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Review Article

The gut-brain axis in long COVID

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ABSTRACT

Long COVID-19, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), is a complex multisystem disorder characterized by persistent neurological, gastrointestinal, and psychological symptoms. Emerging evidence suggests that dysfunction of the gut-brain axis plays an important role in the development and persistence of Long COVID manifestations. SARS-CoV-2 infection may cause long-term alterations in gut microbiota composition, resulting in dysbiosis, impaired intestinal barrier integrity, and chronic immune activation. Reduced abundance of beneficial microorganisms and decreased production of microbial metabolites, particularly short-chain fatty acids, may disrupt intestinal homeostasis and neuroimmune communication. Increased intestinal permeability and inflammatory signaling can contribute to systemic inflammation, vagus nerve dysfunction, and neuroinflammatory processes associated with cognitive impairment, fatigue, mood disturbances, and gastrointestinal symptoms. Therapeutic strategies targeting the gut-brain axis, including probiotics, prebiotics, postbiotics, fecal microbiota transplantation, and vagus nerve stimulation, represent promising approaches for symptom management. Further research is required to clarify their efficacy and establish personalized interventions. Improved understanding of gut-brain interactions in Long COVID may support the discovery of new biomarkers and targeted therapies for post-infectious disorders.

Submitted: 07 April 2026
Revised: 14 June 2026
Accepted: 22 June 2026
Published: 29 June 2026

ISSN: 2449-8955

KEYWORDS: SARS-CoV-2; Long COVID; Post-acute sequelae; Gut-brain axis

DOI: http://dx.doi.org/10.5281/zenodo.21445507

INTRODUCTION

Long COVID, also referred to as post-acute sequelae of SARS-CoV-2 infection (PASC), is a multisystem condition characterized by persistent symptoms that may continue for weeks or months after the acute phase of COVID-19. Common manifestations include fatigue, cognitive dysfunction, gastrointestinal (GI) complaints, sleep disturbances, anxiety, and depression. Increasing evidence suggests that many of these symptoms are associated with impaired communication along the gut-brain axis (GBA), a bidirectional network integrating neural, immune, endocrine, and metabolic signaling between the gastrointestinal tract and the central nervous system.

SARS-CoV-2 infection has been shown to induce long-lasting alterations in the intestinal microbiota, accompanied by immune dysregulation and persistent low-grade inflammation. These changes may disrupt gut barrier integrity, alter microbial metabolite production, and impair gut-brain communication, thereby contributing to both neurological and gastrointestinal symptoms observed in Long COVID.

One of the hallmarks of Long COVID is persistent gut dysbiosis, characterized by a reduced abundance of beneficial bacteria, including *Faecalibacterium prausnitzii*, *Bifidobacterium* spp., and *Akkermansia muciniphila*, together with an expansion of pro-inflammatory microorganisms. This microbial imbalance decreases the production of short-chain fatty acids (SCFAs), particularly butyrate, which plays a key role in

maintaining intestinal barrier function, regulating immune responses, and supporting neuroimmune communication. The severity of gut dysbiosis has been associated with the persistence of both gastrointestinal and neurological manifestations following SARS-CoV-2 infection [1,2].

Microbial alterations may also increase intestinal permeability, allowing bacterial products such as lipopolysaccharides (LPS) to enter the systemic circulation and sustain chronic inflammatory responses. Elevated levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), have been linked to neuroinflammation, autonomic dysfunction, and impaired neurotransmitter homeostasis [3,4]. In addition, disruption of vagus nerve signaling may compromise gastrointestinal motility and weaken anti-inflammatory reflexes, further amplifying both digestive and cognitive symptoms. These interconnected mechanisms resemble those observed in post-infectious irritable bowel syndrome, suggesting that persistent gut-brain axis dysfunction represents an important component of Long COVID pathophysiology [5].

NEUROLOGICAL DISORDERS AND GUT-BRAIN AXIS DYSFUNCTION IN LONG COVID

Neurological manifestations represent some of the most frequent and debilitating complications of Long COVID, often persisting for months or even years after resolution of the acute infection. Patients commonly experience cognitive impairment, referred to as “brain fog,” characterized by reduced concentration, impaired memory, slowed information processing, and mental fatigue. Other frequently reported symptoms include headaches, sleep disturbances, anxiety, depression, dizziness, autonomic dysfunction, and neuropathic pain. Although the exact mechanisms underlying these neurological abnormalities remain incompletely understood, increasing evidence indicates that persistent dysfunction of the gut-brain axis (GBA) may contribute significantly to their development and progression [5,6].

The gut microbiota plays a critical role in maintaining neurological homeostasis through regulation of immune responses, production of neuroactive metabolites, and modulation of the vagus nerve pathway. In Long COVID, persistent alterations in microbial composition may result in reduced abundance of beneficial SCFA-producing bacteria, including *Faecalibacterium prausnitzii* and other commensal species involved in maintaining intestinal and immune balance. Reduced availability of short-chain fatty acids (SCFAs), particularly butyrate, may impair intestinal barrier function and disrupt microglial regulation within the central nervous system. Dysregulated microglial activation promotes chronic neuroinflammation, oxidative stress, and impaired synaptic plasticity, mechanisms that may contribute to persistent cognitive dysfunction [6,7].

Systemic inflammation induced by SARS-CoV-2 infection represents another important factor involved in neurological complications. Increased levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferons, may compromise blood-brain barrier integrity and facilitate neuroimmune activation. Persistent inflammatory signaling can interfere with neurotransmitter metabolism, affecting serotonin, dopamine, and γ-aminobutyric acid (GABA) pathways, which may contribute to mood disorders, anxiety, sleep disruption, and impaired cognition observed in Long COVID patients [8] (Figure 1).

Mitochondrial dysfunction and oxidative stress have also been proposed as central mechanisms contributing to prolonged neurological symptoms. Impaired mitochondrial energy metabolism may reduce neuronal resilience and contribute to chronic fatigue, reduced cognitive performance, and exercise intolerance. Furthermore, prolonged neuroinflammation and mitochondrial impairment have been implicated in pathways associated with neurodegenerative diseases, raising concerns that persistent immune activation after SARS-CoV-2 infection could increase vulnerability to age-related neurological disorders, although long-term clinical evidence remains limited [9].

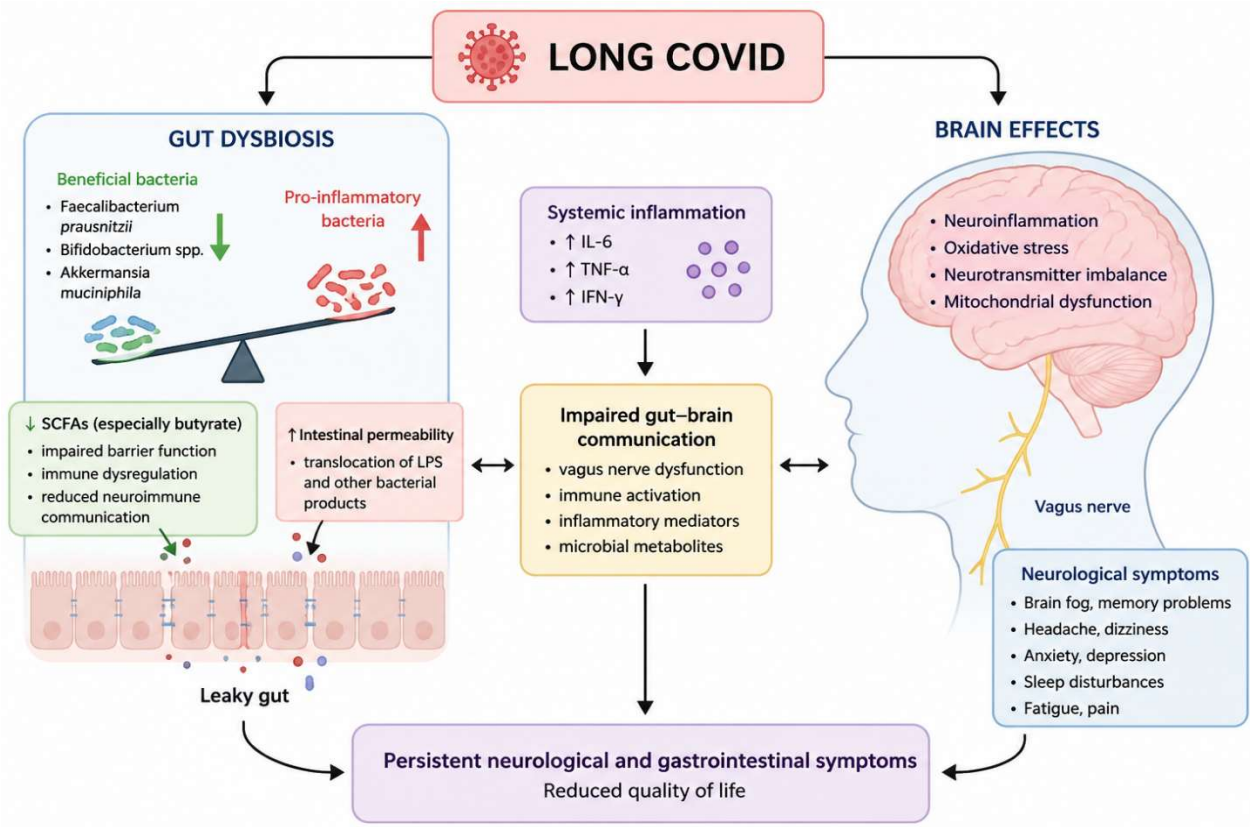

Figure 1. Proposed role of the gut–brain axis in the pathophysiology of Long COVID.

Overall, neurological manifestations of Long COVID appear to result from a complex interaction between gut microbiota alterations, immune dysregulation, autonomic imbalance, and impaired neuroimmune communication. Understanding the role of the gut-brain axis in these processes may provide opportunities for developing targeted interventions aimed at reducing neuroinflammation, restoring microbial homeostasis, and improving neurological recovery in affected individuals.

THERAPEUTIC STRATEGIES TARGETING THE GUT-BRAIN AXIS IN LONG COVID

Current therapeutic approaches for Long COVID increasingly focus on restoring gut-brain axis homeostasis by targeting microbial imbalance, chronic inflammation, immune dysregulation, and neuroimmune dysfunction. Due to the heterogeneous nature of Long COVID, no standardized treatment protocol has been established, and current interventions are mainly directed toward symptom reduction and restoration of physiological balance. Strategies aimed at modulating the gut microbiome and regulating inflammatory pathways represent promising approaches, particularly in patients presenting with combined gastrointestinal and neurological manifestations [10,11].

Microbiota-targeted interventions, including probiotics, prebiotics, and postbiotics, represent some of the most extensively investigated therapeutic strategies. Probiotic supplementation with beneficial bacterial strains, particularly Lactobacillus and Bifidobacterium, may improve intestinal barrier integrity, enhance immune regulation, and reduce excessive inflammatory signaling. These microorganisms can influence gut-brain communication through the production of bioactive metabolites, modulation of cytokine release, and regulation of neurotransmitter pathways, including serotonin and GABA metabolism [12]. Prebiotics, such as inulin, fructooligosaccharides, and resistant starches, selectively stimulate the growth of beneficial bacterial populations and increase the production of short-chain fatty acids (SCFAs), particularly butyrate. SCFAs contribute to epithelial barrier maintenance, immune regulation, and modulation of microglial activity,

suggesting a potential role in reducing neuroinflammation associated with Long COVID [13]. Postbiotics, including microbial-derived metabolites and purified compounds such as butyrate, may provide additional therapeutic benefits by exerting anti-inflammatory, antioxidant, and immunomodulatory effects without requiring the administration of live microorganisms [14].

Fecal microbiota transplantation (FMT) has emerged as another potential strategy for patients with severe microbiome disruption. By transferring a diverse microbial community from healthy donors, FMT may restore microbial richness, improve intestinal permeability, and regulate immune responses. Although FMT has demonstrated efficacy in several gastrointestinal disorders, including recurrent Clostridioides difficile infection and some inflammatory bowel conditions, its application in Long COVID remains experimental. Preliminary observations suggest potential benefits; however, controlled clinical trials are necessary to determine patient selection criteria, long-term safety, and therapeutic efficacy [15].

In addition to microbiome-based approaches, several natural compounds with anti-inflammatory and neuroprotective properties have been investigated. Curcumin and resveratrol have demonstrated the ability to modulate inflammatory pathways, reduce oxidative stress, and influence gut microbial composition. These compounds may represent complementary approaches for targeting mechanisms involved in persistent inflammation and neurological dysfunction, although clinical evidence in Long COVID patients remains limited [16].

Given the frequent occurrence of autonomic dysfunction in Long COVID, neuromodulation approaches, particularly non-invasive vagus nerve stimulation (VNS), have attracted increasing interest. The vagus nerve represents a major communication pathway within the gut-brain axis and plays an important role in regulating immune responses through the cholinergic anti-inflammatory pathway. VNS has been shown to reduce inflammatory cytokine production, improve autonomic balance, and influence gastrointestinal motility, suggesting potential benefits for patients experiencing fatigue, cognitive impairment, and digestive symptoms [17].

Despite promising preliminary findings, most therapeutic approaches targeting the gut-brain axis in Long COVID remain at an early stage of development. Future randomized clinical trials should focus on identifying patient subgroups most likely to benefit from microbiome-based interventions and establishing personalized therapeutic strategies integrating nutritional, microbial, immunological, and neuromodulatory approaches.

CONCLUSIONS

Long COVID represents a complex post-viral condition in which persistent gastrointestinal, neurological, and systemic symptoms may result from prolonged disturbances in gut-brain axis function. Alterations in the gut microbiota, impaired intestinal barrier integrity, chronic immune activation, neuroinflammation, and autonomic dysfunction appear to interact as interconnected mechanisms contributing to disease persistence.

Restoring gut-brain axis balance represents a promising therapeutic direction for improving outcomes in patients with Long COVID. Microbiome-targeted interventions, including probiotics, prebiotics, postbiotics, and fecal microbiota transplantation, together with approaches aimed at regulating vagal activity and reducing inflammation, may provide new opportunities for symptom management. However, further clinical studies are required to determine their effectiveness, safety, and potential role in personalized treatment strategies.

A deeper understanding of the relationship between intestinal microorganisms, immune responses, and neurological function may contribute to the development of novel diagnostic markers and targeted therapies. Research focused on microbiome-based approaches and gut-brain axis modulation could provide valuable insights not only for Long COVID but also for other post-infectious and neuroinflammatory disorders.

Conflict of Interest: The author declares no potential conflict of interest.

Source of Funding: This work has not received any financial support.

Ethical Statement: This study does not contain any studies with human subjects or animals.

Data availability: All the data supporting the results of this study are included in the article.

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