Will COVID-19 Lead to ME/CFS in Some People?

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Solve ME/CFS Initiative Webinar
August 27, 2020

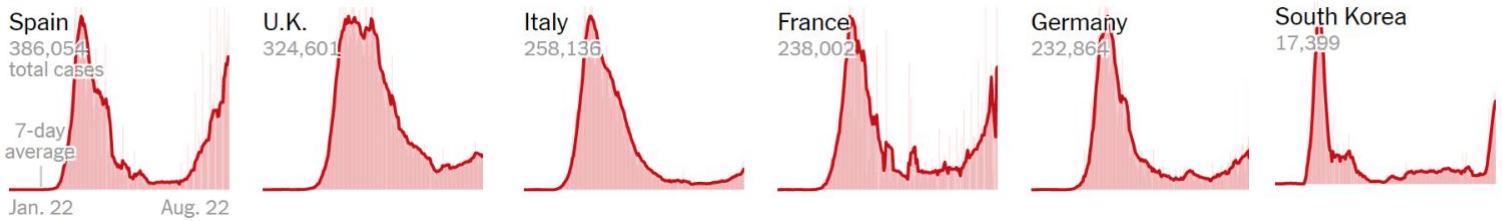
No conflicts of interest

COVID-19 Statistics As Of 8/23/20

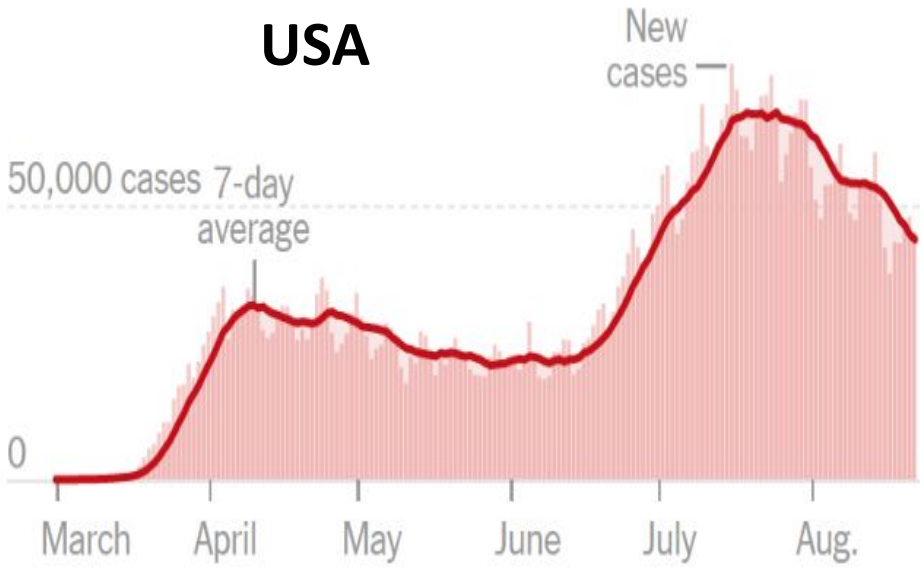
	United States	*World*
Total Cases	5.6 million	23.2 million
Total Deaths	176,248	804,727

From: New York Times/WHO/CDC

Of COVID Cases, By Country: Trend Over Past 7 Months



USA



TOTAL CASES

5.6 million+

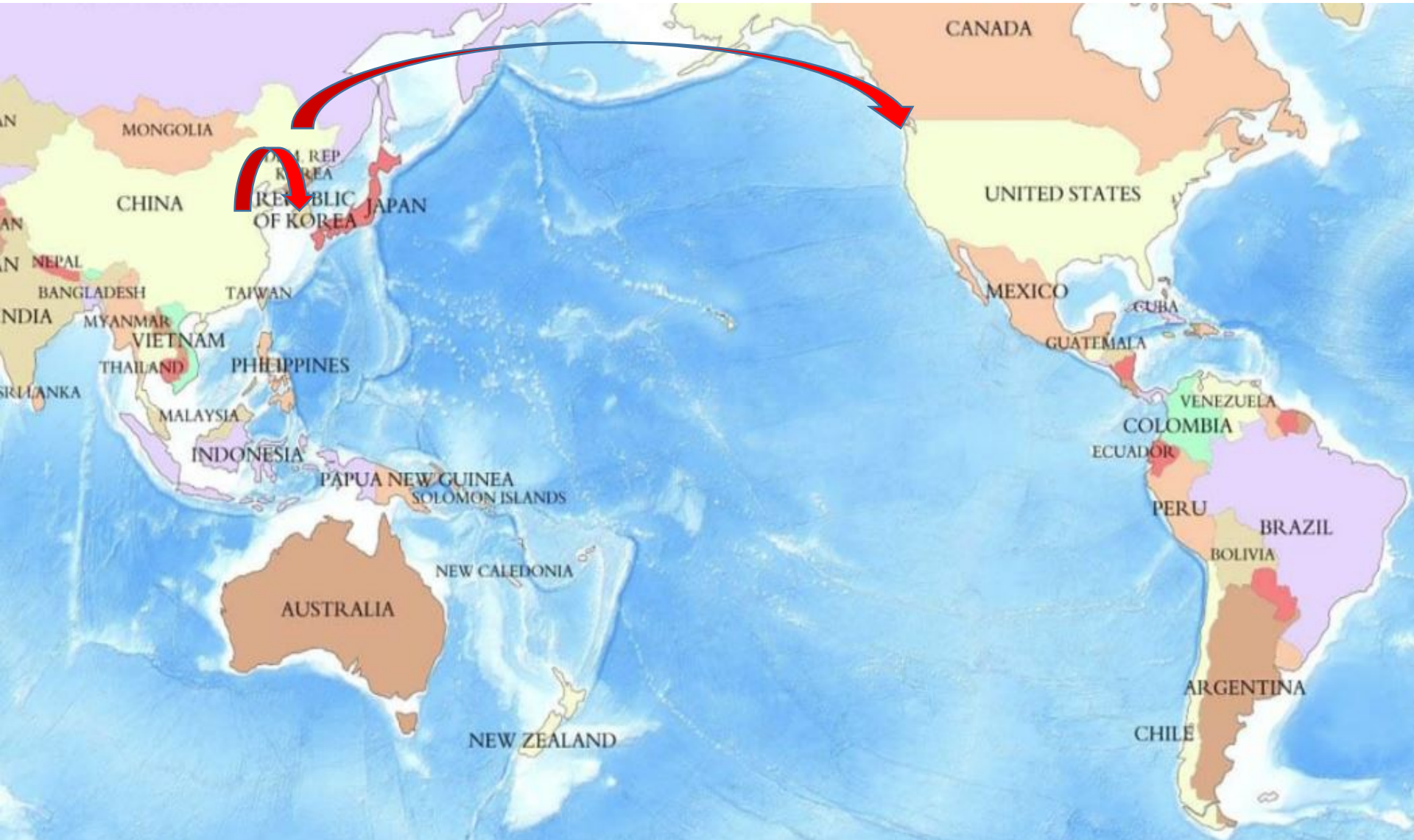
DEATHS

176,248

Includes confirmed and probable cases where available

From: NY Times/WHO/CDC

January 20, 2020: The First Cases of COVID-19 in the USA and S. Korea



How Are We Doing: USA vs S. Korea

Cases and # Deaths/100,000 people

First cases of COVID-19: January 20, 2020

	South Korea	*USA*	*USA Higher Times...*
Cases/ 100,000	34	1,737	51 X
Deaths/ 100,000	<1	54	54 X

From: NY Times/WHO/CDC

Have Lockdowns, Social Distancing, Masks, Etc. Achieved Anything?

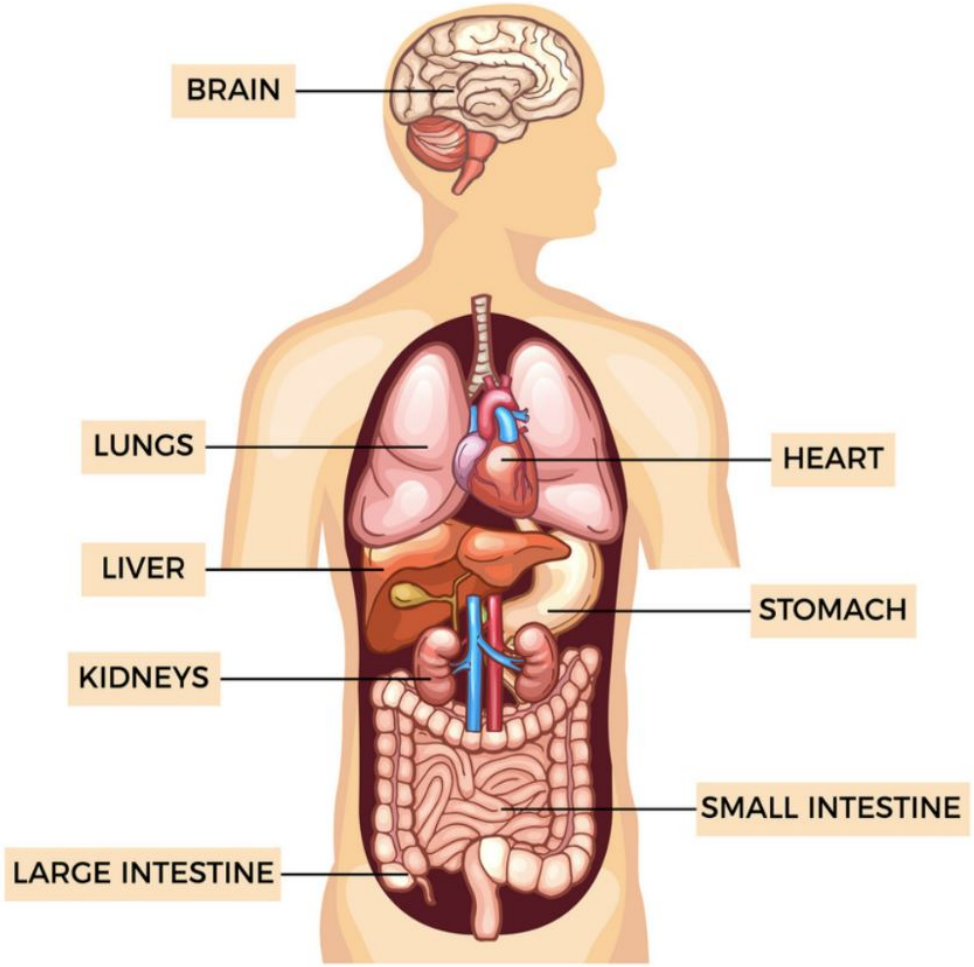
U.S., China, S Korea, Italy, Iran, France

	United States	*All 6 Countries*
# Cases Averted	60 million	495 million
# Deaths Averted	300,000*	~2.5 million*

Hsiang S et al. *Nature* 2020 Jun 8; [e-pub]. (https://doi.org/10.1038/s41586-020-2404-8)

* Assumes 0.5% mortality rate, a conservative estimate

What Are COVID's Effects On the Body?



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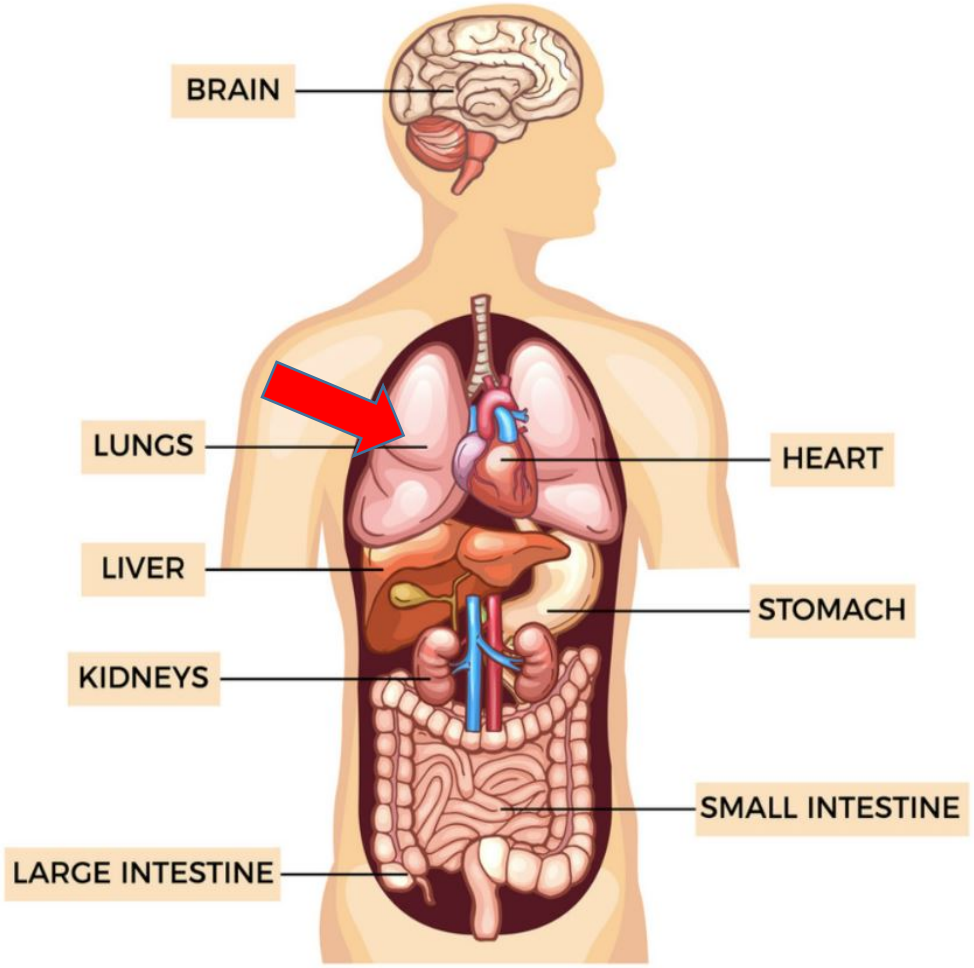

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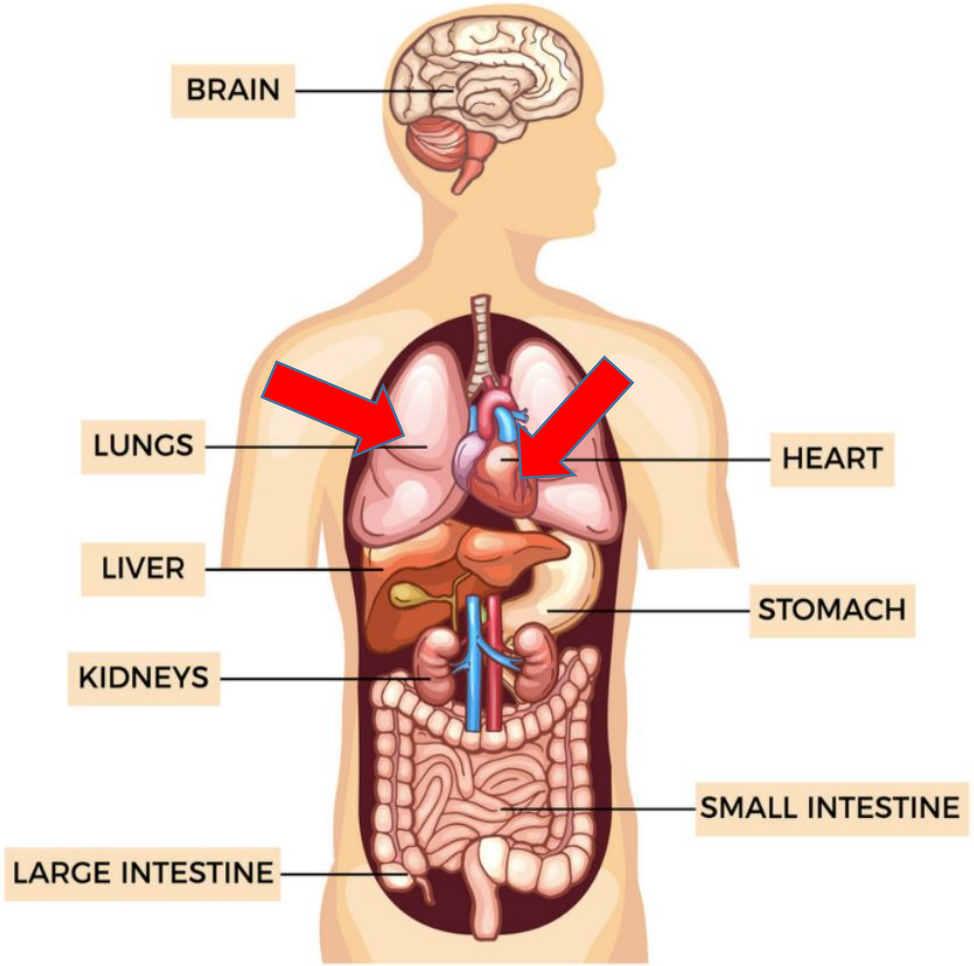
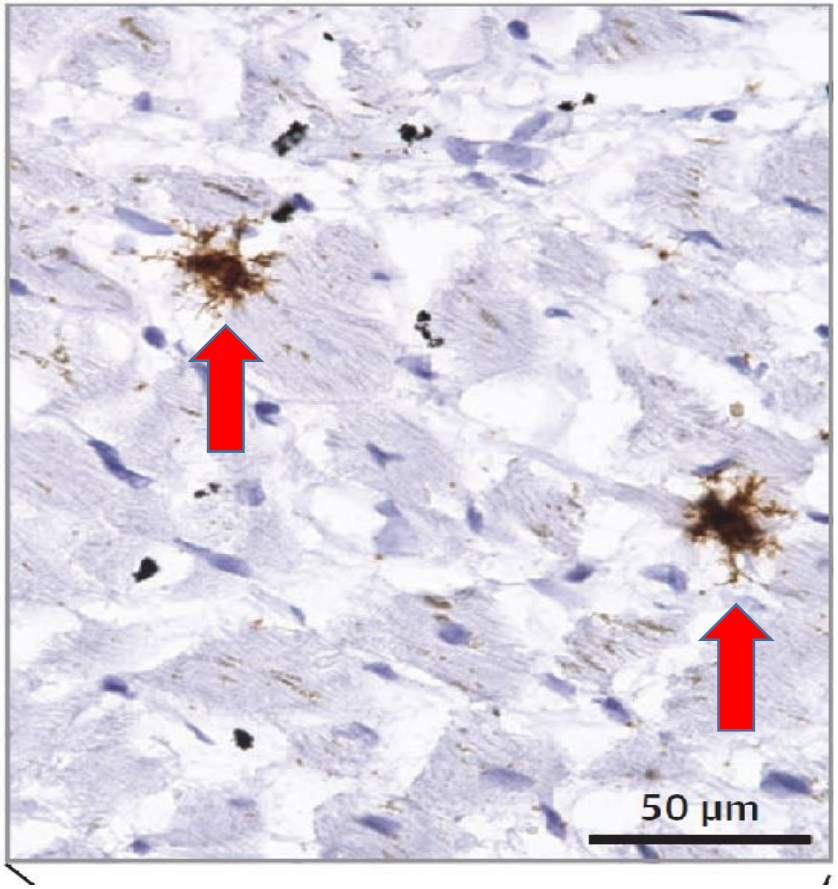
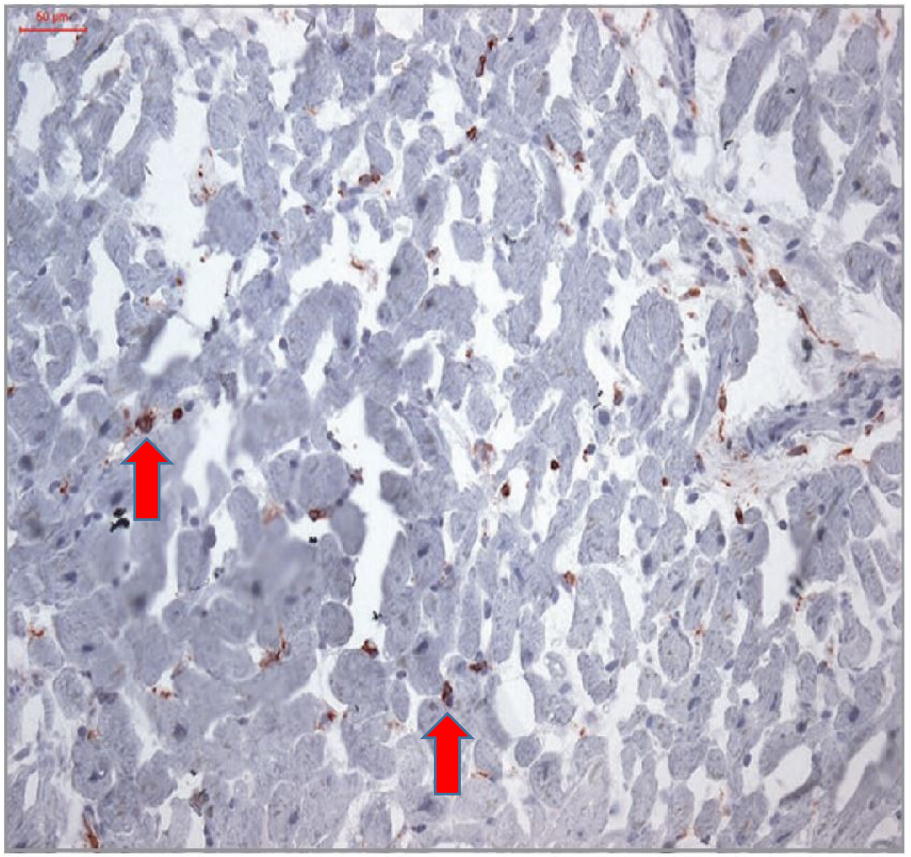


Coronavirus Infection of the Heart

SARS-CoV-2 in heart muscle



Activated lymphocytes in heart muscle



From: Lindner D, et al. JAMA Cardiology 2020 (pub. Online 7/27/20)
And Puntmann VO, et al. JAMA Cardiology 2020 (pub. Online 7/27/20)

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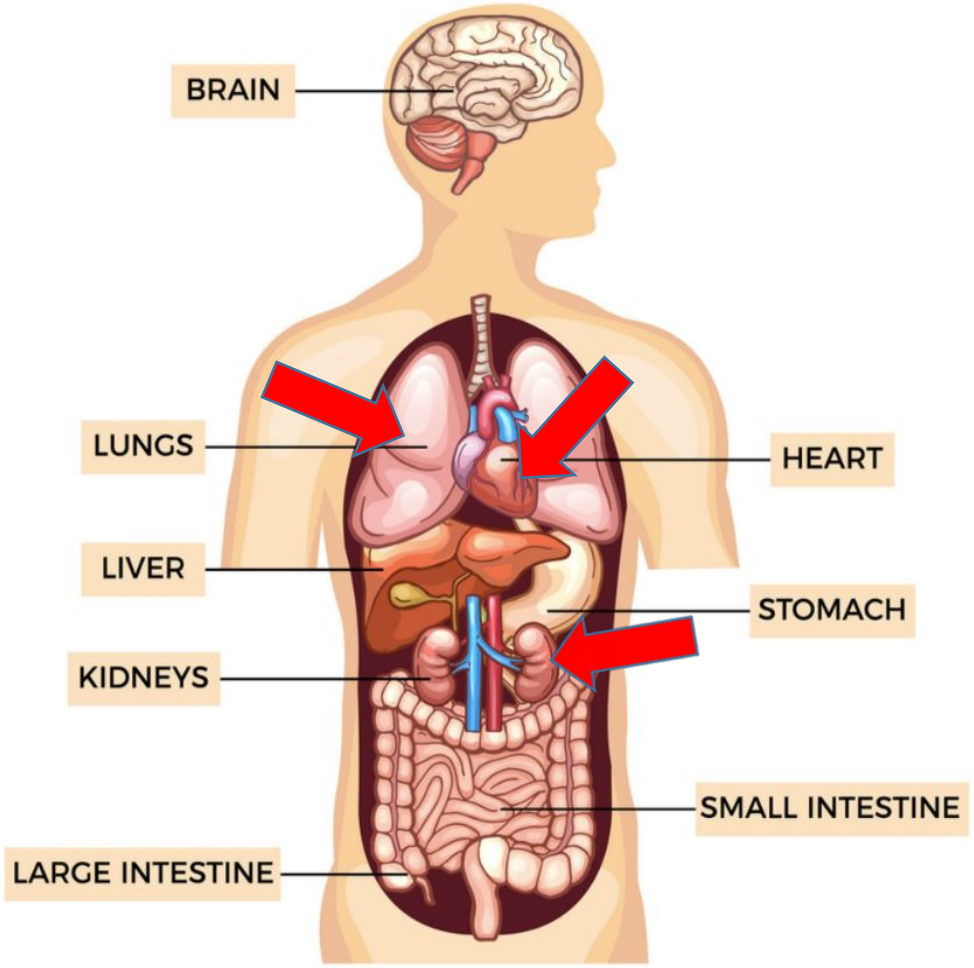

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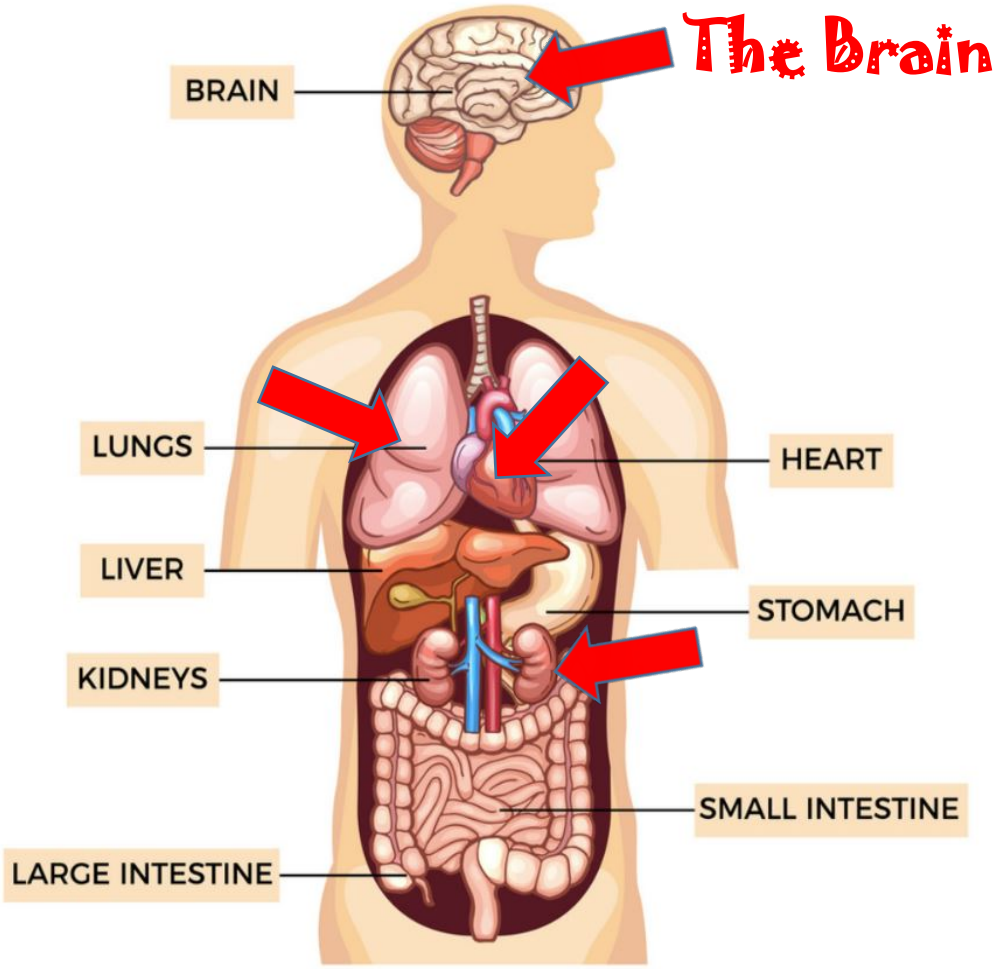


Neuroinflammation

Activation of the innate & adaptive immune systems by stimuli both inside & outside the brain

What Happens to Someone Who Contracts the COVID Virus?

- Absolutely nothing: no symptoms, no lingering illness
- Mild symptom: cough, fever, achiness
- More serious symptoms: breathlessness, high fevers, exhaustion—monitored closely at home
- Hospitalization, supplemental oxygen ± ventilator
- Lung failure, kidney failure, heart failure, strokes
- Death

What Happens to Someone Who Contracts the COVID Virus?

- Mild symptom: cough, fever, achiness → Recovery OR Long hauler
- More serious symptoms: breathlessness, high fevers, exhaustion—monitored closely at home → Recovery OR Long hauler
- Hospitalization, supplemental oxygen ± ventilator
- Lung failure, kidney failure, heart failure

→ Recovery OR / Long hauler OR / Death

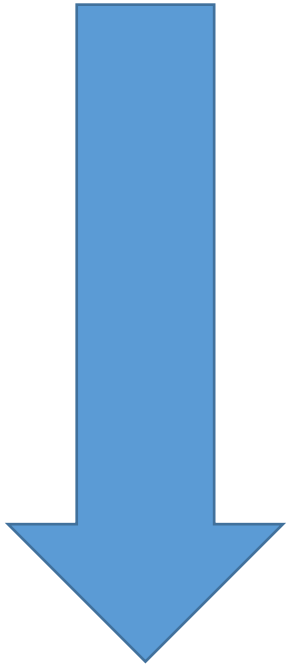
The “Long Haulers”

- Many COVID-19 patients recover completely: back to prior state of health
- Recover almost: mild residual symptoms
- Recover a little: severe residual symptoms that meet criteria for ME/CFS; and/or with chronic lung, heart, kidney or brain dysfunction

The Long Haulers

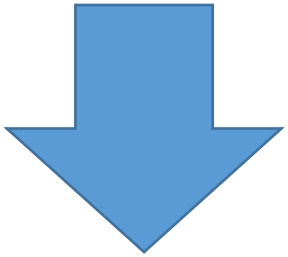
The Story of Two COVID-19 Patients

Middle-aged man, mild COVID pneumonia



Sleeps all day, cannot work: a long hauler

Elderly woman with leukemia and arterial disease: becomes severely ill from COVID, has cardiac arrest, is resuscitated, finally leaves the hospital



Has minimal lung damage, and feels fine

From: Couzin-Frankel J. Science 2020;369:614

Why Can Outcomes Be So Different?

- The amount of virus that enters the body
- Inherited genes that make us more or less vulnerable
- Chronic illnesses (like high blood pressure, obesity) that us more vulnerable
- The quality of medical care

So COVID-19 can affect many organs, but what's the evidence that it can cause ME/CFS?

Why Might ME/CFS Develop After COVID?

- ME/CFS often, but not always, begins as an apparently infectious illness—symptoms like a “cold” or “flu”
- ME/CFS can develop after well documented acute infections, even when those infections have been properly diagnosed and treated

Infections That Can Be Followed by ME/CFS or Similar Chronic Illness

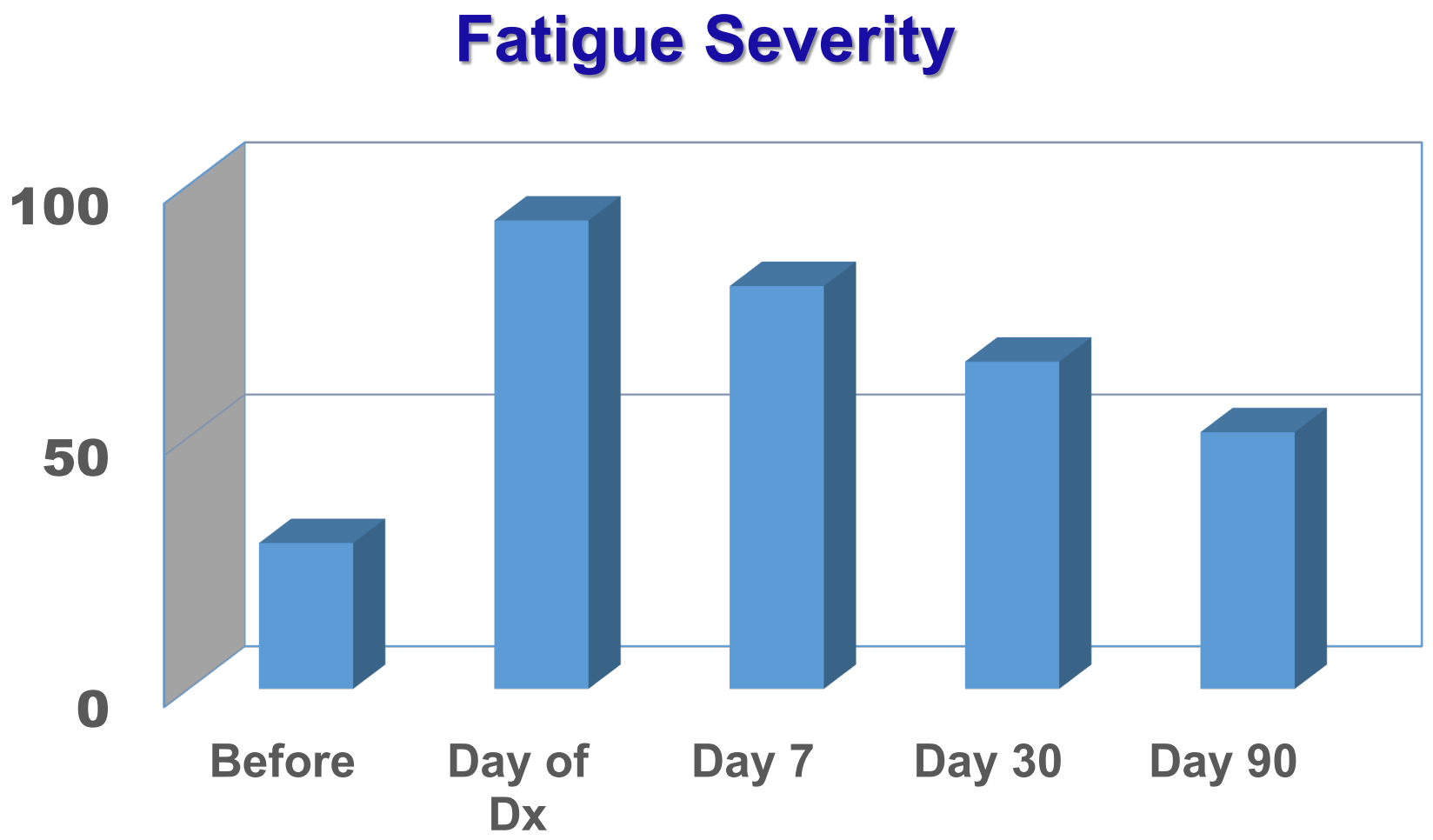
- Infectious-like illnesses[1-3]
- Epstein-Barr virus[4,6,7]
- Lyme disease[5]
- *Coxiella burnetti*[7]
- Ross River virus[7]
- *Mycoplasma pneumoniae*[8]
- Enteroviruses[9]
- Human herpes-6[10]
- Ebola[11]
- West Nile Virus[12]
- SARS[13]
- Dengue[14]
- Parvovirus[15]
- COVID-19???

1 Shelokov A, et al. NEJM 1957:257:345.
2 Poskanzer DC, et al. NEJM 1957:257:356.
3 Acheson ED. Am J Med 1959;4:569.
4 Jones JF, et al. Ann Intern Med 1985;102:1.
5 Sigal LH. *Am.J.Med*. 88:577-581, 1990.
6 White PD, et al. *Br J Psychiatry* 1998;173:475
7 Hickie I, et al. BMJ;2006;333:575.
8 Salit IE, at al. Can Dis Wkly 1991;17:E:9.
9 Chia JKS. *J Clin Pathol* 2005;58:1126.
10 Komaroff AL. *J Clin Virol* 2006;37:S39.
11 Epstein L, et al. *NEJM 2015;*373:2483.
12 Sejvar JJ, et al. *J Neuropsychol* 2008;2:477.
13 Moldofsky H, et al. *BMC Neurol 2011;*11:37.
14 Seet RC, et al. *J Clin Virol* 2007;38:1.
15 Kerr JR, et al. *J.Gen.Virol*. 2010;91:893.

Fatigue And Infections

- Fatigue is common during many *acute* infections, including almost all types of pneumonia
- Some level of fatigue can persist for a while *after* infections have been properly treated
- Debilitating fatigue (and other symptoms) can last months/years following some infections (post-infectious fatigue)

Persistent Fatigue Following Non-COVID Pneumonia



From: Metlay JP, et al. J Gen Intern Med 1997;12:423.

Why Might ME/CFS Develop After COVID?

- **Because it is looking like it does:**

  "It's extraordinary how many people have a postviral syndrome that's very strikingly similar to myalgic encephalomyelitis/chronic fatigue syndrome. They just don't get back to normal energy or normal feeling of good health."

  -- Dr. Anthony Fauci, Medscape Interview

IOM/CDC Case Definition of ME/Chronic Fatigue Syndrome

1. Substantial impairment in the ability to function at home or at work, lasting *for more than 6 months*, accompanied by profound fatigue, of new or definite onset (not lifelong), not substantially alleviated by rest AND
2. Post-exertional malaise AND
3. Unrefreshing sleep

PLUS at least one of:

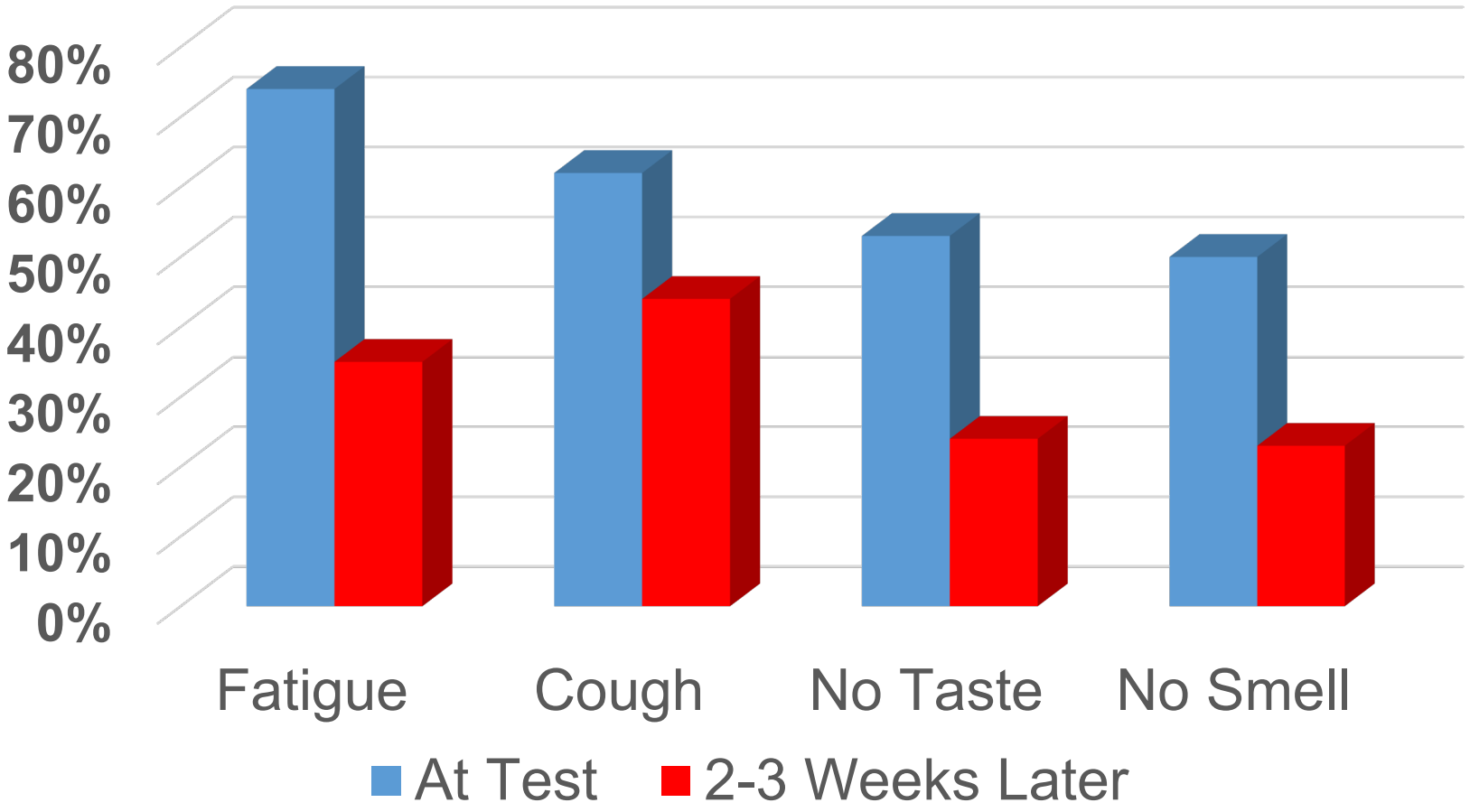
4. Cognitive impairment OR
5. Orthostatic intolerance

Redefining an Illness. Institute of Medicine, 2015.

So Does ME/CFS Follow COVID-19?

- Although the COVID pandemic began in December, most cases have begun only in the past 2-3 months in the U.S.
- So it will take several more months before we are in a position to know if ME/CFS—according to case definitions—develops post-COVID, and how often
- But what do we know so far?

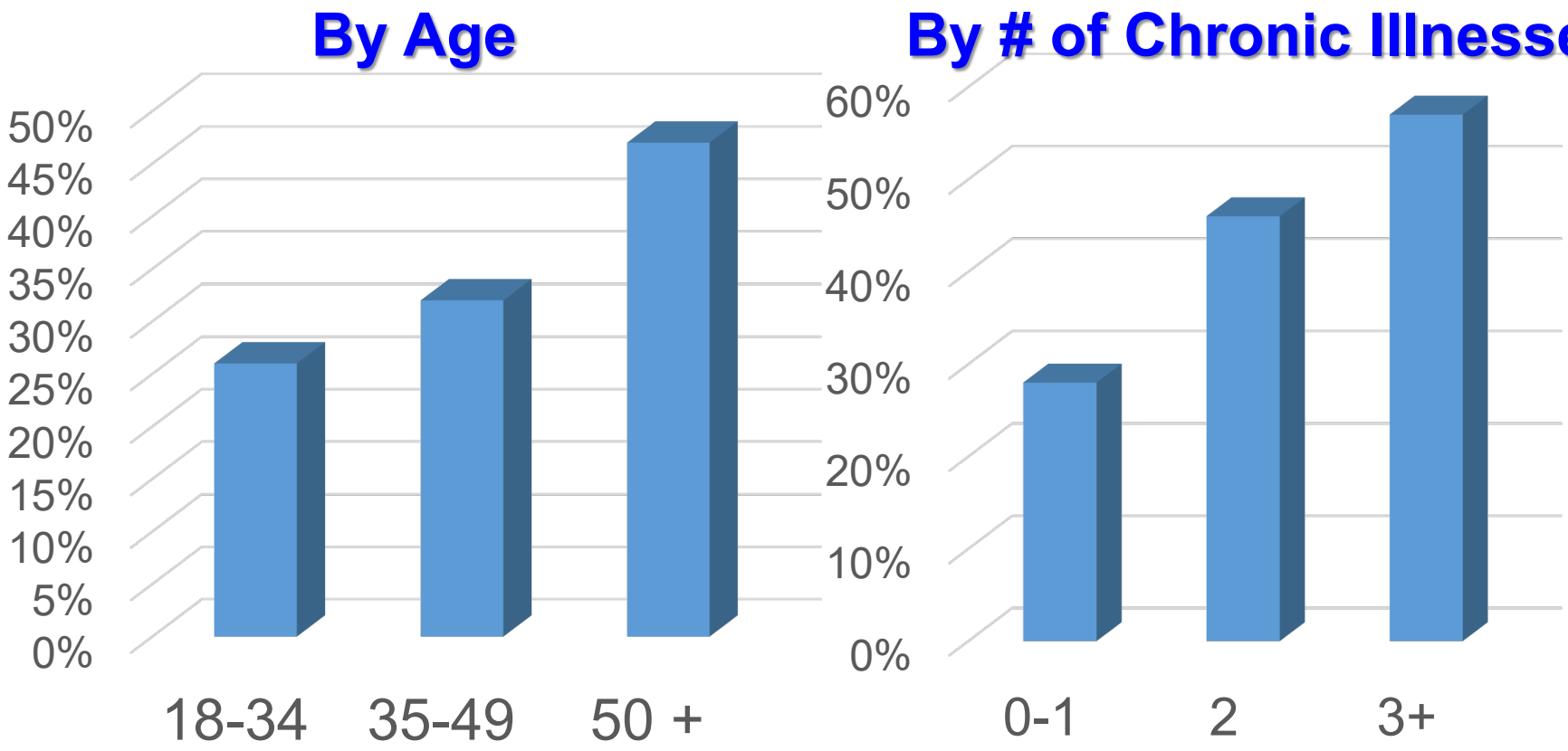
Continued Symptoms in Adult Outpatients Testing Positive For COVID-19



From: Tenforde MW, et al. MMWR July 24, 2020

Continued Symptoms in Adult Outpatients Testing Positive For COVID-19

% Who Did Not Return to Usual Health 2-3 Weeks Later



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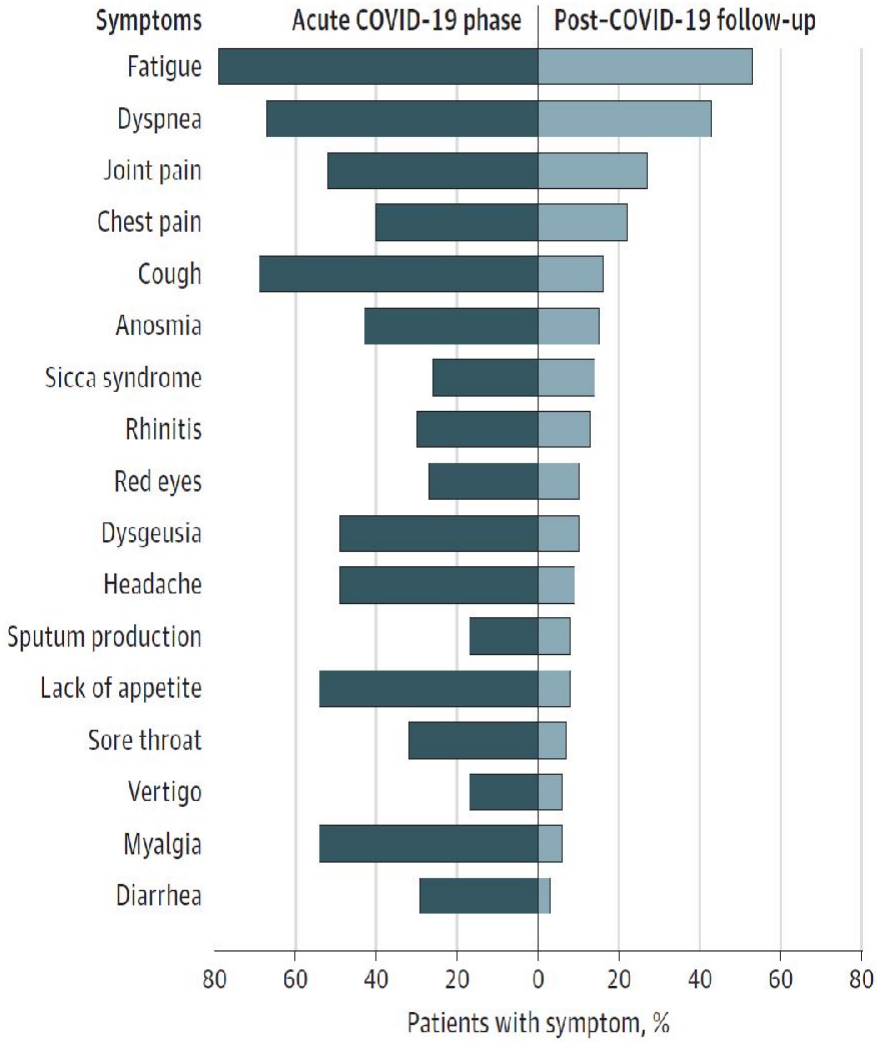
Symptoms During and After COVID-19
Experience from Italy

143 definite COVID-19 patients, now free of virus

- **Mean age 56.5 years**
- **37% women**
- **20% low oxygen levels**

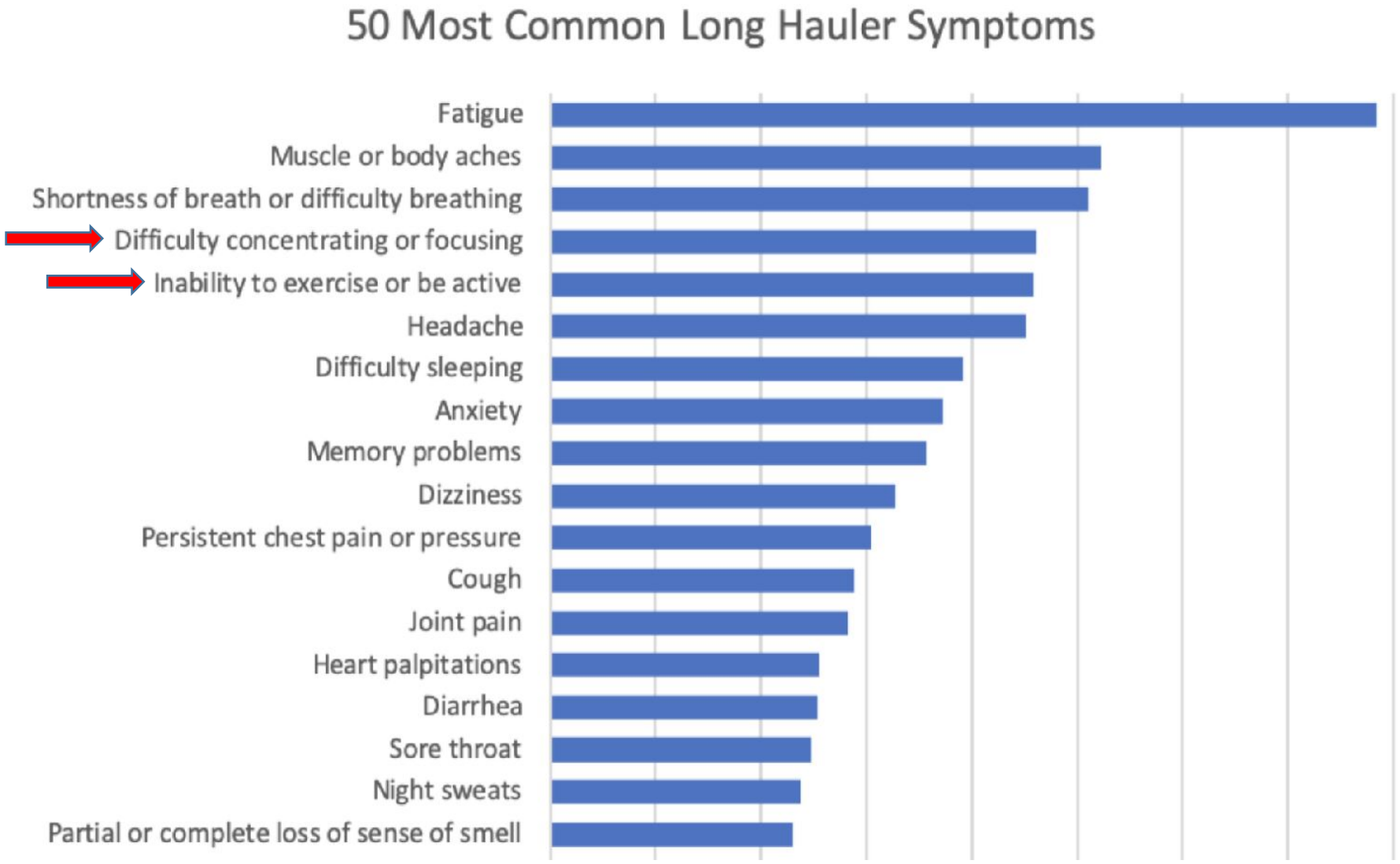
60 days after getting sick:

- **55% had at least 3 ongoing symptoms (none fever)**
- **41% had worsened quality of life**



From: Carfi A, et al. JAMA 2020;324:603

Survey of Facebook Survivors Group



From: Survivor Corp Facebook group survey, N= 1,567, Indiana U School of Medicine

COVID Support Group*

- Online survey of 1500 people with confirmed or suspected COVID-19, mostly from U.S. or U.K.
- 82% reported symptoms lasting over 2 months; 54% with symptoms > 3 months
- 80% between ages of 30-60
- 41% felt the doctors had not listened to or believed them

** Reported by "long hauler" Karyn Bishof*

Being Taken Seriously

When First Becoming Sick

- **People with COVID-19 were disbelieved in February – May because doctors didn't yet realize how many organs could be affected and symptoms caused**
- **The failure of enough accurate testing caused many to be misdiagnosed**

Subsequently

- **"You can't still have COVID...when the virus leaves your body you're better."**
- **"There is no documented lingering illness after COVID: it's not in the textbooks."**

From: Yong E. Long-haulers are redefining COVID-19. The Atlantic 8/20

Body Politic COVID Support Group

Neurologic Symptoms

- Extreme, persisting fatigue (91%)
- Headaches (88%)
- Poor quality sleep (84%)
- Lack of concentration (86%)

Heart Symptoms

- Palpitations (73%)
- Chest pain (77%)

Lung Symptoms

- Cough (70%)
- Shortness of breath (87%)

So A State of Chronic Fatigue And Other "ME/CFS Symptoms" Can Follow COVID-19

What is the biological explanation?

Is it the same biological explanation as in people with ME/CFS that did not start with COVID-19?

"ME/CFS is like the flu, but like a flu that never goes away."

-- Many, many patients

What do we feel like when we get the flu....

why do we feel that way...

and why does it go away?

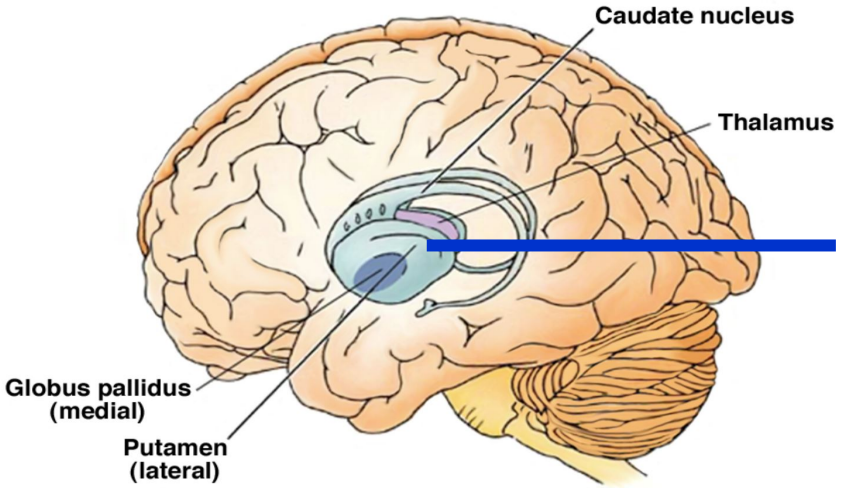
Hard-Wired Sickness Symptoms:
A Hunkering Down Mechanism

- Seen in most animals, even invertebrates
- A *temporary, acute* response to injury and infection: the brain decreases energy-consuming activities causing lethargy, social withdrawal, achiness, sleepiness, loss of libido, difficulty thinking, depression, reduced appetite – to focus body's energy stores on fighting infection & healing injury. When injury/ infection are healed, the behavior is *turned off*.
- Are there circumstances in which this acute physiology could become *chronic*, with sickness symptoms becoming chronic: *not turned off*?

From: Morris G, et al. BMC Medicine 2013;11:64

What Causes the Symptoms of ME/CFS?

Speculative Model: Many Triggers, Final Common Pathway



Fatigue nucleus: in basal ganglia/ prefrontal cortex/ ant. cingulate/ hypothalamus?

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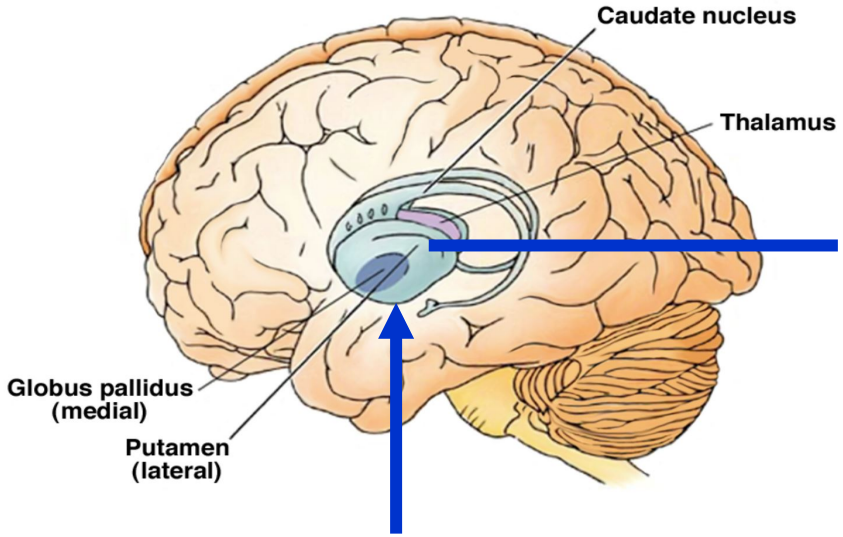

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Activation of brain's innate immune system (e.g., microglia) yields cytokines that trigger fatigue nucleus

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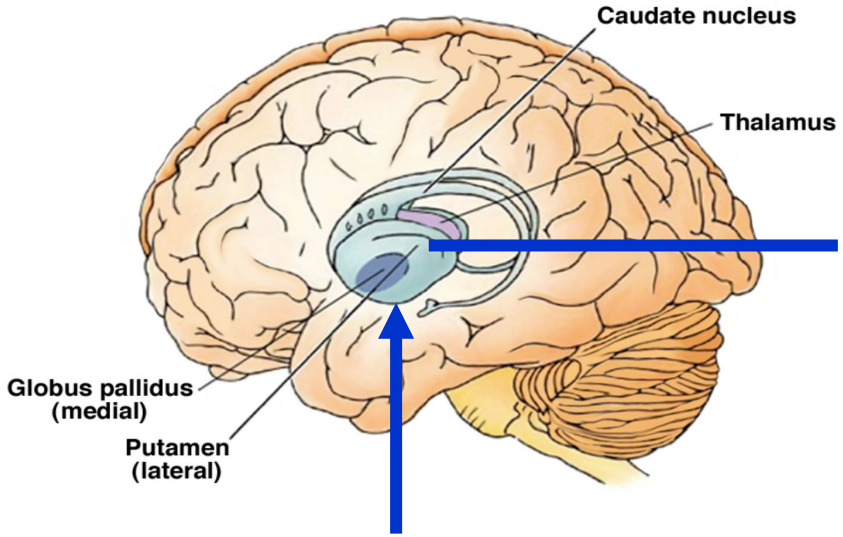


Fatigue nucleus: in basal ganglia/ prefrontal cortex/ ant. cingulate, hypothalamus?

- Infection of the brain
- Auto-Abs
- Toxins
- Obesity
- Chronic stress
- ⬆ leptin

→ **Activation of brain's innate immune system (e.g., microglia) yields cytokines that trigger fatigue nucleus**

← **Infection/ inflammation elsewhere in the body, signaling the brain**

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.

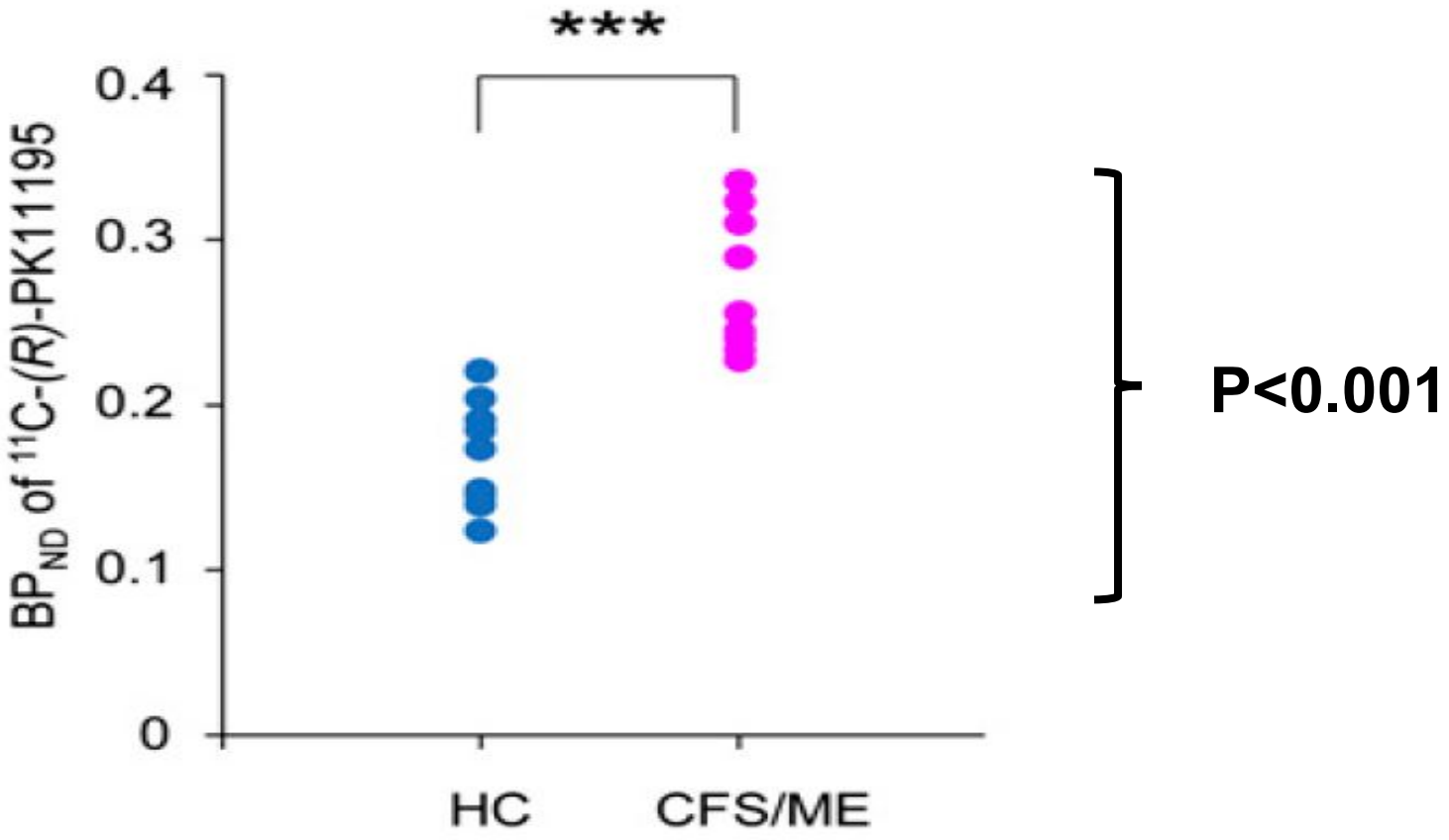
What's the Evidence for this Theory?

Theory: **Activation of the brain's immune system (neuroinflammation) stimulates a "fatigue nucleus" (a group of neurons) to cause all of the symptoms of an acute infection like the flu, and possibly of ME/CFS. So:**

1. **Is there evidence of neuroinflammation in ME/CFS and does it cause fatigue?**

2. **Is there a fatigue nucleus, and where is it?**

PET Evidence of Brain Inflammation Distinguishes ME/CFS from Healthy



CFS: N=9 Controls: N=10.

From: Nakatomi Y, et al. J Nucl Med 2014; 55:945–950

MR Spectroscopy of the Brain Suggests Neuroinflammation

15 women with ME/CFS and 15 matched healthy controls
MR spectroscopy of the whole brain measuring metabolic markers of inflammation and temperature

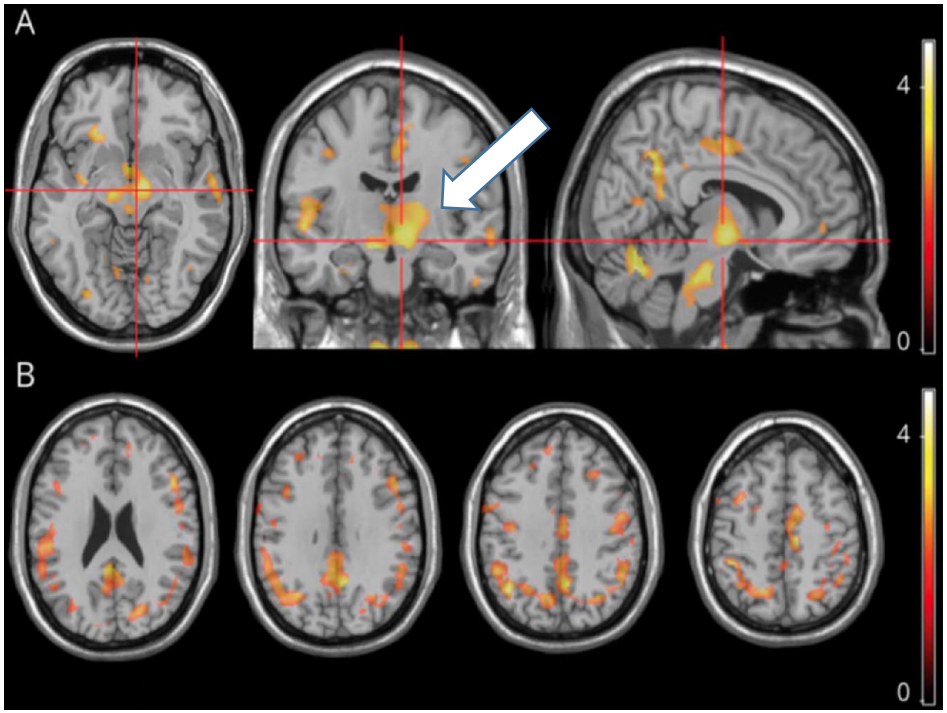
↑ choline/creatinine most prominent in left anterior cingulate (region that responds to ↑ inflammatory cytokines by causing fatigue and pain)

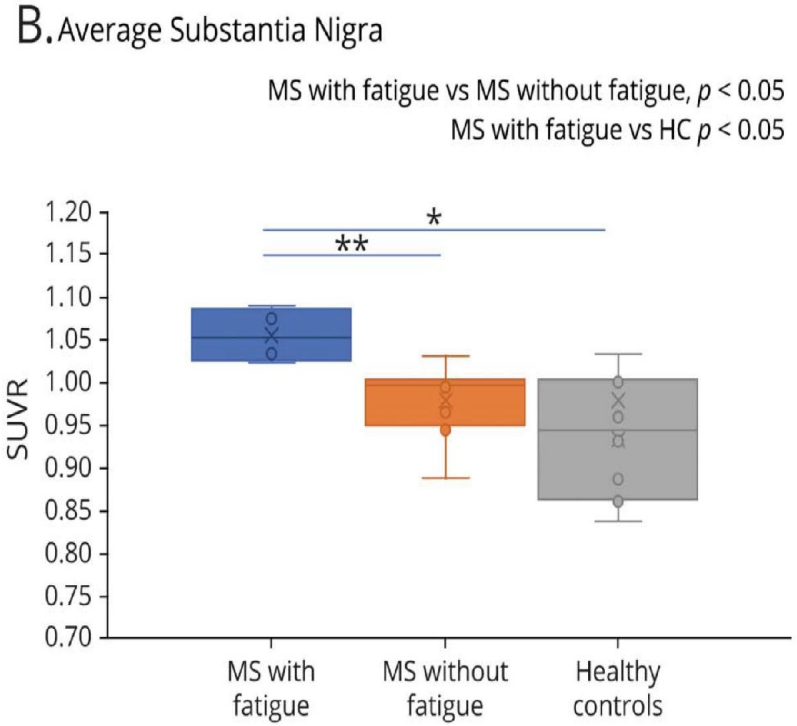
Metabolite ratios in 7 regions correlate with fatigue

Increased temperature and lactate throughout brain

From: Mueller C, et al. Brain Imaging and Behavior 2019; doi.org/10.1007/x11682-018-0029-4

Neuroinflammation Correlates With Fatigue in Multiple Sclerosis: MRI/PET Study





Neuroinflammation (activation of microglia and astrocytes), particularly in substantia nigra, correlates with fatigue score (P=0.002), and *not* with number of MS lesions or brain atrophy.

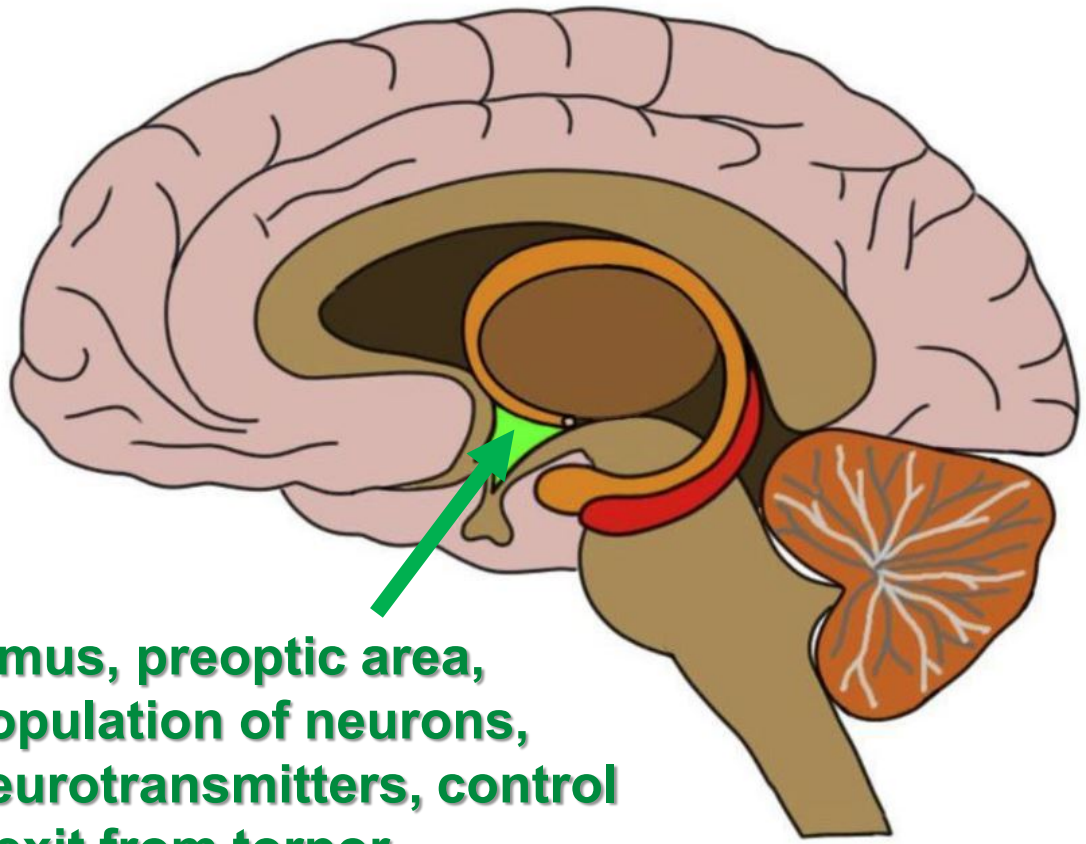
From: Singhal T, et al. Neurol Neuroimmunol Neuroinflamm 2020;7:e854.

What's the Evidence for this Theory?

1. So neuroinflammation does appear to be a cause of fatigue?

2. Is there a fatigue nucleus, and where is it?

Location Of A Torpor Nucleus in Mice



Hypothalamus, preoptic area, specific population of neurons, specific neurotransmitters, control entry and exit from torpor

Hrvatin S, et al. Nature 2020;583:115-21.
Takahashi TM, et al. Nature 2020;583:109-14.
Saper CB, Machado NLS. Nature 2020;583:34-5.

What Starts the Sickness Symptoms?

- Stimulation of a fatigue nucleus by an activated immune system in the brain (neuroinflammation) is very plausible
  - But what *ends* sickness symptoms, when we get a normal flu and...
  - Why is it that the sickness symptoms *don't end* when a person gets ME/CFS?

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- Why is it that the sickness symptoms *don't end* when a person gets ME/CFS?

But Don't Misunderstand....

- I'm not saying that the theory of neuroinflammation stimulating a fatigue nucleus is *the only* reason for ME/CFS
  - Autoimmunity
  - Impaired energy metabolism/oxidative stress
  - Immune system abnormalities
  - Autonomic nervous system abnormalities
  - Other?

Neuroinflammation

Immune abnormalities

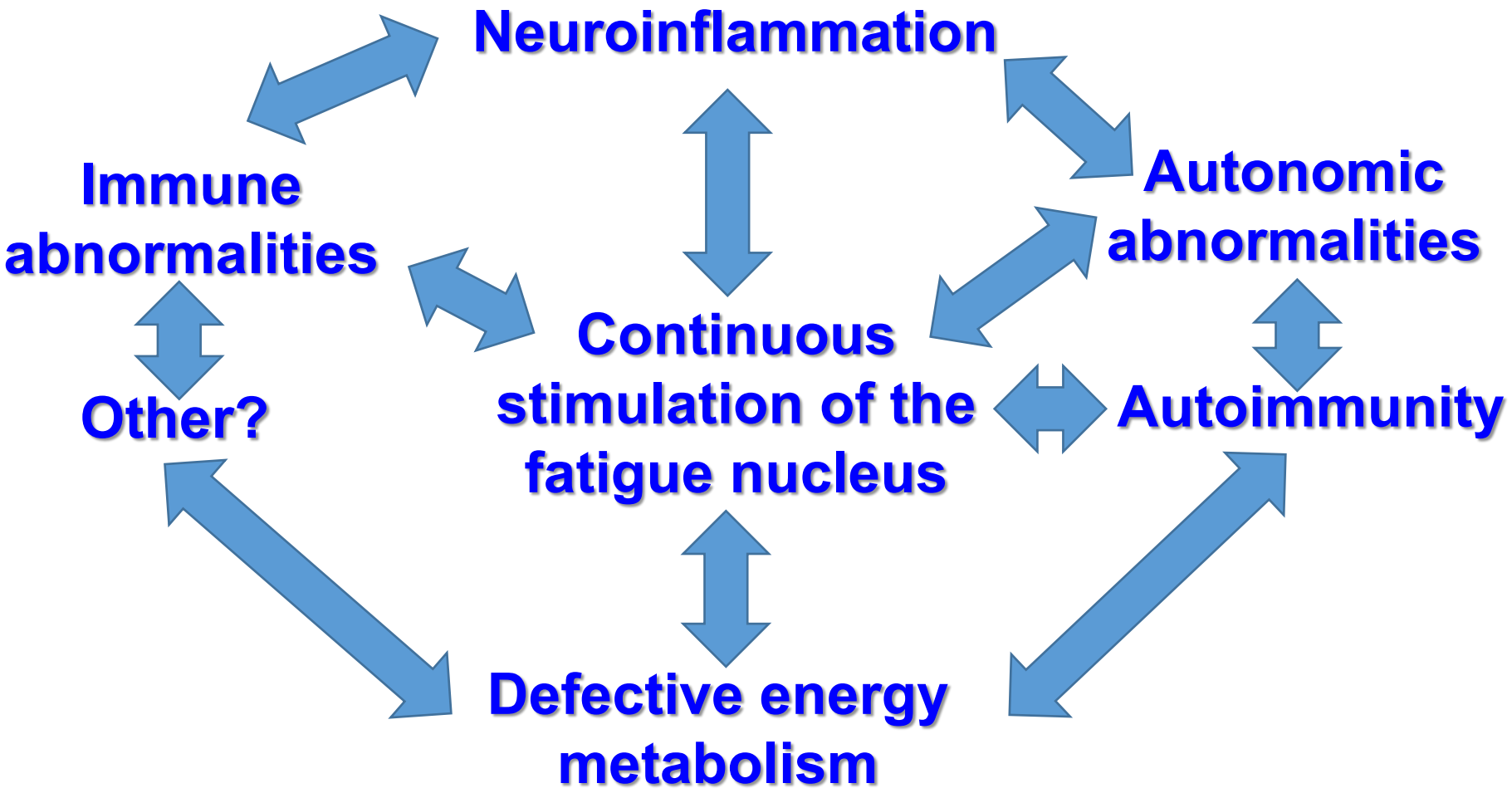
Autonomic abnormalities

Continuous stimulation of the fatigue nucleus

Other?

Autoimmunity

Defective energy metabolism


Neuroinflammation
Immune abnormalities
Autonomic abnormalities
Other?
Continuous stimulation of the fatigue nucleus
Autoimmunity
Defective energy metabolism

Conclusions

- There probably will be a post-COVID form of ME/CFS
- It is very important to study it:
  - to learn about and help treat the post-COVID condition
  - and possibly to learn more about ME/CFS not related to COVID-19
- The technology available today to understand the underlying biology of ME/CFS is remarkable

Questions to Study

- How common is post-COVID-19 ME/CFS?
- How long does it last?
- What happens when a person with ME/CFS gets COVID-19: Symptoms, laboratory test/biological changes?
- Are there differences between people with ME/CFS and people without ME/CFS when they get COVID-19:
  - Are people with ME/CFS more or less vulnerable to getting COVID-19?
  - Are neurological, metabolic, and immunologic findings different?

Final Remarks

- A remarkable amount of media attention post-COVID “long haulers”: renewed interest in ME/CFS
- Studies of long-haulers are underway all over the world – U.S., U.K., China, elsewhere
- Once again, one reason for this interest is an activated community of people afflicted by the illness – people studying it on their own, and pushing the biomedical community to study it.

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"A lot of people who don't have the energy to educate the world are educating the world."

-- Lauren Nichols*

From: Yong E. Long-haulers are redefining COVID-19. The Atlantic 8/20

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No conflicts of interest