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Association between influenza A virus and SARS-CoV-2 infections and mood disorders

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A R T I C L E I N F O

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A B S T R A C T

Acute respiratory infections (ARIs) are among the most common infectious diseases encountered in clinical practice, with approximately 70–80 % of cases attributed to viral pathogens. Among these, seasonal influenza A virus (IAV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) persistently pose public health threats due to their high genetic variability, strong transmissibility and significant pathogenicity. Recently, accumulating evidence has suggested that these viruses can not only cause typical respiratory symptoms but also affect the central nervous system (CNS) through neuroinvasion and inflammation, thereby increasing the risk of developing or exacerbating mood disorders such as anxiety and depression. This makes them significant complications affecting patient prognosis and public health resources.

This comorbidity between infection and mood disorders exhibits a complex bidirectional relationship. Beyond viral CNS involvement, individuals with mood disorders appear to be more susceptible to IAV and SARS-CoV-2 infections and may be at greater risk of developing severe illness. This comorbidity not only significantly impairs quality of life and clinical outcomes but also places a substantial burden on healthcare systems and public health infrastructure.

Therefore, this review aims to summarize the clinical characteristics of IAV and SARS-CoV-2 infections comorbid with mood disorders. Based on existing evidence, we innovatively distinguish two mechanism pathways: an externally driven pathway dominated by psychological stress (acute stress), and an internal biological pathway represented by immune dysregulation and gut microbiota imbalance. This classification will provide a theoretical framework and research direction for accurately identifying acute stress responses and persistent neuropathology, as well as for future basic research and targeted intervention strategies.

1. Introduction

Acute viral respiratory infections remain a major global public health challenge, with profound impacts on human life, socioeconomic functioning and daily life. These viruses not only inflict substantial morbidity and mortality, but also impose significant strain on healthcare resources, diminish productivity and cause societal disruption owing to their high transmissibility. Among this disease spectrums, IAV and SARS-CoV-2 infections stand out for their particular significance.

IAV, due to its propensity for antigenic drift and shift, easily causes seasonal influenza outbreaks in populations, with up to 1 billion confirmed cases worldwide each year (World Health, 2015), resulting in 5–8 million severe cases and approximately 300,000 deaths (Krammer et al., 2018). Additionally, certain subtypes have historically triggered large-scale deadly pandemics (e.g., the 1918–1919 H1N1 influenza pandemic resulted in over 40 million deaths (Short et al., 2018), the

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2009 novel H1N1 IAV outbreak caused at least 123,000 deaths (Simonsen et al., 2013)). On the other hand, SARS-CoV-2 triggered a global pandemic within a short period, resulting in over 7 million deaths (World Health, 2024). It is also noteworthy that the current co-circulation of IAV and SARS-CoV-2 significantly increases the risk of co-infection. Evidence from both clinical and pre-clinical studies strongly supports the heightened severity of such cases. Clinical studies have further confirmed that such co-infection markedly aggravates disease severity: compared with SARS-CoV-2 infection alone, co-infected patients exhibit a 4.14-fold higher risk of requiring mechanical ventilation and a 2.35-fold higher risk of death (Swets et al., 2022). Consistent with these clinical observations, preclinical models indicate that viral co-infection elicits synergistic effects, marked by increased viral replication and amplified inflammatory responses, ultimately resulting in more severe pulmonary pathology (Wong et al., 2023). Therefore, such co-infection not only markedly elevates the risks of severe illness and mortality but also imposes an immediate and substantial disease burden on families and society.

However, the threat of the virus did not dissipate with the end of the acute phase. Although the world has entered the post-pandemic era and the acute threat of COVID-19 has largely subsided, the lingering problem of long COVID has emerged as a significant chronic disease burden. Long COVID is defined by the World Health Organization (WHO) as a condition characterized by a range of symptoms that emerge within three months of SARS-CoV-2 infection, persist for at least two months and cannot be explained by other diagnoses (Soriano et al., 2022). Recent large-scale meta-analyses estimate that the pooled global prevalence of long COVID approaches 36 % among individuals with a history of SARS-CoV-2 infection (Hou et al., 2025). Its clinical manifestations are highly heterogeneous, including persistent fatigue, shortness of breath, cognitive impairment, and autonomic dysfunction (Nalbandian et al., 2021), leading to substantial and long-lasting impairment of quality of life and work capacity. In addition, while influenza has traditionally been regarded as a typical acute self-limiting disease, growing evidence indicates that influenza infection is also associated with a variety of long-term health risks (Nguyen et al., 2025; Ouranos et al., 2024). Notably, a recent comparative study reported that individuals hospitalized for IAV had a higher likelihood of requiring medical care for several neurologic disorders—including migraine, epilepsy, neuropathy, movement disorders, and dementia—within the subsequent year compared with those hospitalized for COVID-19 (de Havenon et al., 2024). These findings underscore that both viruses can produce substantial and distinct long-term neuropathological consequences.

It is noteworthy that these viruses have brought far more than a physical health crisis, exerting a profound and far-reaching impact on mental health that should not be overlooked. This burden stems from two distinct but intertwined sources: widespread psychosocial stressors related to public health interventions and the direct consequences of viral infection. Amid stressors such as isolation, economic uncertainty and widespread social disruption, the prevalence of mood disorders has increased markedly. For instance, Taquet et al. found that during the COVID-19 pandemic, owing largely to these widespread psychosocial stressors and public health interventions, global prevalence of major depression and anxiety rose by 27.6 % and 25.6 %, respectively (Taquet et al., 2021). Among these mood disorders, anxiety and depressive disorders are particularly prominent. Within this context, the bidirectional relationship between IAV/SARS-CoV-2 infections and mood disorders warrants attention. Patients with pre-existing mood disorders are more vulnerable to viral invasion and suffer poorer outcomes: their relative risk of SARS-CoV-2 infection increases by approximately 67 % (Liu et al., 2021), their incidence of lower respiratory tract infections (including influenza) rises by 32 % (Elpers et al., 2023) and they face significantly elevated risks of severe disease and mortality following infection (Yang et al., 2020). Moreover, viral infections are potent triggers of mood disorders, contributing to the onset or exacerbation (Bornand et al., 2016; Liu et al., 2021; World Health, 2022). For example, Delia et al. reported a positive correlation between prior influenza infection and subsequent depression risk, with greater infection frequency corresponding to higher risk (Bornand et al., 2016).

The consequences of this bidirectional effect are substantial and well-documented. Anxiety and depression are major contributors to the global disease burden, causing functional impairment, chronic comorbidities and elevated suicide rates (GBD 2019 Diseases and Injuries Collaborators, 2020). Combined with IAV or SARS-CoV-2 infection, they create a vicious cycle that significantly heightens the risks of severe disease, mortality and long-term socioeconomic costs (COVID-19 Mental Disorders Collaborators, 2021; Yang et al., 2020). Given the ongoing evolution and circulation of IAV and SARS-CoV-2, the prevalence and burden of anxiety and depression may further escalate.

Accordingly, elucidating the mechanisms underlying infection-related mood disorders is of great scientific importance. However, a major challenge is to clarify the independent roles and mechanisms of psychosocial stressors and viral infection in the development of mood disorders. Given this, this review aims to systematically map the clinical associations of anxiety and depression following IAV and SARS-CoV-2 infection and to critically evaluate the convergent neuroimmune mechanisms underlying these mood disorders. Furthermore, by distinguishing infection-induced biological effects from psychosocial stress-related factors, this review delineates the current limitations in existing evidence and outlines directions for future research on causal mechanisms.

2. Clinical characteristics of IAV/SARS-CoV-2 and mood disorder comorbidity

Mood disorders—primarily encompassing anxiety and depressive disorders—are traditionally defined by core clinical symptoms such as persistent low mood or irritability, anhedonia, fatigue, sleep or appetite disturbances, impaired concentration and suicidal ideation in severe cases. However, in the context of IAV and SARS-CoV-2 infections, mood-related symptoms frequently diverge from these classical Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) presentations. These infection-associated manifestations may arise through two distinct mechanisms: the acute psychosocial stress triggered by the infection event and the persistent biological effects caused by viral pathophysiology. The coexistence of these drivers gives rise to a biphasic temporal pattern, with mood symptoms emerging both during the acute infection period and again after viral clearance, forming a trajectory that differs markedly from conventional mood disorders (Murata et al., 2022). A critical challenge is that symptoms arising from these distinct pathways are often not differentiated in clinical practice, which obscures interpretation and compromises therapeutic precision. Accordingly, this section seeks to delineate and characterize the clinical manifestations primarily driven by each mechanism by clarifying their temporal profiles and underlying causal pathways.

2.1. Acute stress-driven

During acute viral infections or major public health crises, individuals commonly exhibit a spectrum of nonspecific stress-related emotional symptoms, including anxiety, mood instability, insomnia and fatigue. In more severe cases, these disturbances may progress to social withdrawal and heightened suicide risk (Brooks et al., 2020; Hossain et al., 2020; Zhu et al., 2023). These symptoms directly arise from external stressors associated with the 'infection event', including quarantine, illness-related stigma and financial strain, rather than from the virus's direct neurobiological effects. Key evidence supporting this conclusion derives from both the widespread prevalence of these symptoms and the gradual psychological adaptation of individuals to circumstances. In a large-scale longitudinal observational study conducted in the UK (Fancourt et al., 2021), levels of depression and anxiety peaked during the initial phase of the first national lockdown and declined markedly within 2–5 weeks, even as restrictions remained at their strictest. Importantly, this trend occurred in both infected and uninfected populations, indicating that shared psychosocial circumstances, rather than direct viral effects, were the predominant determinants of these symptoms. The resolution of symptoms following the reduction of stressors is consistent with psychoneuroendocrine adaptation processes.

Therefore, a clear distinction between self-limiting, stress-related symptoms and virus-induced, pathology-driven manifestations is essential to prevent clinical misattribution and to accurately characterize virus-specific biological impairments.

2.2. Persistent neuropathology

Compared with acute stress–induced symptoms, post-infection mood disorders are characterized by delayed onset or persistent core features. For instance, approximately 25.7 % of patients with COVID-19 continued to experience mood-related symptoms three months after nucleic acid test negativity (Li et al., 2024), depressive symptoms have been reported to emerge 30–150 days following IAV infection (Bornand et al., 2016) and epidemiological studies have revealed a delayed peak in depression incidence that closely coincides with the immune activation cycle after respiratory infections (Jung et al., 2021). These observations strongly suggest that the underlying drivers of symptoms transition from external psychosocial stressors to sustained internal biological processes.

In terms of clinical symptoms, these virus infection-associated mood disorders are distinct from the core symptoms of depressive disorders defined by the DSM-5. They exhibit a distinct spectrum of symptoms, including persistent fatigue, sleep disorders, reduced appetite, social withdrawal, diminished interest in daily activities and cognitive decline (Okusaga et al., 2011). Among these, post-exertional malaise (PEM) represents a hallmark qualitative feature, characterized by a functional collapse lasting 12–48 h after even minimal physical or cognitive exertion. This phenomenon strongly points to an underlying disturbance in physiological energy metabolism rather than simple psychological fatigue (Baraniuk, 2025). PET studies in patients with long COVID offer mechanistic insights, revealing reduced cerebral metabolic activity and microglial activation within limbic structures such as the amygdala and hippocampus (Hosp et al., 2021). A clinical translational study using TSPO PET tracers further demonstrated significantly elevated TSPO VT in the ventral and dorsal striatum among long COVID patients with persistent depressive or cognitive symptoms, supporting the presence of ongoing neuroinflammatory activity in these individuals (Braga et al., 2023). Collectively, these clinical findings indicate that post-viral mood- and fatigue-related symptoms encompass not only subjective emotional disturbances but also measurable alterations in brain function detectable through advanced neuroimaging. In addition, this neuroinflammatory activation correlates with structural alterations, evidenced by a marked reduction in hippocampal spine density following IAV infection (Hosseini et al., 2018), collectively implicating aberrant synaptic pruning as a potential contributor to mood-related symptoms. Functional magnetic resonance imaging (fMRI) further reveals disrupted connectivity between the limbic system and the prefrontal cortex (Douaud et al., 2022), providing a functional basis for mood dysregulation in post-infection patients. Furthermore, SARS-CoV-2 infection exhibits unique persistent neuropathological features: even months after the clearance of infectious virus, the olfactory bulb (OB) and olfactory epithelium (OE) still exhibit ongoing activation of myeloid and T cells, elevated pro-inflammatory cytokines and sustained interferon signaling (Frere et al., 2022). This prolonged local immune response has been associated with long-term behavioral abnormalities, including anxiety- and depression-like symptoms, underscoring its relevance to persistent post-COVID presentations. Furthermore, persistent neuroinflammation may result from continued systemic inflammatory signaling and increased immune-cell infiltration into the central nervous system. Elevated plasma levels of neurofilament light chain (NfL), a marker of neuronal injury, and glial fibrillary acidic protein (GFAP), a marker of astrocyte activation, have been detected in both hospitalized and non-hospitalized PASC patients (Hanson et al., 2022), providing molecular evidence of compromised blood–brain barrier (BBB) integrity. Disruption of the BBB establishes a chronic route for circulating inflammatory mediators and immune cells to enter the CNS, thereby perpetuating microglial activation.

3. Mechanistic studies of IAV/SARS-CoV-2 and mood disorder comorbidity

The pathogenesis of anxiety and depression is still unclear, especially in the context of viral infection, where bidirectional mechanisms become even more complex and research remains limited. Combined with the aforementioned clinical features, the development of mood disorders is mainly driven by the synergistic interaction between psychological stress and immune response. In view of this, the following section delineates how psychological stress contributes to the development of mood disorders through neuroendocrine–immune interactions, and how infection-induced immune cascades mediate the link between IAV/SARS-CoV-2 infections and mood disorders. Furthermore, since IAV and SARS-CoV-2 infections can significantly disrupt gut microbiota homeostasis (Scalzo et al., 2025), thereby altering peripheral immunity and neurotransmitter levels and given that these processes are also modulated by psychological stress (Gao et al., 2024; Smail et al., 2025), the gut–brain axis may represent a key pathway mediating the bidirectional relationship between viral infection and mood disorders (Fig. 1).

3.1. Psychological stress

Both SARS-CoV-2 and IAV trigger stress responses originating from two interrelated domains: psychosocial stressors, including economic hardship and illness-related stigma, and biological stress arising directly from viral infection. Notably, psychosocial stress activates limbic neural circuits that relay "top-down" signals to the hypothalamic–pituitary–adrenal (HPA) axis (Seo et al., 2019). The convergence of these stress pathways establishes a self-perpetuating psychoneuroimmunological cycle, characterized by hyperactivation of the HPA axis and sympathetic nervous system (SNS), ultimately resulting in elevated cortisol levels (James et al., 2023; Knezevic et al., 2023; Weissman and Mendes, 2021).

In the short term, the activation of HPA axis suppresses excessive inflammation. However, under chronic stress, sustained hypercortisolism not only amplifies inflammatory responses, but also inhibits hippocampal neurogenesis and downregulates brain-derived neurotrophic factor (BDNF) expression (Li et al., 2019). These alterations disrupt the hippocampal-prefrontal-amygdala circuit (Vaisvaser et al., 2013), thereby inducing or exacerbating mood disorders such as anxiety and depression.

However, immune disorders and psychological dysfunction induced by chronic stress persist after the stressor is eliminated (Cohen and Herbert, 1996), driven by epigenetic mechanisms. Evidence suggests that chronic stress induces hypermethylation within promoter regions of key genes such as BDNF, effectively silencing their transcriptional activity (Ikegame et al., 2013) This enduring molecular imprint underlies long-term neuroplasticity deficits and heightened vulnerability of emotion-regulating neural circuits. Current understanding of HPA axis in post-infectious mood disorders remains limited. These conditions are often presumed to be characterized by hypercortisolemia. However, accumulating evidence indicates that in some mild COVID-19 cases or in individuals under chronic stress, HPA axis exhaustion may instead lead to hypocortisolemia (Yavropoulou et al., 2022). This hypo-reactive phenotype appears closely associated with PEM and persistent fatigue, which are hallmark yet mechanistically elusive features of long COVID.

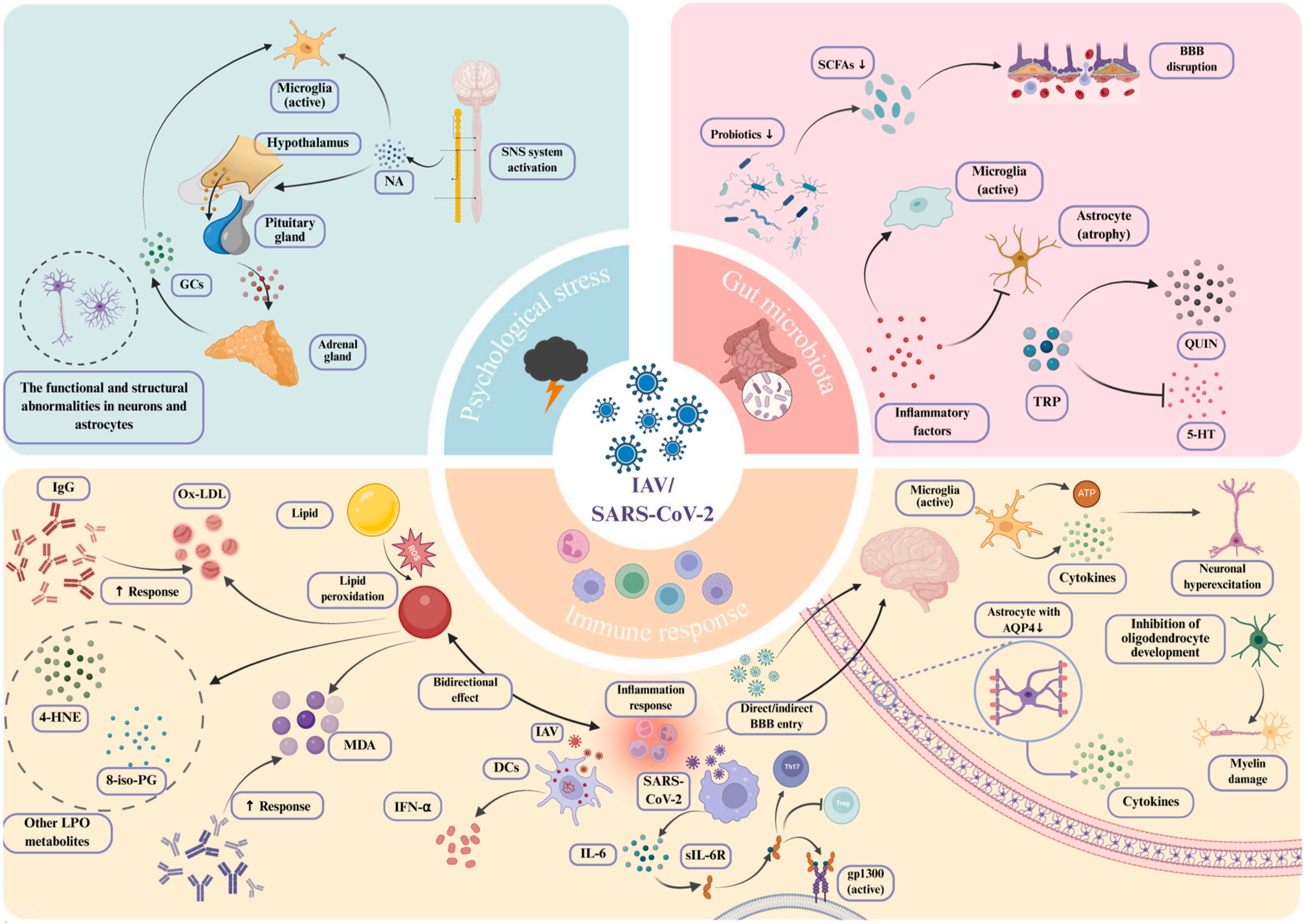

Fig. 1. Schematic overview of mechanistic studies explaining the pathogenesis of comorbidity between IAV/SARS-CoV-2 infections and mood disorders. (1) Psychological stress: Activation of the HPA axis and sympathetic nervous system (SNS) leads to increased levels of glucocorticoids (GCs) and noradrenaline (NA). Chronic overactivation of the HPA axis and SNS disrupts immune regulatory feedback and alters limbic neurocircuitry, thereby increasing susceptibility to mood disorders. (2) Immune response (three sequential processes): (i) Lipid peroxidation: Virus- or cytokine-induced reactive oxygen species (ROS) attack membrane lipids, generating MDA, oxidized low-density lipoprotein (OxLDL), and other lipid peroxidation (LPO) metabolites that may form complexes with immunoglobulins (IgG/IgM), amplifying oxidative damage and triggering neuroinflammation. (ii) Inflammatory response: Activated immune cells (e.g., dendritic cells [DCs] and macrophages) release IFN-α, IL-6 and other cytokines that induce systemic inflammation and increase BBB permeability. (iii) Neuroinflammation: Cytokines or signaling molecules cross the BBB to activate microglia, astrocytes, and oligodendrocytes. Dysregulation of glial cell function may contribute to the onset of mood disorders. (3) Gut microbiota: Viral infection and systemic inflammation disrupt the gut microbiome, depleting beneficial metabolites such as SCFAs and TRP-derived 5-HT precursors, while increasing harmful metabolites.

Future research should therefore aim to delineate these two opposing HPA axis states, namely hyperreactivity and hyporeactivity, since failure to distinguish between them will hinder the development of targeted, mechanism-based interventions.

3.2. Immune response

3.2.1. Lipid peroxidation

Much of the regulation of immune function relies on redox mechanisms, with antioxidant defenses playing a key role (Morris et al., 2022). Lipid peroxidation is an important manifestation of oxidative stress, and lipid peroxidation plays an important role in the pathogenesis of anxiety and depression. In a systematic review and meta-analysis, it was found that patients with depression had elevated levels of lipid peroxidation markers, such as malondialdehyde (MDA), 4-hydroxynonenal (4-HNE) and 8-isoprostanes (8-iso-PG), and that reverse cholesterol transport (RCT) and related fat-soluble antioxidant levels decreased (Almulla et al., 2023). In addition, there is an increase in IgG response to oxidized low-density lipoprotein (ox-LDL) and an increase in IgM immunoreactivity to MDA, suggesting that lipid peroxidation induces activation of the immune system (Almulla et al., 2023), and that over-activation of the immune system increases the release of pro-inflammatory factors, leading to neuroinflammation (Wang et al., 2023). Immune inflammation is closely related to the occurrence of anxiety and depression; on the other hand, scholars have found that the accumulation of lipid peroxidation may trigger the occurrence of anxiety and depression by altering neurotransmitter levels and neuroplasticity in the brain (Wang et al., 2023).

Furthermore, oxidative stress has been found to play an important role in viral infections such as IAV and SARS-CoV. In a clinical investigation, it was found that the level of oxidative stress in COVID-19 patients was significantly higher than that in healthy controls, and the level of lipid peroxidation (LPO) was positively correlated with the severity of COVID-19 (Martín-Fernández et al., 2021). In addition, IAV also causes lipid peroxidation, leading to cell death during infection (Huang et al., 2023). Therefore, lipid peroxidation not only triggers neuroinflammation, but also affects neurotransmitter levels and neuroplasticity.

Although current evidence demonstrates an association between LPO markers and both viral infections and mood disorders, most studies are cross-sectional, leaving the causal direction unresolved. It remains unclear whether elevated LPO markers act as upstream drivers of pathology or as downstream consequences of inflammatory processes. Clarifying this temporal relationship is essential for determining whether lipid peroxidation constitutes a therapeutic target or merely serves as a disease biomarker. Future research should therefore adopt prospective longitudinal designs to delineate the precise temporal dynamics of LPO markers within disease progression.

3.2.2. Inflammatory response

Elevated levels of inflammation are strongly associated with an increased risk of new-onset mood disorders (Cui et al., 2024). For respiratory viral infections causing mood disorders, it has been suggested that dysregulated immune responses underlie virus-driven symptoms of anxiety and depression (Seyedmirzaei et al., 2023). Specifically, IAV with SARS-CoV-2 triggers the activation of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs), by infecting host cells, thereby initiating inflammatory signaling pathways and causing the release of pro-inflammatory cytokines. However, IAV and SARS-CoV-2 have immune escape ability, which can escape or delay the triggering of intracellular innate immune responses associated with type I and type III IFNs, preventing the body from initiating an adaptive immune response in a timely manner. To control viral infections, the innate immune system compensates for the lack of adaptive immunity by boosting its response (Nguyen et al., 2024; Sette and Crotty, 2021), which may cause elevated plasma levels of cytokines such as CXCL10, IL-6, and IL-8 (Aid et al., 2020; Dunning et al., 2018; Lucas et al., 2020), and a high number of neutrophils in the blood and lungs of end-stage patients (Li et al., 2020; Nguyen et al., 2024; Schurink et al., 2020). This immune imbalance can trigger a “cytokine storm” that can exacerbate the disease.

However, this immune imbalance is not limited to the lungs or peripheral organs, but may also act directly or indirectly on the CNS through a variety of mechanisms, thereby increasing the risk of mood disorders. During influenza virus infection, IFN-α is involved in the immune response (Okusaga et al., 2011). This cytokine induces resistance to glucocorticoids by altering the translocation and DNA-binding activity of the glucocorticoid receptor (Pace et al., 2007), thereby exacerbating the immune-inflammatory response and, particularly within the hippocampus, increasing the risk of depression (Gisslinger et al., 1993). Furthermore, serum IL-6 levels have been shown to be significantly elevated in patients with post-acute sequelae of SARS-CoV-2 infection (PASC), which encompasses mood disorders such as anxiety and depression (Bierle et al., 2021; Durstenfeld et al., 2022). Due to the limited presence of IL-6 receptors in the CNS, the inflammatory effects of IL-6 are primarily mediated via trans-signaling pathways. Peripheral IL-6 binds to soluble IL-6 receptors (sIL-6R), forming a complex that interacts with cells expressing the gp130 co-receptor, which is widely distributed in the CNS (Villar-Fincheira et al., 2021). Additionally, this IL-6 complex promotes differentiation of T helper 17 (Th17) cells and suppresses regulatory T (Treg) cells, resulting in a T-cell imbalance that is also implicated in the pathophysiology of depression (Kappelmann et al., 2021). Cytokines have also been reported to cause depletion of the TPR, ultimately leading to a reduction in 5-HT and thus increasing the risk of mood disorders (Dursun et al., 2001; Okusaga et al., 2011).

Although the “inflammation hypothesis” outlines a coherent pathway linking infection to mood disorders, its clinical applicability is limited by substantial heterogeneity. Evidence shows that systemic elevations in pro-inflammatory cytokines are neither universal among patients with mood disorders (Felger and Lotrich, 2013) nor observed across all post-viral patient groups (Talla et al., 2023). These findings highlight the need for translational research to incorporate clinical subtyping in order to differentiate inflammation-driven from non–inflammation-driven presentations, thereby informing the appropriate use of targeted anti-inflammatory or immunomodulatory therapies.

3.2.3. Neuroinflammation

Viruses act as key triggers, utilizing diverse pathways, including neurotropic dissemination and peripheral immune cell trafficking, to gain access to the CNS compartment. This action modulates CNS homeostasis, resulting in localized neuroinflammation and/or distal effects mediated by the neuroimmune axis. As neurotropic viruses, SARS-CoV-2 enters the CNS mainly through the nasal mucosa, sieve plate and olfactory bulb or through retrograde axonal transport (Gupta et al., 2020; Lechien et al., 2020; Spinato et al., 2020); neurotropic influenza viruses reach the brain via the neurological pathway, mainly through retrograde axonal transport to the first vagus and trigeminal nerves (Bohmwald et al., 2018). These viruses are capable of breaching the BBB and directly triggering neuroinflammatory responses. Notably, beyond these shared pathways, recent mechanistic work has identified a SARS-CoV-2–specific mechanism: the viral envelope (E) protein, even in the absence of replicating virus, induces depression-like behaviors and dysosmia in mice by activating the Toll-like receptor 2 (TLR2) pathway, leading to microglial activation and neuroinflammation. This provides a molecular basis for how non-infectious viral components can generate persistent post-acute neuropsychiatric symptoms in COVID-19 (Su et al., 2023). Moreover, their dysregulation of glial cell activity represents an additional key contributor to neuroinflammation. Although non-neurotropic respiratory viruses—such as influenza virus subtypes H1N1 and H3N2—cannot directly invade the CNS, they can activate glial cells via peripheral immune responses, thereby inducing inflammation and damage within the nervous system (Bohmwald et al., 2018; Hosseini et al., 2018). Therefore, viral perturbation of glial cells—whether through direct CNS invasion or indirect peripheral immune activation—represents a key mechanism by which neuroinflammation contributes to the development of anxiety- and depression-related mood disorders.

Microglia, as the primary immune effector cells of the CNS, are responsible for clearing necrotic cellular debris, pathogens, and pruning synapses to maintain CNS homeostasis. Furthermore, neuronal communication with microglia has an important role in depression-associated mood disorders, such as the CX3CL1-CX3CR1 axis. Cerebrospinal fluid CX3CL1 levels are elevated in patients with SARS-CoV-2 and IAV infections (Zhang et al., 2024), and CX3CL1 promotes monocyte migration to the CNS (Mohammadhosayni et al., 2021), and activation of the CX3CR1 receptor via binding to the microglia (Liu et al., 2020; Lyons et al., 2009). Activated microglia can induce host neuronal hyperexcitability and psychomotor behavioral disorders by increasing ATP concentration and promoting cytokine release. It has been reported that when the cerebellar anterior lobe is over-infiltrated with cytokines, mice may develop depressive behaviors (Yamamoto et al., 2019); in addition, it may cause synaptic over-pruning or even synaptic loss (Hosseini et al., 2021), which is also associated with the development of anxiety and depression. However, this mechanism exhibits heterogeneity: specific viral subtypes like IAV H1N1 reduces the expression of CX3CL1 in the hippocampus of mice (Zhang et al., 2024), and the reduction or deletion of CX3CL1 also leads to impaired neuroglial regulation and cognitive function (Zhan et al., 2014), which causes the development of mood disorders.

Astrocytes play a key role in synapse formation, neurotransmitter metabolism and maintenance of ionic homeostasis. However, viral infection–induced mood disorders reveal a paradoxical pattern in which structural responses coexist with functional impairment. For example, astrocytic proliferation, reflected by elevated expression of GFAP, has been observed in patients with COVID-19 (Yang et al., 2021). Nevertheless, this structural alteration likely represents a state of impaired astrocytic function. Mechanistically, inflammatory signaling can activate matrix metalloproteinases (MMPs), which degrade components of the extracellular matrix and consequently disrupt the anchoring of aquaporin-4 (AQP4) (Yue and Hoi, 2023). This disruption is further supported by evidence showing reduced co-expression of AQP4 in astrocytes in the brains of COVID-19 patients (Rosu et al., 2022). AQP4 is a water channel mainly distributed at the ends of astrocytes. Its dysfunction not only impairs K+ buffering capacity and synaptic transmission (Kong et al., 2014), but also impair the metabolic clearance function of the glymphatic system, leading to accumulation of neurometabolic byproducts and inflammatory mediators. These changes further impair neurotrophic support and hinder neuroplasticity within key mood-regulating regions such as the hippocampus and prefrontal cortex (Kamali et al., 2012). Furthermore, the effects of IAV infection on astrocytes were subtype-specific: H7N9 infection significantly up-regulated the expression of pro-inflammatory factors, such as TNF-α, IL-6, IL-8, CCL2, and IFN-β, and some of these cytokines were more highly expressed in astrocytes than in neurons (Ng et al., 2018); H5N1 activated the network of antiviral genes in astrocytes, which in turn H5N1 activates the astrocyte-associated antiviral gene network and promotes the expression of various cytokines and chemokines, and significantly up-regulates the expression of synaptic transmission-associated genes, such as P2RY13, GABRA1 and HRH2 (Lin et al., 2015), and this differentiation may provide clues to the diversified mechanisms of the interactions between different viruses and anxiety and depression.

Oligodendrocytes play an important role in neuronal axon support and protection, nerve conduction and metabolic regulation. IAV and SARS-CoV-2 disrupt oligodendrocyte organization and impair their physiological functions. Relevant studies have shown that after injection of the influenza virulence protein PB1-F2 into the dentate gyrus of mouse hippocampus, PB1-F2 binds to Nogo to inhibit oligodendrocyte development, disrupting myelin formation, neural development, and synaptic connectivity, and inducing anxiety- and depression-like behaviors in mice (Wang et al., 2024). In the context of SARS-CoV-2 infection, a reduced number of oligodendrocytes has been observed in COVID-19 patients compared to healthy individuals. This may result from microglia directly suppressing neurogenesis by secreting cytokines such as IL-6 (Monje et al., 2003), indirectly stimulating neurotoxic astrocytic reactivity to kill oligodendrocytes via the release of toxic lipids (Guttenplan et al., 2021) and by reducing neuronal expression of brain-derived neurotrophic factor (eg., BDNF) (Monje and Iwasaki, 2022). Consequently, repair of myelin structural damage induced by such injuries critically depends on the differentiation and regeneration of oligodendrocyte precursor cells (OPCs) (Skaper, 2019). However, a critical therapeutic bottleneck exists in the mechanisms of myelin injury: the persistent inflammatory environment following viral sequelae not only directly kills oligodendrocytes via reactive nitrogen species (RNS), but more importantly, it continuously disrupts OPCs differentiation and myelin regeneration (Yao et al., 2010). This failure of regeneration is central to the persistence of post-viral sequelae, yet our understanding of the molecular mechanisms by which chronic inflammatory signals precisely regulate OPCs differentiation trajectories remains extremely limited.

3.3. Gut microbiota

Both IAV and SARS-CoV-2 infections can cause gastrointestinal symptoms such as diarrhea, suggesting that these viruses can cause intestinal flora disruption through intestinal infection. Studies have confirmed that SARS-CoV-2 maintains active infection and sustained transcriptional activity in the gastrointestinal tract of patients who lack the manifestation of gastrointestinal symptoms and after respiratory symptoms subside (Zuo et al., 2021). Clinical studies on PASC further support this link, demonstrating that gut microbiome dysbiosis, marked by depletion of beneficial commensal bacteria, correlates strongly with systemic immune activation and the severity of somatic and neuropsychiatric symptoms, including anxiety and depression (Scalzo et al., 2025; Smail et al., 2025). These findings suggest that dysbiosis may function not only as a biomarker but also as a potential pathological contributor to long-term COVID-19–related outcomes. Consistent with this, broader evidences show a significant correlation between mood disorders such as anxiety and depression and gut microbiota disturbances (Skonieczna-Żydecka et al., 2018). However, given the insufficient research evidence of virus-flora-neuropsychiatric symptoms interaction, the underlying mechanisms still need to be explored in depth.

From the perspective of microbial ecology, the ecological dysregulation of the intestinal flora induced by IAV and SARS-CoV-2 infections is not only manifested by the abnormal proliferation of opportunistic pathogens, but also by the significant depletion of beneficial commensal bacteria (e.g., Bifidobacterium, Lactobacillus) with anti-inflammatory and metabolic regulatory functions (Ou et al., 2023; Zuo et al., 2020). This ecological imbalance leads to increased levels of inflammatory cytokines and decreased levels of short-chain fatty acids (SCFAs) (e.g., butyrate) (Sencio et al., 2020; Zeng and Tang, 2024). In IAV infection, this dysbiosis is particularly relevant to the “gut–lung axis”, where SCFA depletion critically impairs pulmonary antiviral and antibacterial immunity, increasing susceptibility to secondary bacterial infections (e.g., pneumococcal superinfection) and shaping long-term inflammatory outcomes that are more closely linked to respiratory pathology rather than direct neuroinvasion (Ou et al., 2023). SCFAs themselves exert broad anti-inflammatory effects (Li et al., 2018) and are critical for maintaining both intestinal and BBB integrity (Braniste et al., 2014; Kelly et al., 2015). Beyond these barrier-protective and immunomodulatory functions, a growing body of evidence indicates that gut microbiota–derived metabolites can directly enhance host defenses against SARS-CoV-2 by shaping T cell activity and innate immune responses (Brown et al., 2022; Nagata et al., 2023). Disruption of these metabolite–mediated pathways following viral infection may therefore contribute to sustained immune dysregulation and downstream neuroinflammation (Nagata et al., 2023). For example, butyrate restores BBB function in germ-free (GF) mice by enhancing tight junction protein expression and ameliorating neuronal defects (Stilling et al., 2016). When the intestinal barrier is compromised, bacterial translocation and metabolite leakage into systemic circulation can induce persistent low-grade inflammation and disrupt the regulation of the HPA axis, resulting in elevated cortisol levels (Zeng and Tang, 2024). However, in chronic post-viral syndromes such as PASC, HPA axis hyporesponsiveness and reduced cortisol levels are more common. This indicates that the mechanisms connecting gut microbiota dysbiosis to HPA axis dysfunction may be heterogeneous. In this context, SCFA deficiency may contribute to post-viral mood disorders by impairing the negative feedback regulation of the HPA axis.

At the molecular level, intestinal flora may mediate the development of anxiety and depression through the “gut-immunity-brain axis” (Cryan and Dinan, 2012). On the one hand, dysbiosis and inflammatory microenvironment activate the kynurenine (KYN) metabolic pathway (Fan et al., 2021; Zhang et al., 2020). Following viral infection, sustained elevation of the antiviral cytokine interferon-γ (IFN-γ) induces the expression of indoleamine 2,3-dioxygenase (IDO) (Dantzer et al., 2008). Moreover, higher IFN-γ levels have been consistently linked to greater severity of depressive symptoms (Lai et al., 2023). This shifts IDO-mediated tryptophan (TRP) metabolism toward the neurotoxic metabolite quinolinic acid (QUIN) and reduce 5-hydroxytryptophan (5-HT) synthesis, which would increase the risk of mood disorders in patients. However, the IFN-γ–driven TRP depletion hypothesis faces a major limitation: given that more than 95 % of 5-HT is synthesized in the gut (Császár and Bókkon, 2022), it remains unclear whether post-viral gut dysbiosis contributes to mood disorders predominantly through central TRP depletion or by directly disrupting intestinal 5-HT production and signaling, with downstream effects transmitted to the brain via the vagus nerve. This uncertainty represents an important unresolved gap in current mechanistic understanding.

On the other hand, some inflammatory factors, toxic substances or neuroleptic respiratory viruses break through the BBB and enter the brain, which not only causes elevated levels of cytokines such as IL-1β and IL-6 and activation of NLRP3 inflammasomes in neuronal cells (Pan et al., 2014), but also activates and atrophies microglial and astrocytes respectively (Woodburn et al., 2021). Furthermore, the gut microbiota maintains normal function of microglia by regulating their maturation and morphology (Erny et al., 2015), whereas the absence of flora leads to abnormal microglia development (Erny et al., 2015), and SCFAs partially reverse such pathological changes (Erny et al., 2015). Although the broad regulatory effects of SCFAs on microglial morphology and function have been demonstrated experimentally, most existing evidence comes from GF mouse models, which have limited ecological validity. A major bottleneck in current research is the lack of molecular evidence showing how specific non-SCFA metabolites, produced by microbial strains that are selectively reduced rather than completely absent after viral infection, precisely modulate microglial activation. This limitation restricts the development of targeted and mechanism-based microbiota interventions. These changes in glial cells affect brain networks related to learning, memory and emotion regulation, ultimately inducing symptoms of depression or anxiety (Woodburn et al., 2021).

4. Discussion and conclusion

This review systematically examines the potential pathological mechanisms underlying IAV- and SARS-CoV-2–induced mood disorders across multiple dimensions, including psychological stress, immune responses and the gut microbiota–brain axis. Building upon these mechanistic insights, we additionally propose key priorities for future translational research and clinical applications.

First, translational research should prioritize interventions aimed at correcting glial dysfunction. In light of the paradoxical pattern in which astrocytic structural proliferation coexists with impaired functional clearance after viral infection, future studies need to focus on strategies that restore glial homeostasis. This includes developing inhibitors that disrupt the interaction between the IAV PB1-F2 protein and Nogo to reduce myelin damage, and exploring strategies to modulate AQP4 expression and anchoring to restore neurovascular integrity and brain-lymphatic clearance. Concurrently, chronic microglial neurotoxicity should be addressed by modulating their inflammatory activity and preventing direct oligodendrocyte injury mediated by factors such as RNS and TNF-α.

Second, kynurenine monooxygenase (KMO) inhibitors are regarded as key targets for modulating the gut microbiota–KYN pathway. Sustained neuroinflammation following viral infection activates this pathway, leading to the accumulation of the upstream neurotoxic metabolite 3-hydroxykynurenine (3-HK) (Collier et al., 2021; Hughes et al., 2022), a critical precursor for generating the potent downstream neurotoxin QUIN (Wang et al., 2025). Beyond inducing neuroinflammation through oxidative stress and free radical production, 3-HK can act synergistically with QUIN to exacerbate neuronal injury and apoptosis (Guidetti and Schwarcz, 1999). Inhibiting KMO reduces the formation of both 3-HK and QUIN, diverting metabolic flux toward the neuroprotective KYN pathway and thereby mitigating neuroinflammation while providing neuronal protection. Future research should focus on exploring how gut metabolites can precisely modulate KMO activity to achieve targeted intervention from peripheral to central systems.

Finally, when aiming for precise attribution and therapeutic target validation in mood disorders following viral infection, researchers face a critical methodological challenge: acute stress stemming from various external factors constitutes the primary confounding variable, obscuring the distinction between stress-driven and pathology-driven symptoms. To effectively overcome these "multiple confounding factors" in clinical research, leveraging approaches such as Mendelian randomization or prospective cohort studies that incorporate detailed time-series data is imperative. This robust methodology allows for the precise delineation of the temporal sequence and causal relationships underlying viral biological consequences, thus providing a solid foundation for developing targeted interventions.

Taken together, IAV and SARS-CoV-2 represent major public health threats at seasonal epidemic and global pandemic scales, respectively. Both exhibit high transmissibility and exert sustained population-level impacts over prolonged periods. Beyond their immediate physical effects, these viruses also confer substantial long-term health risks, most notably the onset or worsening of anxiety- and depression-related mood disorders. Clinically, mood disorder symptoms follow a bimodal temporal pattern, appearing both during the acute phase of infection and again after nucleic acid test negativity. This pattern indicates that two distinct mechanisms are involved: acute psychosocial stress and persistent neuropathological processes. Therefore, recognizing this heterogeneity is essential. Future research and clinical practice should adopt refined staging and etiological attribution, clearly distinguishing psychosocial-driven from viropathology-driven symptoms. Such differentiation will be crucial for developing stage-appropriate diagnostic and therapeutic strategies capable of addressing the complex neuropsychiatric sequelae associated with respiratory viral infections.

CRediT authorship contribution statement

Yanling Xiang: Writing – original draft. **Wanqi Wang:** Writing – review & editing. **Jinyi Zhu:** Writing – review & editing. **Zexing Chen:** Writing – review & editing. **Wanyi Huang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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