What Pathological Changes May Cause The Symptoms Of Long COVID?

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Bateman Horne Center CME Course
November 1, 2022

No conflicts of interest

Topics Covered

- How the symptoms of Long COVID are shared with other post-infectious syndromes
- The underlying pathophysiological changes in Long COVID
- The possible triggers of Long COVID, including reactivation of latent viruses
- How the underlying pathophysiology of Long COVID causes its symptoms: one theory

Comparison of Symptoms: ME/CFS vs. Long COVID

	ME/CFS	LC
Fatigue	√	√
Post-exert. malaise	√	√
Headaches	√	√
Sleep disorder	√	√
▼ cognition	√	√
▼ memory	√	√
▼ attention	√	√
Depression	√	√
Anxiety	√	√
▼ activity	√	√
Myalgia	√	√
Muscle weak	√	√
▲ pain	√	√
Arthralgia	√	√

	ME/CFS	LC
Chem sensitivities	√	√
Hot/cold spells	√	√
Anorexia	√	√
Ortho. intolerance	√	√
Palpitations	√	√
Dyspnea	√	√
GI (n/v, diarrhea)	√	√
Fever/chills	√	√
Cough	√	√
Sore throat	√	√
Lymph ▲, pain	√	√
▼ smell/taste		√
Speech problems		√
Rash/hair loss		√

From: Wong TL, Weitzer DJ. Medicina 2021, 57, 418 (syst. rev. of 21 studies)

Post-Infectious Fatigue Syndromes

- Infectious-like illnesses[1-3]
- Epstein-Barr virus[4,6,7]
- Lyme disease[5]
- *Coxiella burnetti*[7]
- Ross River virus[7]
- *Mycoplasma pneumoniae*[8]
- Enteroviruses[9]
- Human herpesvirus-6[10]
- Ebola[11]
- West Nile Virus[12]
- SARS[13]
- Dengue[14]
- Parvovirus[15]
- Giardia[16]
- COVID-19[17]

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2 Poskanzer DC. *NEJM* 1957:257:356.
3 Acheson ED. *Am J Med* 1959;4:569.
4 Jones JF. *Ann Intern Med* 1985;102:1.
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16 Litleskare S. *Gast Hepatol* 2018;16:1064
17 Komaroff AL. *Front Med 2021;*7, 606824.

How Common Is Long COVID?

Prospective Study of Persistent Symptoms

33,281 PCR+ cases; 62,957 never-infected, matched controls; followed *18 months* with repeated online questionnaires

- **Returned to full health: 52%**
- **Partially recovered: 42%**
- **Not recovered: 6%**

Risk factors for non-recovery: Hospitalization, older age, female sex, lower SEC, past Hx chronic illnesses

From: Hastie CE, et al. Nat Comm 2022;13:5663

The possible triggers of Long COVID, including reactivation of latent viruses

Biologic Triggers of Pathology

- Persistent reservoirs of virus ►ongoing immune response
- Injury and repair in multiple organs ► inflammation
- Reactivation of neurotropic pathogens, e.g., herpesviruses, endogenous retroviral gene activation
- SARS-CoV-2 ►gut dysbiosis ►autoimmunity

Proal AD, VanElzakker MB. Front Microbiol 2021;12:698169
Ramakrishnan RK, et al. Front Immunol 2021;12:686029
Merad M, et al., Science 2022;375:1122–1127

Viruses

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Even if the virus has been killed, some of its nucleic acid & antigens can persist in "harbors", & can trigger immune response

The latent virus can periodically reactivate and multiply & trigger immune response

Human Endogenous Retroviruses

- Nucleic acid sequences from ancient retroviruses constitute 8% of the human genome
- Initially considered totally inactive, just the detritus of evolution
- While no strong evidence that these sequences can produce full viruses, there is growing evidence that a small fraction of their genes can be reactivated to produce viral proteins and that these proteins can affect human health.

Evidence That SARS-CoV-2 Remains In the Body

SARS-CoV-2 RNA/Ag In Many Organs

- Complete autopsies of 44 patients, including 4 who died from something other than COVID-19
- Highly sensitive assays for viral nucleic acid and viral protein, and for replicating virus
- Viral RNA in tissues throughout the body in ***all*** patients for up to 230 days after acute COVID-19—including the brain
  - Even when undetectable in **blood** and…
  - Even in the few people with ***mild*** acute COVID-19
- Virus is replicating in organs other than the lungs for at least 7 days after onset of acute COVID-19
- Minimal histopathological evidence of viral cytopathology or of immune cell infiltrates, outside of lungs

From: Stein SR, et al. Research Square (non-refereed preprint)

Persistent Viral RNA/Antigen In Long COVID

- Months after virus no longer detectable in nasopharynx, SARS-CoV-2 RNA and antigen still found in intestinal tissues, liver and stool[1-4], in multiple GI organs[4]
- GI symptoms correlate with such evidence[1], but viral RNA/Ag can be present without GI symptoms[3]
- Longitudinal memory B cell response consistent with persistent reservoirs of virus[2]
- COVID-19 seems to alter gut microbiome to more pro-inflammatory state[3]
- Persistence of viral RNA/Ag much greater in Long COVID vs. recovered COVID[5,6]

[1]Natarajan A, et al. Med 2022;3:371–387; [2]Gaebler C, et al. Nature 2021;591:639-44; [3]Zuo T, et al. Gut 2021;70:276-84; [4]Cheung CCL, et al. Gut 2022;71:226-9; [5]Swank Z, et al. Clin Infect Dis 2022 doi:10.1093/cid/ciac722; [6]Craddock V, et al. MedRxiv, doi:10.1101/2022.08.07.22278520

Persistent SARS-CoV-2 Ag in Long COVID

37 pts with Long COVID and 26 pts recovered from COVID (all PCR+) had repeated blood samples over 12 months.

Ultrasensitive assay for SARS-CoV-2 spike protein.

Low levels of viral protein detected in:

Long COVID: 60%
Recovered COVID: 0%
} **P < 0.00001**

Viral protein levels persisted over months in Long COVID but disappeared in recovered COVID.

From: Swank Z, et al. Clin Infect Dis 2022 DOI: 10.1093/cid/ciac722

Features Distinguishing Long COVID

Compared to recovered COVID and never-COVID groups, Long COVID patients significantly more likely to have:

- **Increased antibodies to specific SARS-CoV-2 antigens**
- **Increased antibodies to EBV lytic antigens**
- **Lower levels of cortisol**
- **Increased activated B cells**
- **Decreased CD4+ central memory cells**
- **Exhausted T cells**
- **Increased production of IL-2 & IL-6 by CD4+ and CD8+ cells**

Putting it all together: **Persistent SARS-CoV-2 antigen, reactivation of latent herpesviruses eliciting an immune response, all leading to chronic inflammation are central.**

From: Klein J…Iwasaki A. Preprint

Evidence That SARS-CoV-2 Reactivates Latent Herpesviruses (EBV) and May Transactivate Endogenous Retroviral Genes

EBV Reactivation in Long COVID

- EBV reactivation common in *severe acute* COVID-19; unclear if inflammatory markers or outcomes worse
- Detection of EBV DNA in plasma during *acute* COVID-19 significantly associated with Long COVID at 1-2 months[1]
- EBV reactivation more frequent in Long COVID (67%) than in recovered COVID (10%): $P < 0.001$[2]
- EBV reactivation strongly associated with Long COVID symptoms 4 months later, particularly fatigue (OR 2.1), whether patients hospitalized with acute COVID-19 or not[3]

[1] *Su Y, et al. Cell 2022;185:881.*
[2] *Gold JE, et al. Pathogens 2021;10:763.*
[3] *Peluso MJ, et al. MedRxiv 10.1101/2022.06.21.22276660*

How Do Residual SARS-CoV-2, Reactivated Latent Viruses, and Changes to the Microbiome Lead to the Symptoms of Long COVID?

What do we feel like when we're sick?

Why do we feel that way?

What chemical signals trigger those symptoms?

Sickness Symptoms

- Fatigue, greatly amplified by exertion
- Difficulty thinking
- Achiness
- Headache
- Poor appetite
- Poor sex drive

"It's like having the flu, except that it never goes away."

How Do These Stereotyped Symptoms Change Our Behavior?

We are much less active, physically and mentally, we sleep much more, we eat/digest less, we have less sex….

…. And as a result we utilize a lot less energy….

…. Preserving the energy we need to fight the infection

Then, when the infection has been eradicated, the switch that turns on the stereotyped, energy-conserving behavior gets switched off.

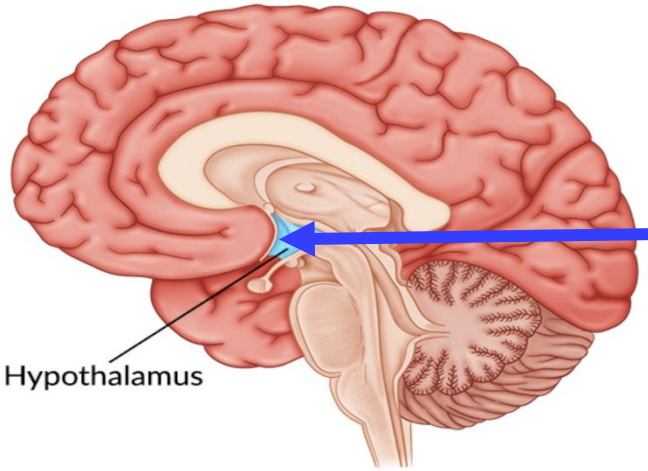
Sickness Behavior

- Seen in most animals, even invertebrates
- An evolutionarily-preserved *temporary* response to injury and infection: to focus body's energy stores on fighting infection & healing injury
- In people with post-infectious fatigue, the stimulus that triggers sickness symptoms and behavior *persists*

Theory: Long COVID Is An Example of Persistent Sickness Behavior The Pathophysiology of Which Is…..

What Causes the Symptoms?

Speculative Model: Many Triggers, Final Common Pathway



Sickness symptoms nucleus: located in hypothalamus?

From: Capuron L, et al. Neuropsychopharmacology 2007;32:2384-92

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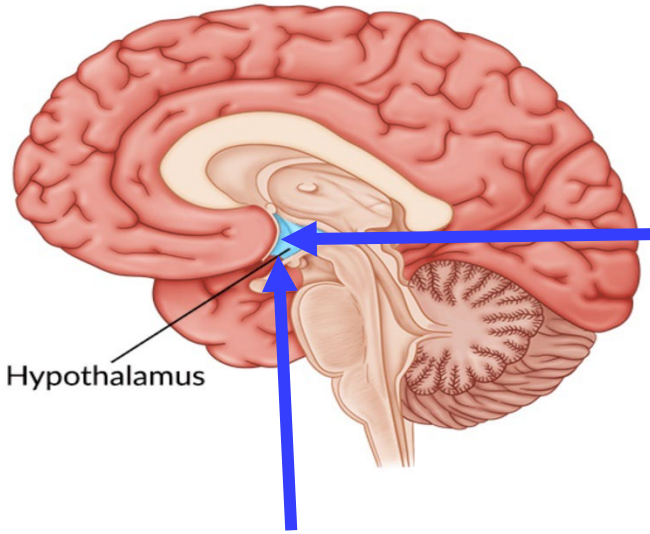

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Activation of brain's innate immune system yields cytokines & other inflammatory molecules that trigger the nucleus

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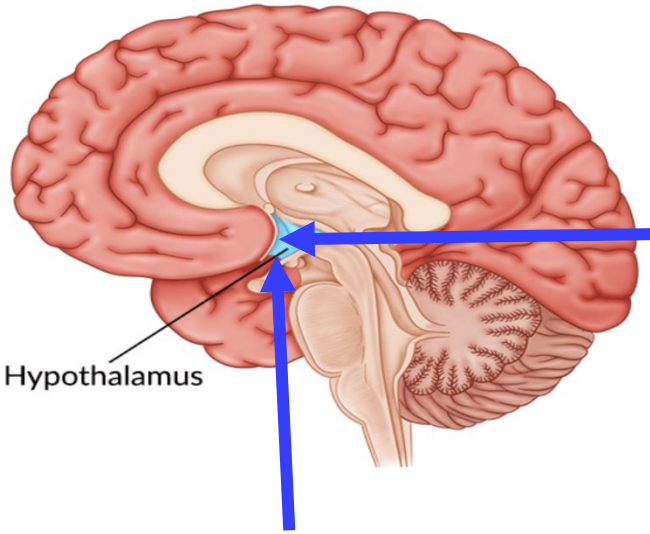


Sickness symptoms nucleus: located in hypothalamus?

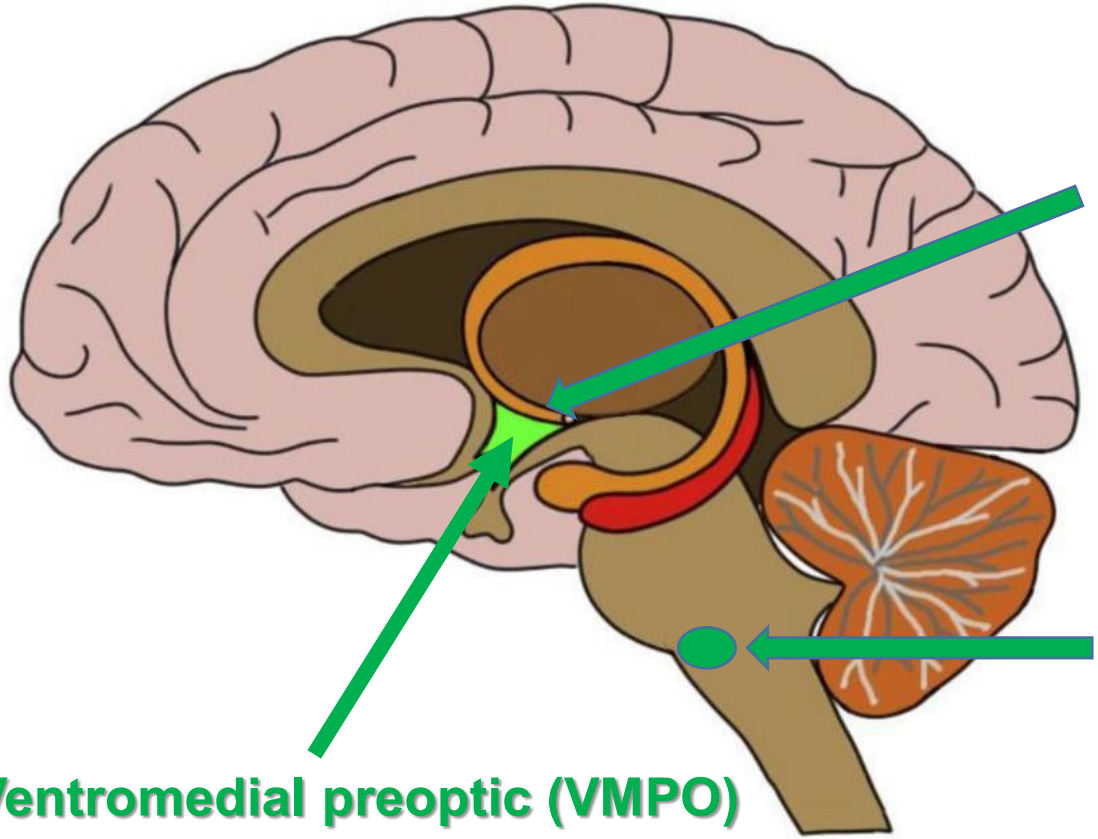
Brain inflammation:
Infection
Autoantibodies
Toxins
Obesity
Stress
▲ leptin

Activation of brain's innate immune system yields cytokines & other inflammatory molecules that trigger the nucleus

Systemic inflammation (outside brain) signaling the brain by humoral and retrograde neural routes

From: Capuron L, et al. Neuropsychopharmacology 2007;32:2384-92; Younger J, et al. J Womens Health 2016;25:752-60; Stringer EA, et al. J Transl Med 2013;11:93.

Discovery of Sickness Symptoms And Torpor Nuclei in Mice



Torpor/hibernation nucleus, in the preoptic area of hypothalamus

Nucleus tractus solitarius & Area postrema (brainstem)

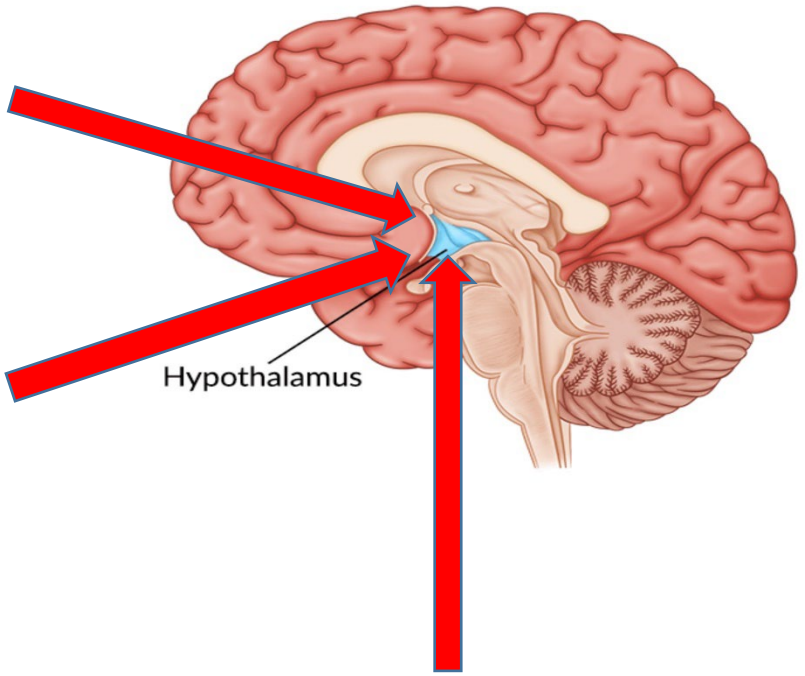
Ventromedial preoptic (VMPO) and organum vasculosum lamina terminalis (hypothalamus)

Osterhout J…Dulac C. Nature 2022;606:937. Ilanges, A. et al. Nature 2022;609:761. Hrvatin S. Nature 2020;583:115. Takahashi T. Nature 2020;583:109

How SARS-CoV-2 and Other Viruses Could Chronically Stimulate the Brain's Nuclei

Virus infects/becomes latent & reactivated in the brain: brain inflammation

Virus infects/becomes latent outside the brain: systemic inflammation ► brain inflammation



Virus alters the microbiome, creating systemic inflammation ► brain inflammation

In Summary

- Post-infectious fatigue syndromes like Long COVID have underlying biological causes, including an infectious trigger (in many), immune activation and neuroinflammation, autoantibodies, dysautonomia, oxidative stress, defective energy metabolism, hypometabolic state, and a pro-inflammatory gut microbiome

- These abnormalities are connected, and reinforce each other

- They probably cause the chronic sickness symptoms by stimulating groups of neurons (nuclei) in the brain that are activated by infection or injury and dedicated to generating sickness behavior.