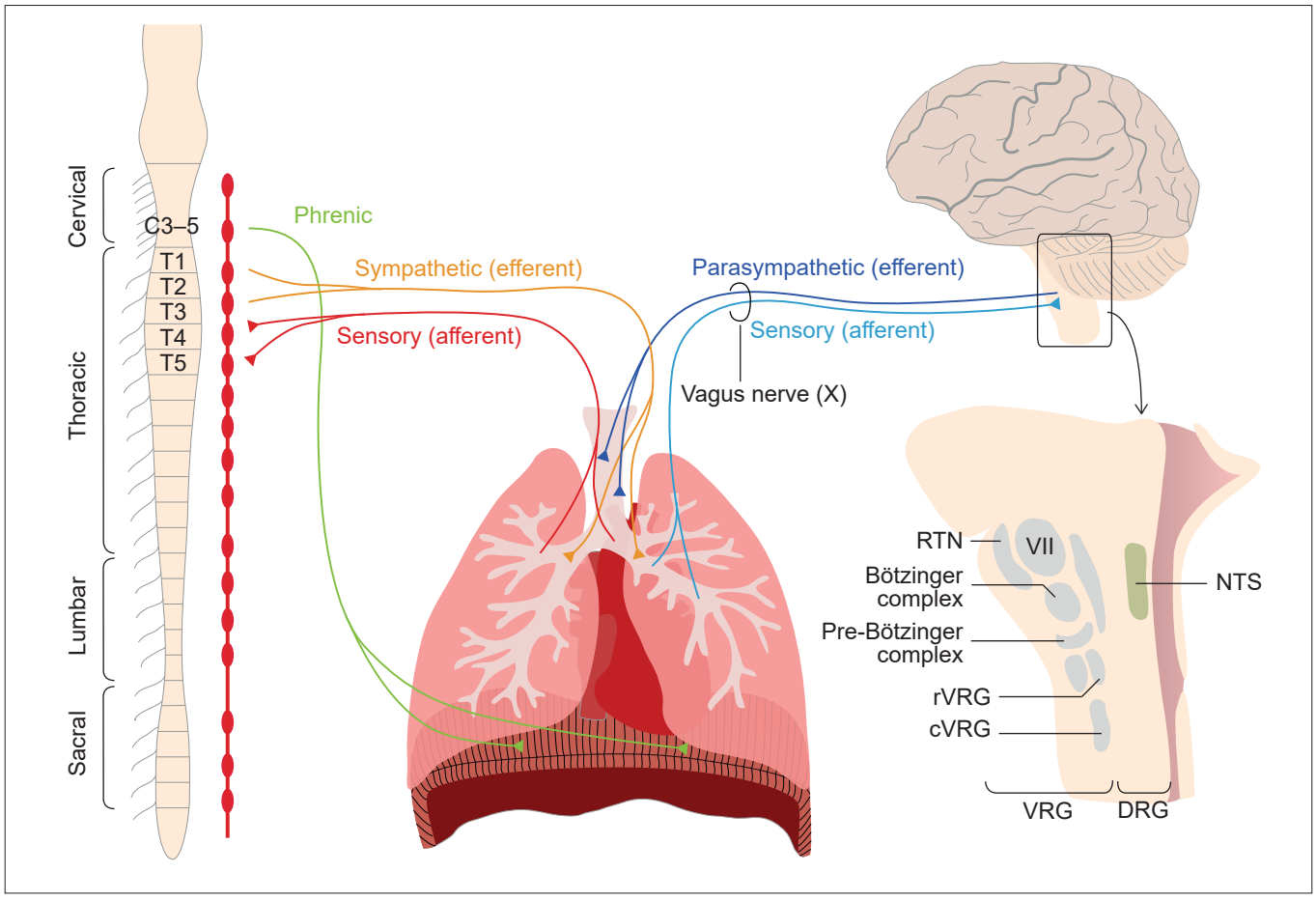

Figure 2. Schematic summary showing the anatomical connections between the brain and lungs. The brainstem governs three distinct pathways to control respiratory functions: the SNS, PSNS, and phrenic nerve. Through the intermediolateral cell column and sympathetic chain ganglia, the SNS relaxes the bronchioles and stimulates muscle relaxation. Primarily via the vagus nerve, the PSNS causes bronchoconstriction through acetylcholine release. The phrenic nerves from the cervical spine enable diaphragm contraction, generating negative pressure in the thoracic cavity for inhalation.
PRG, pontine respiratory group; RTN, retrotrapezoid nucleus; NTS, nucleus of the solitary tract; rVRG, rostral ventral respiratory group; cVRG, caudal ventral respiratory group; DRG, dorsal respiratory group.

for drugs originally intended for the lung also to have a beneficial effect on the brain or vice versa. Furthermore, given the influence of the microbiome on brain function and the development of diseases, it may be worthwhile to explore the effects of pro-/anti-biotic treatments on the lungs to investigate their potential neurological effects.

Inflammatory processes spread from the lungs to other organs through cytokines and activated immune cells, indicating that para-aminobenzoic acid, GABA, or short-chain fatty acids (SCFA) produced by the gut microbiota, or the cytokines themselves, may regulate lung and brain functions (180-182). It is well-documented that exposure to carbon and ozone, or viral infections leading to lung inflammation, can influence the gut microbiome composition via oxidative stress, resulting in increased SCFA production by gut microbes (183,184). Consequently, the influence of the lung-brain axis may extend to include possible mediation by the gut during inflammation.

In summary, the proximity of the lungs and brain in the anatomical structure allows lung-derived cytokines to reach the brain and potentially alter brain homeostasis. The substantial

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co-occurrence of neurological disorders in individuals with respiratory diseases, the essential need for cognitive care in this patient population, and recent findings related to the lung microbiome strongly underscores the intricate interplay between the lungs and brain in physiological and pathological conditions. Thus, the careful evaluation of the cognitive function of patients with lung diseases is highly recommended. Furthermore, understanding and targeting the lung-brain axis presents novel therapeutic opportunities for lung and neurological diseases. Although growing evidence supports the lung-brain axis, further research is required to fully elucidate the complex mechanisms and establish the clinical implications of this interorgan communication.

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