Long COVID: Current State of Knowledge

Working note
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Document History

Version	Date	Changes
1.0	July 10, 2026	Initial draft
2.0	July 12, 2026	Revised structure; added the integrative model

Abstract

Long COVID remains a complex condition whose underlying mechanisms are only partially understood. This document presents, in accessible language, an integrative model based on current scientific knowledge. It describes Long COVID as the likely result of interactions between the persistence of SARS-CoV-2, sustained biological disturbances, localized organ dysfunction, and dysregulation of the control systems linking the brain with the rest of the body. These biological mechanisms give rise to functional disability that is often disproportionate to the abnormalities detected by conventional medical investigations. They are also accompanied by psychological, social, and existential consequences that shape the lived experience of the illness without constituting its primary cause. This approach offers a dynamic view of the human organism, emphasizing the continuous interactions between biological systems, the individual, and the surrounding environment.

Understanding Long COVID: A New Perspective on Disease

For more than two centuries, modern medicine has been based on a simple principle: when a patient experiences a symptom, there is a lesion somewhere in the body that explains it. The physician's role is therefore to identify the affected organ and treat it. This approach has led to remarkable advances. However, Long COVID shows that this framework is not always sufficient.

Many patients experience severe disability even though conventional medical investigations reveal few abnormalities. Specialists successively examine the heart, lungs, brain, muscles, or digestive system without always finding lesions proportional to the severity of the symptoms. This discrepancy can be confusing for both patients and physicians. Gradually, a different way of understanding the disease has begun to emerge.

A First Dimension: Viral Persistence

Everything begins with infection by SARS-CoV-2. In most people, the virus is eliminated within a few weeks. In others, however, it may persist in certain tissues in a form that remains only

partially understood. Once highly controversial, this hypothesis is now supported by a growing body of scientific evidence.

If confirmed, viral persistence could represent the biological driver that sustains the disease for months or even years.

A Second Dimension: Persistent Biological Mechanisms

Prolonged viral persistence may trigger a range of biological mechanisms that affect not just a single organ but the body as a whole.

Among the main mechanisms currently under investigation are:

- dysregulation of the immune system;
- inflammation of the vascular endothelium;
- abnormalities of the microcirculation;
- disturbances of energy metabolism;
- mitochondrial dysfunction;
- additional mechanisms that are still being explored.

These disturbances may subsequently lead to localized dysfunction in different organs, including the brain, heart, lungs, muscles, gastrointestinal tract, pancreas, and other tissues. Each patient exhibits a unique combination of these alterations, which helps explain the remarkable diversity of clinical manifestations.

In our clinical practice, functional brain imaging—including technetium perfusion SPECT, ^{18}F-FDG PET, and magnetic resonance spectroscopy (MRS)—frequently reveals abnormalities in brain function while conventional structural imaging remains normal. These observations, based on the follow-up of nearly 500 individuals since July 2021, suggest that the brain may function differently without necessarily exhibiting structural tissue damage.

A Third Dimension: Neuro-Systemic Dysregulation

However, these biological mechanisms alone do not fully explain one of the defining characteristics of Long COVID: its marked fluctuation. Symptoms may vary from hour to hour, worsen after exertion, or be triggered by physical, cognitive, sensory, or emotional stimuli. Understanding these variations likely requires considering a third level of biological organization.

The brain does far more than generate thoughts or control movement. It continuously receives information from throughout the body and constantly coordinates the autonomic nervous system, the endocrine and immune systems, and the activity of multiple organs.

Through these regulatory networks, the body maintains its internal balance (homeostasis) while continuously adapting to environmental demands (allostasis). This coordination regulates heart rate, breathing, digestion, body temperature, sleep, pain perception, balance, attention, the perception of effort and fatigue, as well as many immune and hormonal responses.

When this coordination becomes less effective, organs may remain structurally intact while responding inappropriately. Tachycardia, hyperventilation, orthostatic intolerance, gastrointestinal disturbances, or cognitive impairment may therefore occur even though no specific structural lesion can be identified in the affected organ.

The concept of neuro-systemic dysregulation provides a coherent framework for understanding why Long COVID is simultaneously fluctuating, multisystemic, and often difficult to demonstrate using conventional medical investigations.

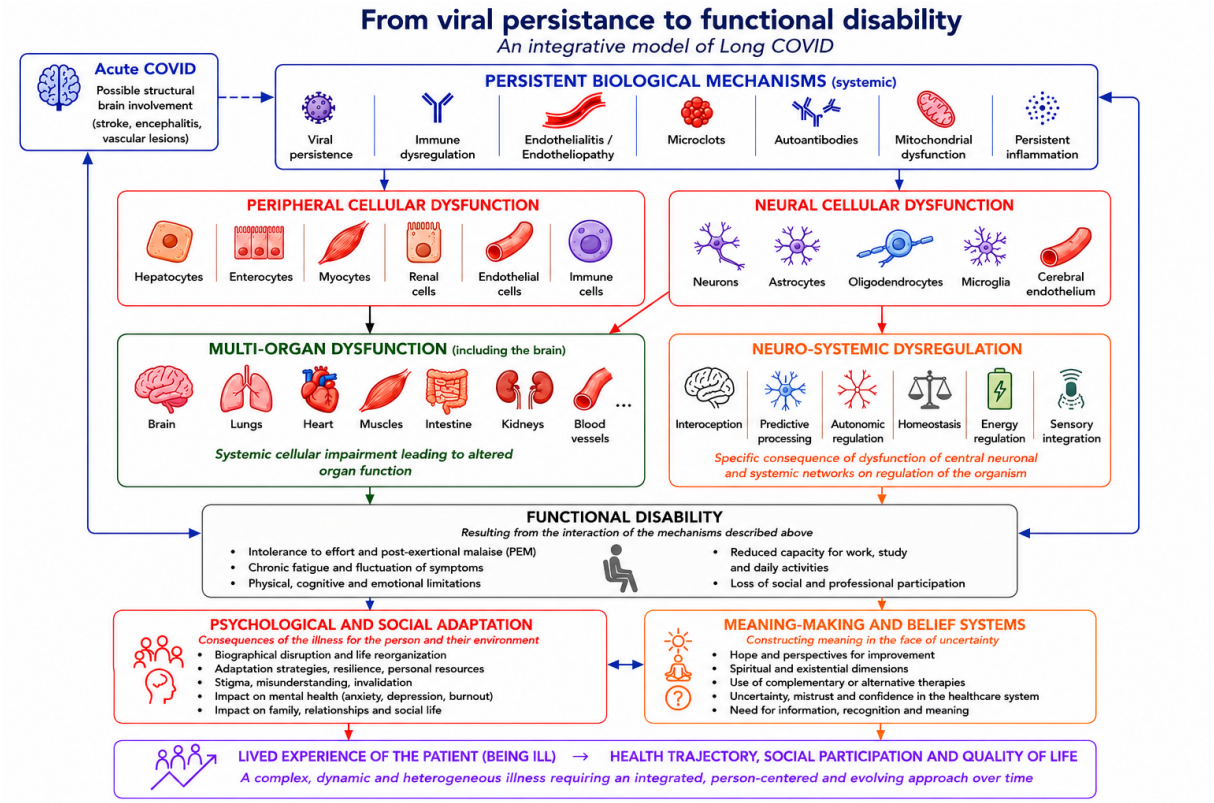

Figure 1: Integrative Multiscale Model of Long COVID. Conceptual representation of the principal mechanisms currently thought to contribute to the development, persistence, and clinical manifestations of Long COVID.

The Emergence of Functional Disability

Long COVID most likely results from the continuous interaction between these different levels of biological organization. Viral persistence may sustain chronic biological disturbances. These, in turn, may promote localized organ dysfunction while progressively impairing the regulatory systems responsible for coordinating organ function. Functional disability would therefore arise not from a single lesion but from the interaction of multiple mechanisms that influence one another. As a consequence, the body gradually loses its ability to adapt to physical, cognitive, or emotional demands.

In many patients, even moderate exertion may trigger a delayed worsening of symptoms lasting hours or even days. This phenomenon, known as *Post-Exertional Malaise* (PEM), is now recognized as one of the defining features of both Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The precise biological mechanisms underlying PEM remain incompletely understood. Several hypotheses are currently being investigated. One possibility is that the increased energy demand induced by physical, cognitive, or emotional exertion interacts with the persistent biological mechanisms that sustain the disease. This hypothesis is currently the subject of active research.

Psychological and Social Adaptation

Long COVID is more than a collection of biological symptoms. It affects children and adults whose lives are already shaped by their personal histories and may coexist with other illnesses, life events, or vulnerabilities.

Like any chronic illness, Long COVID can profoundly disrupt life plans. Education, employment, family life, and social relationships may all be affected. This *biographical disruption* requires a process of adaptation: learning to manage one's energy, accepting new limitations, and gradually rebuilding a sustainable balance.

Uncertainty, administrative and occupational difficulties, and lack of recognition may intensify suffering and contribute to anxiety or discouragement. These psychological manifestations are not the cause of Long COVID; they are common consequences of living with the disease.

The biological, psychological, and social dimensions of Long COVID are therefore not competing explanations but interconnected aspects of the same illness.

Making Sense of the Illness

When confronted with a disease that remains only partially understood, people naturally seek to make sense of their experience. Some find hope in advances in biomedical research, while others draw strength from personal beliefs, family and friends, patient organizations, or complementary approaches.

Scientific uncertainty and the absence of a curative treatment make this search more challenging. Above all, many patients express a need to be listened to, acknowledged, and provided with reliable information. This search for meaning is a normal part of living with chronic illness.

Patients as Essential Partners in Research

Long COVID has stimulated an unprecedented international research effort. Thousands of researchers are now using advanced tools in biology, multiomics, and medical imaging to better understand the disease.

Patients themselves have played a crucial role in this progress. From the earliest months of the pandemic, they described persistent symptoms, post-exertional malaise, cognitive impairment, and the fluctuating nature of the illness. Their observations have significantly shaped today's research agenda.

Nevertheless, many patients remain insufficiently recognized. Despite growing scientific knowledge, many still struggle to obtain an accurate diagnosis, appropriate medical care, or social protection commensurate with the severity of their disability.

Recognizing Long COVID therefore means more than developing new treatments. It also requires acknowledging patients as partners in research and ensuring that this particularly vulnerable population has access to appropriate healthcare, social support, educational accommodations, and workplace adjustments.

Further Reading

A scientific bibliography on Long COVID, continuously updated since 2021, is available on Zotero:
https://www.zotero.org/groups/4929325/long_covid_open_library/library

For an explanation of how this bibliography is organized, see:

Jamoulle, M. (2025). *Structuring Knowledge on Long COVID: A Bibliographic Approach Based on 3CGP (Core Content Classification in General Practice).* ORBi, University of Liège.
https://hdl.handle.net/2268/327758