

# **Introduction and Historical Perspective**

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***NASEM Workshop:***

***Toward A Common Research Agenda  
in Infection-Associated Chronic Illnesses***

***June 29, 2023***

# TOPICS TO BE COVERED

- A similar group of ***symptoms*** are experienced by a subset of people following a variety of acute infections: viral, bacterial and protozoal
- These symptomatically similar syndromes may share similar ***pathophysiology***: emerging evidence from myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Long COVID.
- What triggers the shared pathophysiology and leads to the symptoms of the illness: the sickness behavior theory?
- The impact of these problems on society

# **Post-Acute Infection Syndromes**

**Choutka J...Iwasaki A. Unexplained post-acute infection syndromes. Nat Med 2022;28(5):911-923.**

# Post-Acute Infection Syndromes

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- Infectious-like illnesses<sup>1-3</sup>
  - Epstein-Barr virus<sup>4,6,7</sup>
  - Lyme disease<sup>5</sup>
  - *Coxiella burnetti*<sup>7</sup>
  - Ross River virus<sup>7</sup>
  - *Mycoplasma pneumoniae*<sup>8</sup>
  - Enteroviruses<sup>9</sup>
  - Human herpesvirus-6<sup>10</sup>
  - Ebola<sup>11</sup>
  - West Nile Virus<sup>12</sup>
  - SARS<sup>13</sup>
  - Dengue<sup>14</sup>
  - Parvovirus<sup>15</sup>
  - Giardia<sup>16</sup>
  - COVID-19<sup>17</sup>
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<sup>1</sup> Shelokov A. *NEJM* 1957;257:345.

<sup>2</sup> Poskanzer DC. *NEJM* 1957;257:356.

<sup>3</sup> Acheson ED. *Am J Med* 1959;4:569.

<sup>4</sup> Jones JF. *Ann Intern Med* 1985;102:1.

<sup>5</sup> Sigal LH. *Am.J.Med.* 88:577-581, 1990.

<sup>6</sup> White PD. *Br J Psychiatry* 1998;173:475

<sup>7</sup> Hickie I. *BMJ*;2006;333:575.

<sup>8</sup> Salit IE. *Can Dis Wkly* 1991;17:E:9.

<sup>9</sup> Chia JKS. *J Clin Pathol* 2008;61:43.

<sup>10</sup> Komaroff AL. *J Clin Virol* 2006;37:S39.

<sup>11</sup> Epstein L. *NEJM* 2015;373:2483.

<sup>12</sup> Sejvar JJ. *J Neuropsychol* 2008;2:477.

<sup>13</sup> Moldofsky H. *BMC Neurol* 2011;11:37.

<sup>14</sup> Seet RC, et al. *J Clin Virol* 2007;38:1.

<sup>15</sup> Kerr JR, et al. *J.Gen.Virol.* 2010;91:893.

<sup>16</sup> Litleskare S. *Gast Hepatol* 2018;16:1064

<sup>17</sup> Komaroff AL. *Front Med* 2021;7, 606824.

# **Symptoms of ME/CFS and Long COVID: Similarities and (a few) Differences**

# Symptoms: ME/CFS vs. Long COVID

|                         | <b>ME/CFS</b> | <b>LC</b> |
|-------------------------|---------------|-----------|
| Fatigue                 | ✓             | ✓         |
| Post-exertional malaise | ✓             | ✓         |
| Orthostatic intolerance | ✓             | ✓         |
| Sleep disorder          | ✓             | ✓         |
| ▼ cognition             | ✓             | ✓         |
| ▼ memory                | ✓             | ✓         |
| ▼ attention             | ✓             | ✓         |
| Depression              | ✓             | ✓         |
| Anxiety                 | ✓             | ✓         |
| ▼ activity              | ✓             | ✓         |
| Myalgia                 | ✓             | ✓         |
| Headache                | ✓             | ✓         |
| Arthralgia              | ✓             | ✓         |
| Hot/cold spells         | ✓             | ✓         |

|                        | <b>ME/CFS</b> | <b>LC</b> |
|------------------------|---------------|-----------|
| Anorexia               | ✓             | ✓         |
| Muscle weakness        | ✓             | ✓         |
| Palpitations           | ✓             | ✓         |
| Dyspnea                | ✓             | ✓         |
| GI (n/v, diarrhea)     | ✓             | ✓         |
| Fever/chills           | ✓             | ✓         |
| Cough                  | ✓             | ✓         |
| Sore throat            | ✓             | ✓         |
| Chemical sensitivities | ✓             |           |
| Tinnitus               | ✓             |           |
| Lymph ▲, pain          | ✓             |           |
| ▼ smell/taste          |               | ✓         |
| Speech problems        |               | ✓         |
| Rash/hair loss         |               | ✓         |

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

# Symptoms: ME/CFS vs. Long COVID

|                                | <b>ME/CFS</b> | <b>LC</b> |
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| <b>Orthostatic intolerance</b> | ✓             | ✓         |
| <b>Sleep disorder</b>          | ✓             | ✓         |
| <b>▼ cognition</b>             | ✓             | ✓         |
| <b>▼ memory</b>                | ✓             | ✓         |
| <b>▼ attention</b>             | ✓             | ✓         |
| <b>Depression</b>              | ✓             | ✓         |
| <b>Anxiety</b>                 | ✓             | ✓         |
| <b>▼ activity</b>              | ✓             | ✓         |
| <b>Myalgia</b>                 | ✓             | ✓         |
| <b>Headache</b>                | ✓             | ✓         |
| <b>Arthralgia</b>              | ✓             | ✓         |
| <b>Hot/cold spells</b>         | ✓             | ✓         |

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

**So ME/CFS and Long COVID  
have similar symptoms.**

**But are there *objective*  
biological abnormalities?**

**If so, are they similar?**



# **Review Article On The Pathophysiology of Long COVID**

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**Davis HE, McCorkell L, Vogel LM, Topol EJ.  
Long COVID: major findings, mechanisms and  
recommendations. Nat Rev Microbiol 2023(3):133-46.**

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# **Review Article Comparing Biology of ME/CFS and Long COVID**

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**Komaroff AL, Lipkin WI. ME/CFS and Long COVID share similar symptoms and biological abnormalities: Road map to the literature. Frontiers in Medicine 2023;10:1187163. doi: 10.3389/fmed.2023.1187163**

**Detailed comparison of neurological, immunological, infectious, microbiome, metabolic, and cardio-pulmonary abnormalities.**

**560 references.**

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# **Underlying Biological Abnormalities In Different Systems, In Both Diseases**

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- *Immune system*
  - *Reactivated viruses*
  - **Central and autonomic nervous system**
  - **Metabolism**
  - **Cardiovascular and pulmonary system**
  - **Gut microbiome**
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# **ME/CFS vs. Long COVID:**

## ***Neurological Abnormalities***

| <b><i>Finding</i></b>                                       | <b><i>ME/CFS</i></b> | <b><i>Long COVID</i></b> |
|-------------------------------------------------------------|----------------------|--------------------------|
| <b>Cognitive deficits</b>                                   | <b>X</b>             | <b>X</b>                 |
| <b>Autonomic dysfunction</b>                                | <b>X</b>             | <b>X</b>                 |
| <b>Neuroendocrine abnormalities</b>                         | <b>X</b>             | <b>X</b>                 |
| <b>Neurovascular abnormalities</b>                          | <b>X</b>             | <b>X</b>                 |
| <b>Autoantibodies against neural targets in CNS and ANS</b> | <b>X</b>             | <b>x</b>                 |
| <b>Hypometabolic state in the brain</b>                     | <b>X</b>             | <b>X</b>                 |
| <b>Gray and white matter abnormalities on imaging</b>       | <b>X</b>             | <b>X</b>                 |
| <b>Small fiber neuropathy</b>                               | <b>x</b>             | <b>X</b>                 |
| <b>Neuroinflammation on imaging</b>                         | <b>x</b>             | <b>x</b>                 |

***From: Komaroff AL, Lipkin WI. Front Med 2023;10:1187163***

# ME/CFS vs. Long COVID: *Metabolic Abnormalities*

| <i><b>Finding</b></i>                                            | <i><b>ME/CFS</b></i> | <i><b>Long COVID</b></i> |
|------------------------------------------------------------------|----------------------|--------------------------|
| ↓ ATP production from O <sub>2</sub><br>(impaired OxPhos)        | X                    | X                        |
| ↓ ATP production from glucose<br>(both TCA cycle and glycolysis) | X                    | X                        |
| ↓ ATP production from fatty acids                                | X                    | X                        |
| ↓ ATP production from amino acids                                | X                    | X                        |
| Redox imbalance (oxidative stress<br>and nitrosative stress)     | X                    | X                        |
| Hypometabolic state, blood & brain                               | X                    | X                        |

*From: Komaroff AL, Lipkin WI. Front Med 2023 (in press)*

# ME/CFS vs. Long COVID:

## *Cardipulmonary Abnormalities*

| <i>Finding</i>                                                       | <i>ME/CFS</i> | <i>Long COVID</i> |
|----------------------------------------------------------------------|---------------|-------------------|
| Diminished exercise capacity<br>(↓ $\text{VO}_2$ max)                | X             | X                 |
| Reduced ventilatory efficiency<br>(↑ $\text{VE}/\text{VCO}_2$ slope) | X             | X                 |
| Endothelial dysfunction                                              | X             | X                 |
| ↑ oxidative stress with exercise                                     | X             |                   |
| ↓ venous return to the heart<br>(preload)                            | x             | x                 |
| Platelet abnormalities                                               | x             | x                 |

*From: Komaroff AL, Lipkin WI. Front Med 2023 (in press)*

# Low-Grade Chronic Gut Inflammation

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## Due in part to:

- Reduced numbers of bacteria producing anti-inflammatory molecules (e.g., butyrate and acetate)<sup>1,2</sup>...
- ...and that correlate strongly with severity of fatigue<sup>1</sup>
- Reduced levels of these molecules in stool<sup>1</sup> and plasma<sup>2</sup>
- Dysbiosis wanes over years, but is followed by long-lasting metabolic changes, particularly in lipids<sup>2</sup>
- Resulting gut inflammation allows bacterial products and organisms to enter the systemic circulation<sup>3,4</sup>, possibly causing systemic and neuro-inflammation
- Replicated in multiple cohorts of ME/CFS<sup>1,2</sup>

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<sup>1</sup>Guo et al. *Cell Host & Microbe*. 2023;31:288.    <sup>2</sup>Xiong et al. *Cell Host & Microbe*. 2023;31:273.

<sup>3</sup>Shukla SK, et al. *PLoS One* 2015;10:e0145453.    <sup>4</sup>Giloteaux L, et al. *Microbiome* 2016 4:30

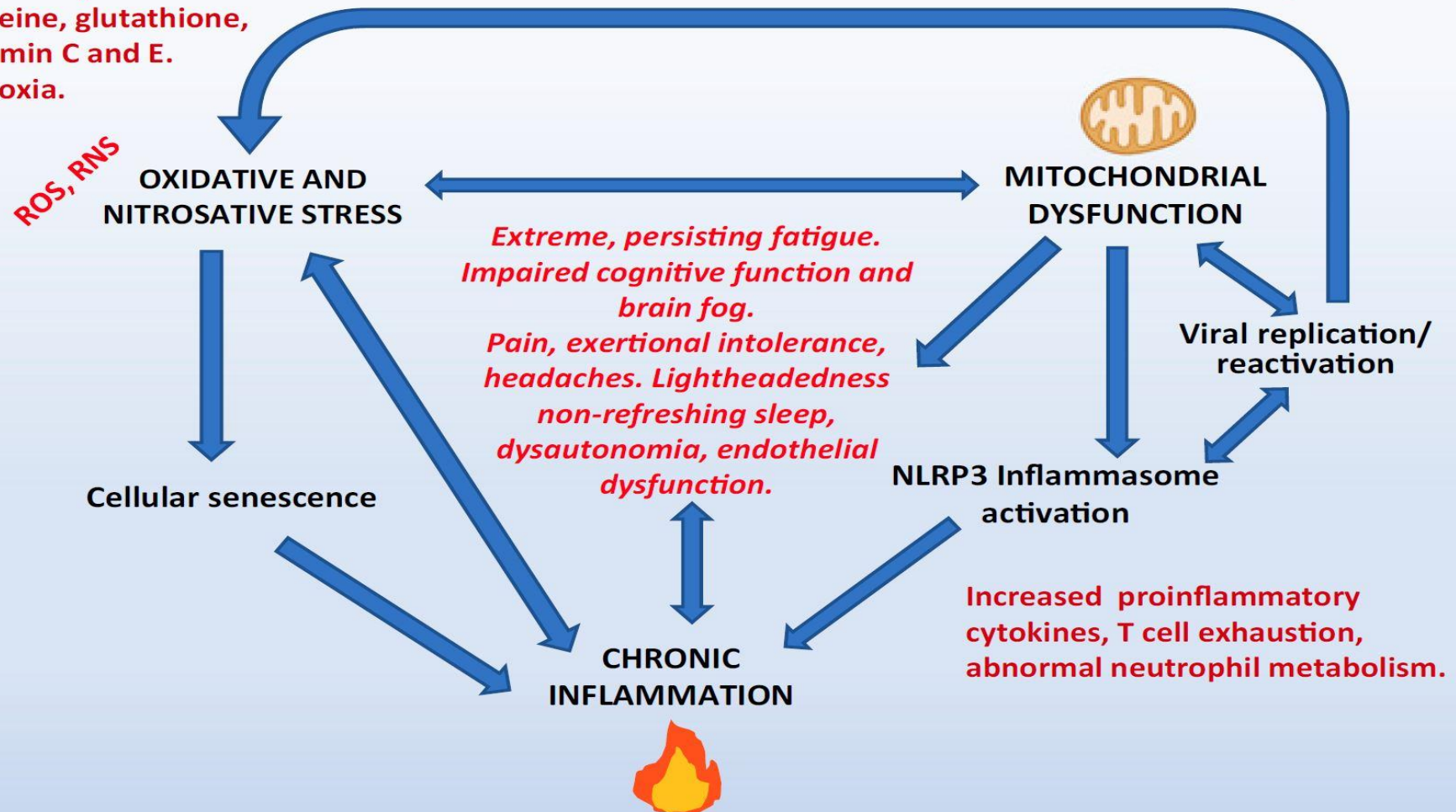
# **What Triggers the Pathophysiology of ME/CFS and Long COVID?**



# Relationship Between Abnormalities

Increased ferritin, homocysteine, superoxide. Dysregulated  $\text{NAD}^+$ , NO and  $\text{H}_2\text{S}$  metabolism. Decreased cysteine, glutathione, Vitamin C and E. Hypoxia.

Impaired TCA cycle, OXPHOS, fatty acid metabolism, urea cycle, mitochondrial bioenergetics.



From: Paul B, Lemle M, Komaroff AL, Snyder SH. PNAS 2021;118(34):e2024358118

**What Causes the *Symptoms*  
Of ME/CFS and Long COVID?  
The Sickness Behavior  
Hypothesis**

# How People Describe Symptoms Of ME/CFS and Long COVID

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**"It's like a flu that never  
goes away."**

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# Is There A Reason Why We Feel The Way We Do When We Get Infected?

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- Sickness symptoms are a hard-wired, evolutionarily-preserved ***protective response***
  - The sickness symptoms lead to behavioral change, to ***sickness behaviors***: less physical and mental activity, less eating and digestion, less sex—less of major ***energy-consuming*** behaviors, ***preserving available ATP*** to fight the infection until it is eradicated
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# **In ME/CFS and Long COVID**

## **This Response *Persists***

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- **The inflammation, and the source of the inflammation (such as microbes or the tissue injury caused by microbes), persists**
  - **The protective response, meant to be temporary, gets “stuck”: the neurochemical mechanism to turn it off is defective**
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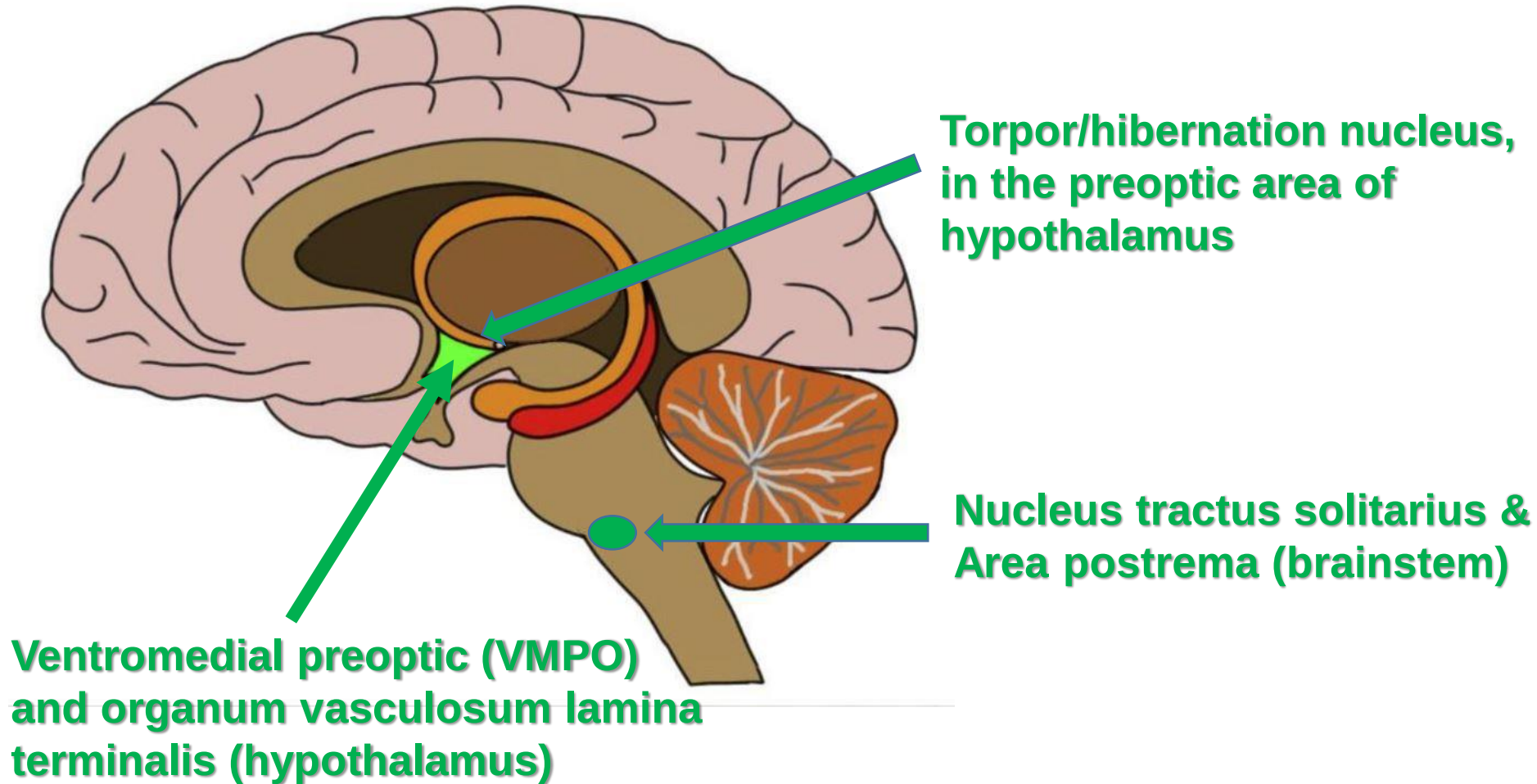
# What Is Causing the Symptoms?

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- So, these “sickness symptoms” persist in people with ME/CFS and Long COVID
  - But what is **causing** the symptoms?
    - Symptoms are experienced in the brain.
    - A set of symptoms that has been preserved by evolution is likely orchestrated by a group of neurons (nucleus) dedicated to that task
    - Molecular switches activate/inactivate those nuclei
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# Discovery of Sickness Symptoms And Torpor Nuclei in Mice



*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*

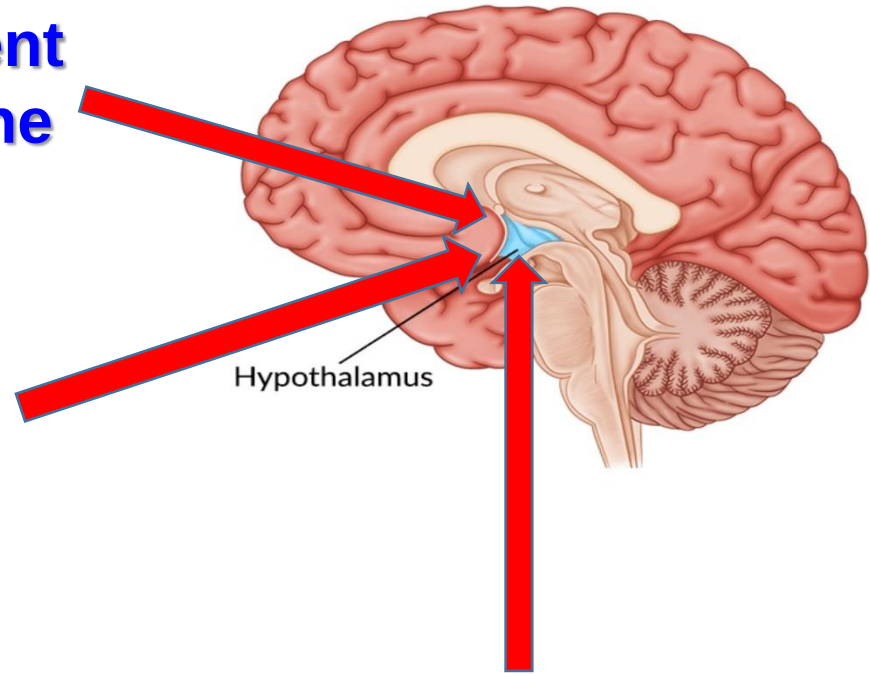
# How SARS-CoV-2 and Other Microbes Could Chronically Stimulate the Brain's Nuclei

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New microbes infect, or latent viruses are reactivated, in the brain: **brain inflammation**

Infection outside the brain: **systemic inflammation** ► **brain inflammation through both humoral and neural pathways**

**Pro-inflammatory gut microbiome, creates systemic inflammation** ► **brain inflammation**





**How Serious Are  
These Problems  
for Society?**

# Impact of ME/CFS & Long COVID in US

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## ME/CFS

- 2.5 million cases<sup>1</sup>
- Direct/indirect costs: \$17-24 billion/year<sup>1</sup>

## Post-COVID Illnesses

- 16 million cases<sup>2</sup>
- Direct/indirect costs: \$ 544 billion/year, \$3.7 trillion over next 5 years<sup>3</sup>

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<sup>1</sup>CDC and National Academy of Medicine, 2015

<sup>2</sup>Brookings Institution; Nat. Ctr. for Health Statistics

<sup>3</sup>Cutler D, Summers LH. JAMA 2020;324:1495

**Conclusion**

# In Summary...

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- ME/CFS and Long COVID and other post-infection illnesses share similar ***symptoms***
  - ME/CFS and Long COVID also share underlying ***pathophysiology***: primarily, central and autonomic nervous system, immune system, infection, gut microbiome, energy metabolism, oxidative stress, cardiopulmonary exercise test and other cardiovascular abnormalities
  - Is this pathophysiology also shared with other post-infection syndromes?
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# In Summary...

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- In both illnesses, the symptoms may reflect the expression of an ancient, evolutionarily-preserved, orchestrated response meant to be protective — a “*sickness behavior response*” — the final common pathway of which involves activation of neurons dedicated to generating sickness symptoms
  - An understanding this underlying biology — particularly the final common pathway leading to symptoms — will ultimately lead to good diagnostic tests and effective treatments
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