# CDC Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Stakeholder Engagement and Communication (MECFS-SEC) Webinar/Conference Call

**Anthony L. Komaroff, M.D.**

**The Biology of ME/CFS: Emerging Models**

September 16, 2019

Federal Relay
Event ID: 4159714
Please visit http://mobilercc.sprintrelay.com on your mobile device

# The Biology of ME/CFS: Emerging Models

*Anthony L. Komaroff, MD*

*Brigham and Women's Hospital, Harvard Medical School*

*September 16, 2019*

*Centers for Disease Control and Prevention Webinar*

*No significant conflicts of interest*

# Mid-1980's: Where Were We?

**An illness characterized by only symptoms and no consistent objective abnormalities:**

- **No consistent physical exam abnormalities**
- **No diagnostic tests**
- **No proven treatments**
- **No information on prognosis**
- **No evidence of underlying biological abnormalities**

**Hence, some wondered if it was really a disease**

# 2019: Where Are We?

**Cases differ from healthy controls (and sometimes disease comparison controls):**

- **Central and autonomic nervous system**
- **Metabolism (particularly energy metabolism)**
- **Immune phenotype and function**
- **Microbiome (?)**

# Neurologic Changes

## Structural & Functional Brain Imaging

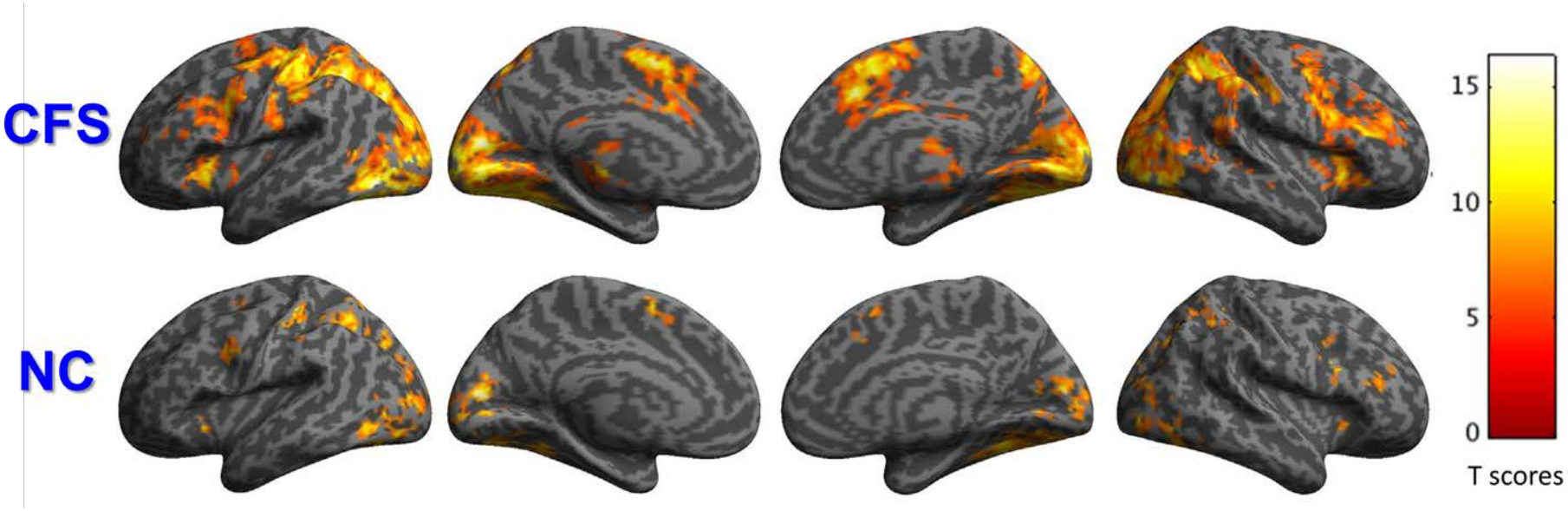
## Autonomic abnormalities

# CNS Involvement in ME/CFS

- ***Neuroendocrine dysfunction:*** **Impairment of multiple limbic-hypothalamic-pituitary axes (involving cortisol, prolactin, & growth hormone) and serotonin (5-HT) system**
- ***Cognition:*** **Impairments in information processing speed, memory and attention—not explained by concomitant psychiatric disorders**
- ***Autonomic dysfunction:*** **Impaired sympathetic and parasympathetic function, 30-80%**
- ***MRI:*** **Multiple anatomic and functional abnormalities**
- ***SPECT:*** **Areas of reduced signal**
- ***PET:*** **Immune cell activation (neuroinflammation)**
- ***EEG abnormalities:*** **⇧ sharp/spike waves, distinctive spectral coherence pattern, impaired connectivity**

# Brain Activation When Challenged
## An fMRI (BOLD) Study During Stroop Test

**When challenged, CFS pts equally accurate but much slower responses. And more brain areas (cortex and subcortical) are activated--esp. amygdala, hippocampus, basal ganglia, thalamus: the brain has to "work harder."**




*From: Shan ZY, et al. NeuroImage: Clinical. 2018;19:279.*

# MR Spectroscopy of the Brain Suggests Neuroinflammation

- 15 women with ME/CFS and 15 matched healthy controls
- Abnormalities were found in multiple brain regions, particularly left anterior cingulate
- Metabolite ratios in 7 regions correlated with fatigue
- Increased ratio of choline/creatinine, and increased lactate, were prominent findings

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

# Metabolic Changes

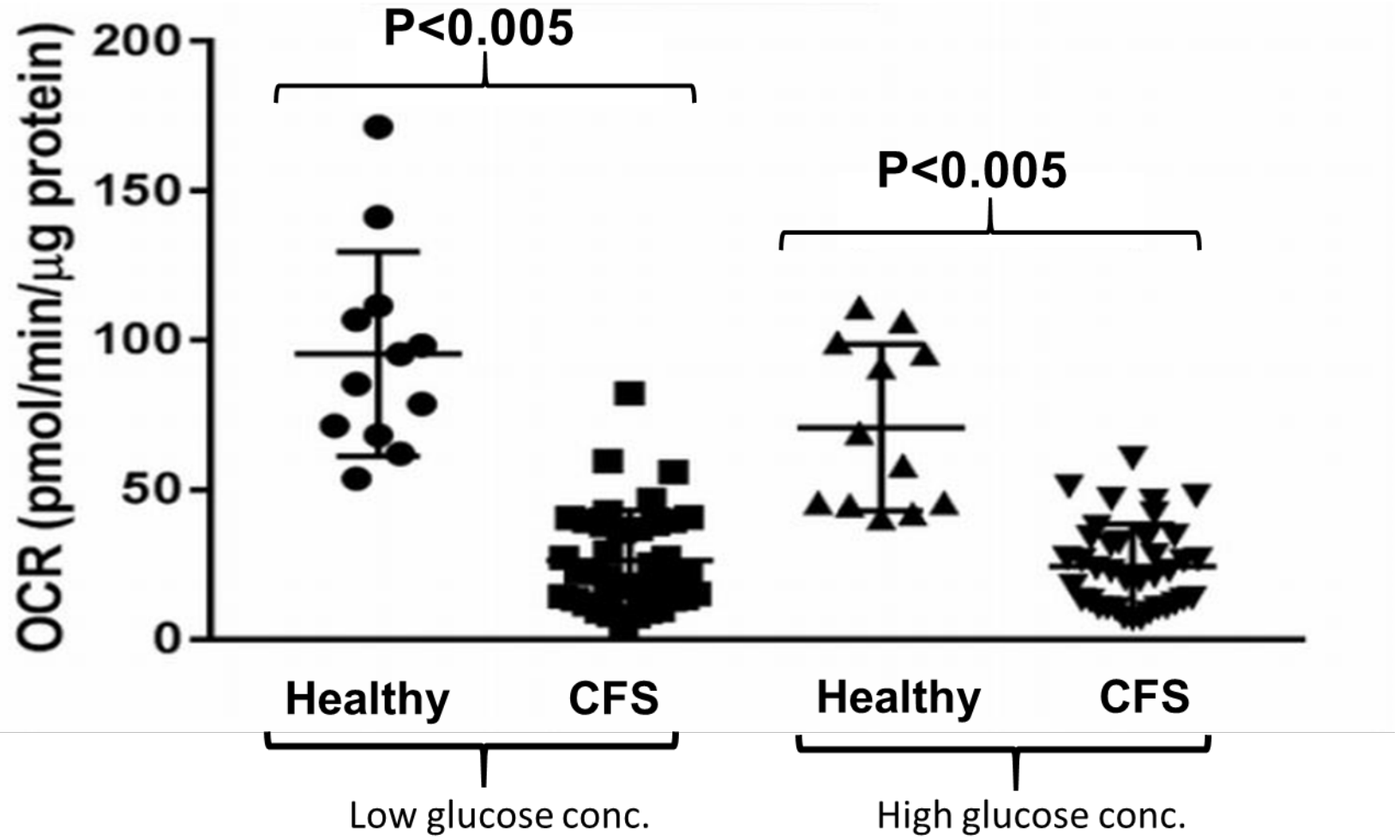
## Impaired ATP production

## Hypometabolism

## Oxidative/Nitrosative Stress

# Impaired OxPhos in ME/CFS

## Reduced Maximal Respiration (& 6 other measures)




*From: Tomas C, et al. PLoS ONE 2017: 12(10): e0186802.*

# Immunologic Changes

**Differences in the numbers of different types of white blood cells**

**Altered function of certain white blood cells**

**Different levels of cytokines**

# Immunological Abnormalities in ME/CFS

- Increased levels of circulating immune complexes
- Increased levels of immunoglobulin G
- Decreased levels of certain IgG subsets
- Increased numbers of CD8 + “cytotoxic” T cells bearing activation antigens (CD38 +, HLA-DR)
- Poorly functioning natural killer (NK) cells
- Increased blood levels of, and lymphocyte production of pro-inflammatory cytokines

# Cytokine Findings

- ***Blood*** **levels of many cytokines are significantly higher in ME/CFS patients than in healthy controls—in the first three years of illness, but not after[1]**
- **Levels of many cytokines in *spinal fluid* also distinguish patients from healthy controls[2]**
- **Levels of many circulating cytokines correlate positively with the severity of symptoms[3]**


*[1]Hornig M, et al. Science Advances 2015 (Feb 27);1:e1400121*
*[2]Hornig M, et al. Molecular Psychiatry (2016) 21, 261–269*
*[3]Montoya JG, et al. PNAS 2017;114:E7150-7158*

# Microbiome

## Skew toward proinflammatory species

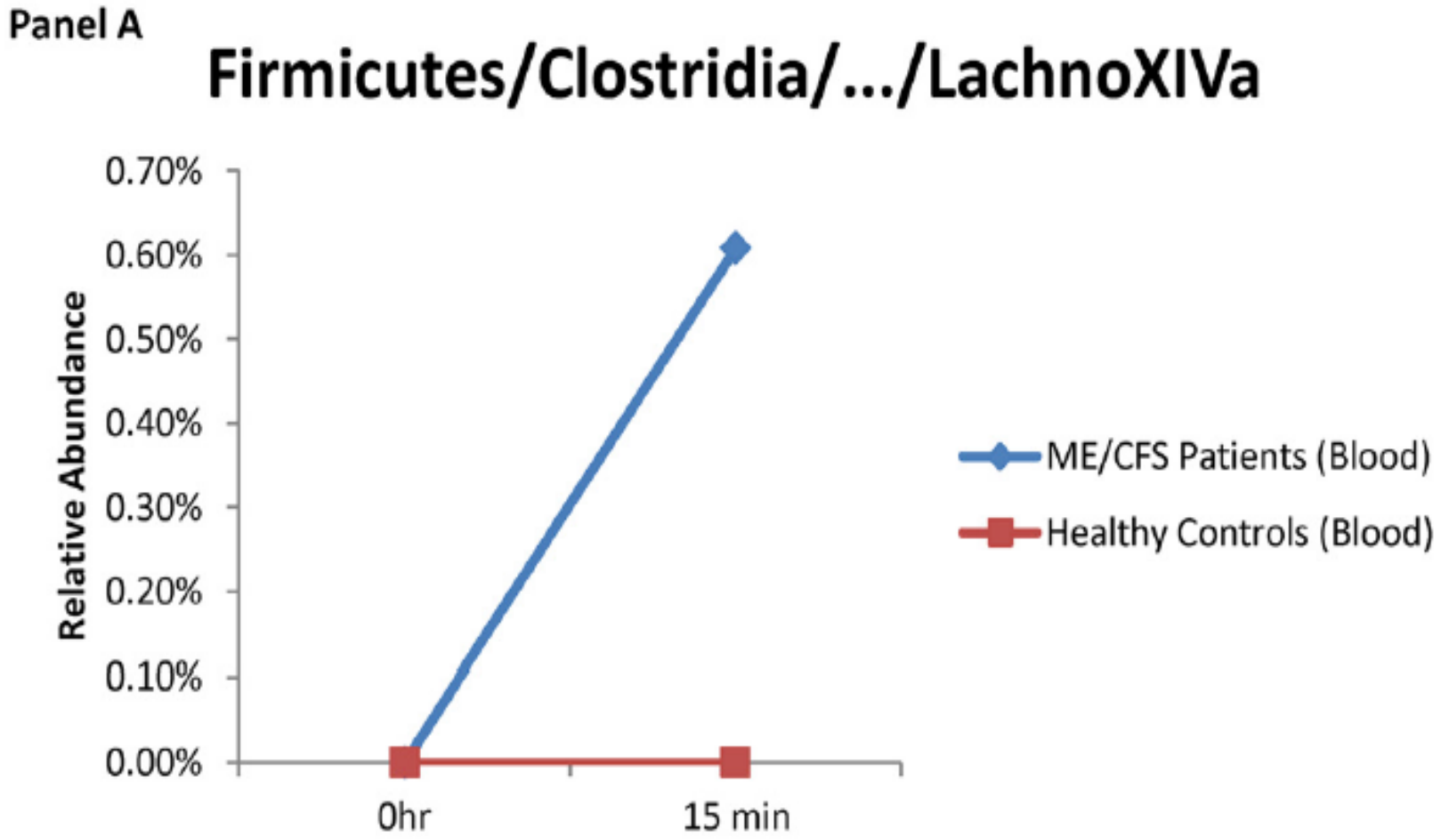
## Evidence of “leaky gut”

# How the Microbiome May Affect The Brain

- **The human microbiome:** Contains more than 100 times as many genes as we have human genes—a 2nd human genome, additional endocrine organ:
- **Microbial** genes produce molecules that affect **human** physiology:
  - Synthesize hormones and neurotransmitters (e.g. norepinephrine, serotonin, dopamine, ACh, GABA)
  - Synthesize molecules of inflammation (cytokines, prostaglandins) and elicit the production of inflammatory molecules by the gut immune system
  - Inflammation causes the gut to become "leaky": the tight junctions that bind gut epithelial cells together become loosened — allowing bacteria and bacterial toxins to enter the blood, eliciting a systemic innate immune response

*From: Navaneetharaja N, et al. J Clin Med 2016;5:55*

# Exercise Causes Gut Bacteria to Enter the Blood in People with ME/CFS

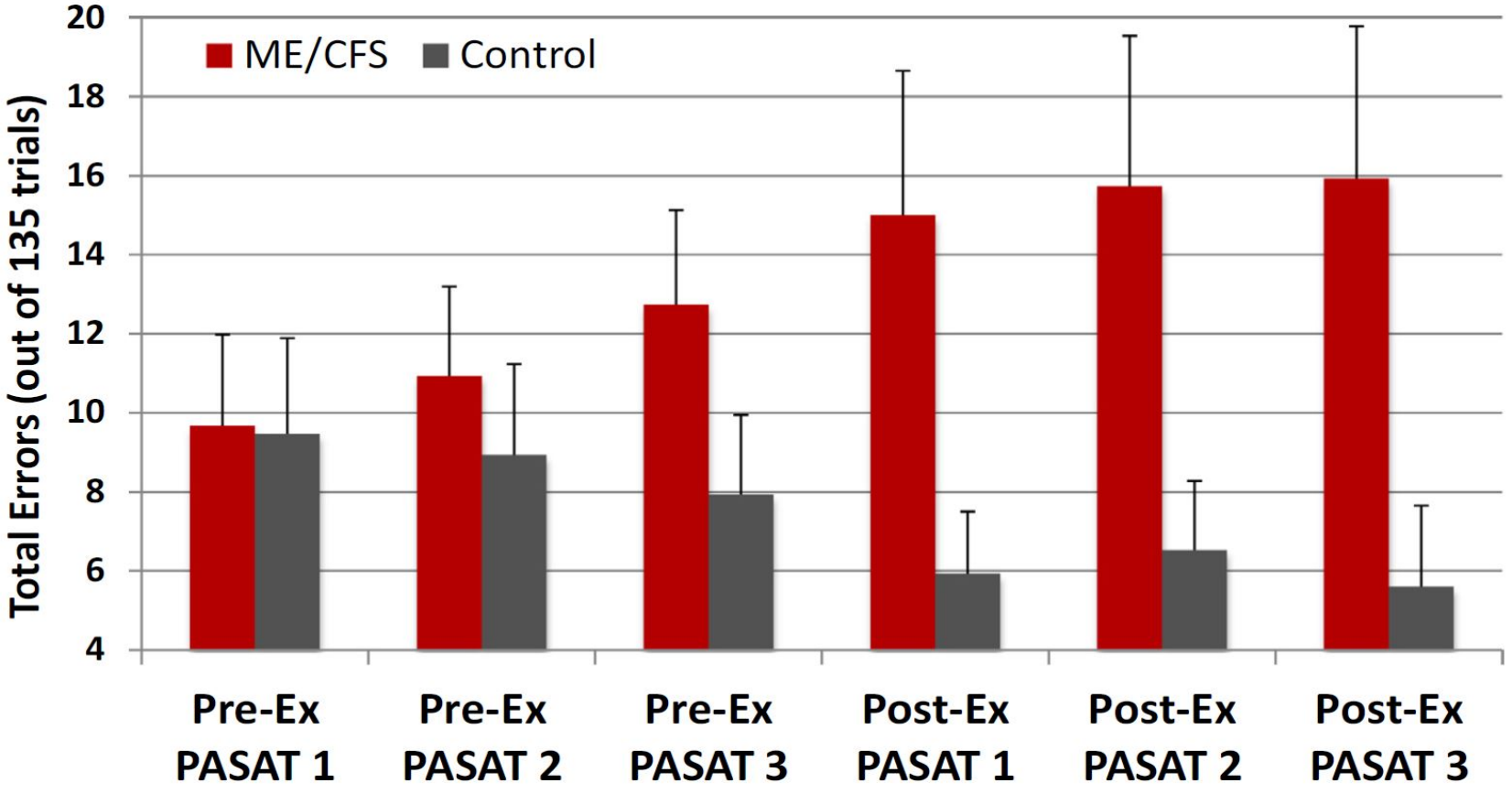



*From: Shukla SK, et al. PLoS ONE 2015;10(12): e0145453. doi:10.1371/journal.pone.0145453*

# Post-Exertional Malaise

# Effect of Exercise on Cognition

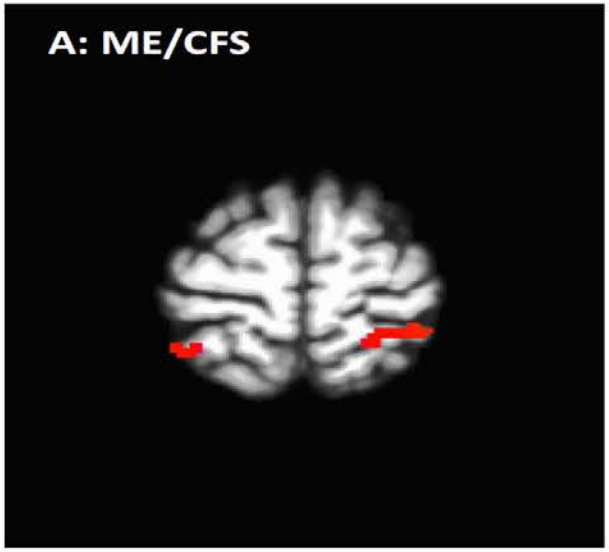
## Number of testing errors with 3 repeated tests, pre- and post-exercise

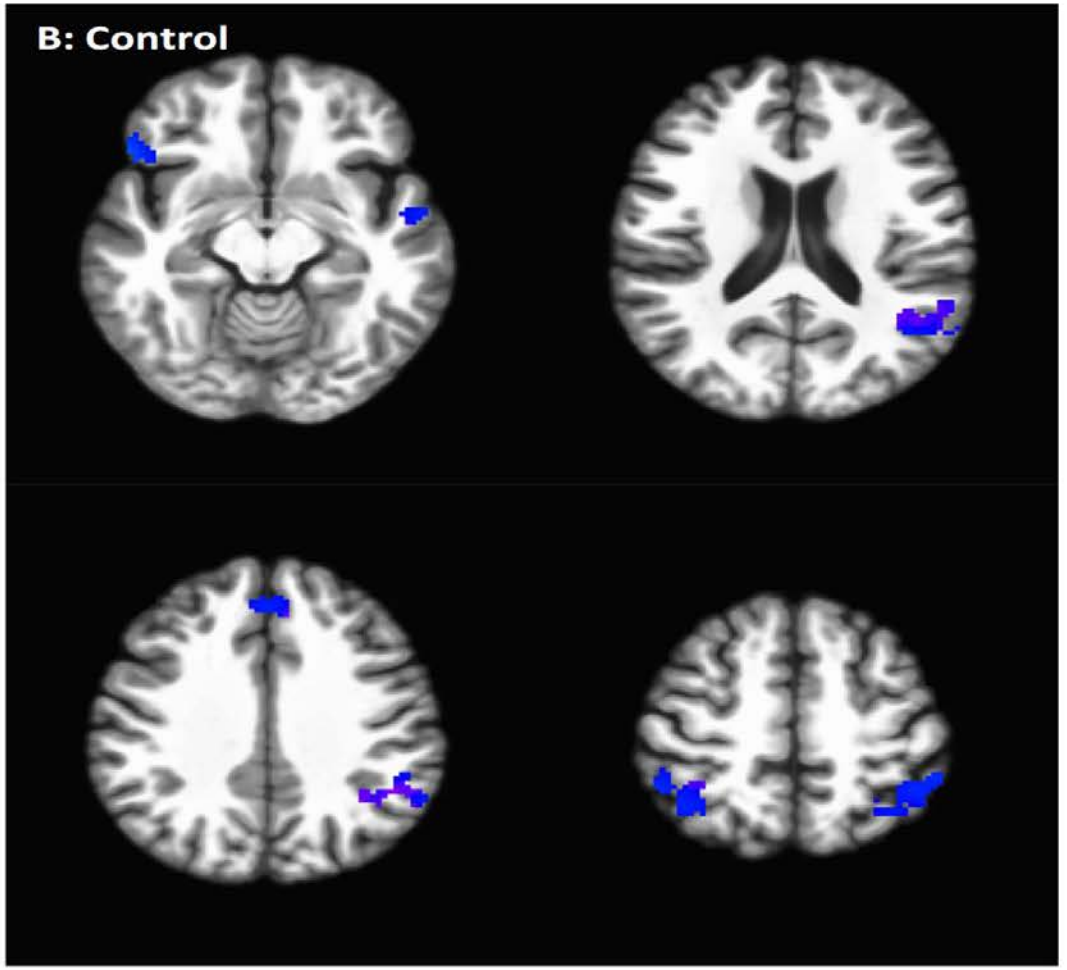



*From: Cook DB, et al. Brain, Behavior & Immunity. 2017;62:87.*

# Brain Activity Post vs. Pre-Exercise

## Red=Working harder; Blue=Working less hard




*From: Cook DB, et al. Brain, Behavior & Immunity. 2017;62:87.*

# Putting It All Together

Central & autonomic nervous system

Metabolism

White blood cell (immune system) types and function

Microbiome differences

# Several Alternative Models

- Sickness behavior/inflammation[3,4,5]
- Dauer/hibernation-torpor[6]
- Cell danger response/incomplete healing[7]
- Microbiome[8]


*[3]Morris G, et al. BMC Med 2013;11:64.*
*[4]Dantzer R, et al. Trends Neurosci 2014;37:39-46.*
*[5]VanElzakker MB. Front Neurol 2019; 10.3389/fneur.2018.01033*
*[6]Naviaux RK, et al. Proc Natl Acad Sci USA 2016;113:E5472-80.*
*[7]Naviaux, R.K., Mitochondrion, 2018 https://doi.org /10.1016/ j.mito.2018.08.001*
*[8]Nagy-Szakal D, et al. Microbiome 2017;5:44.*

# The Sickness Behavior/ Inflammation Model for ME/CFS

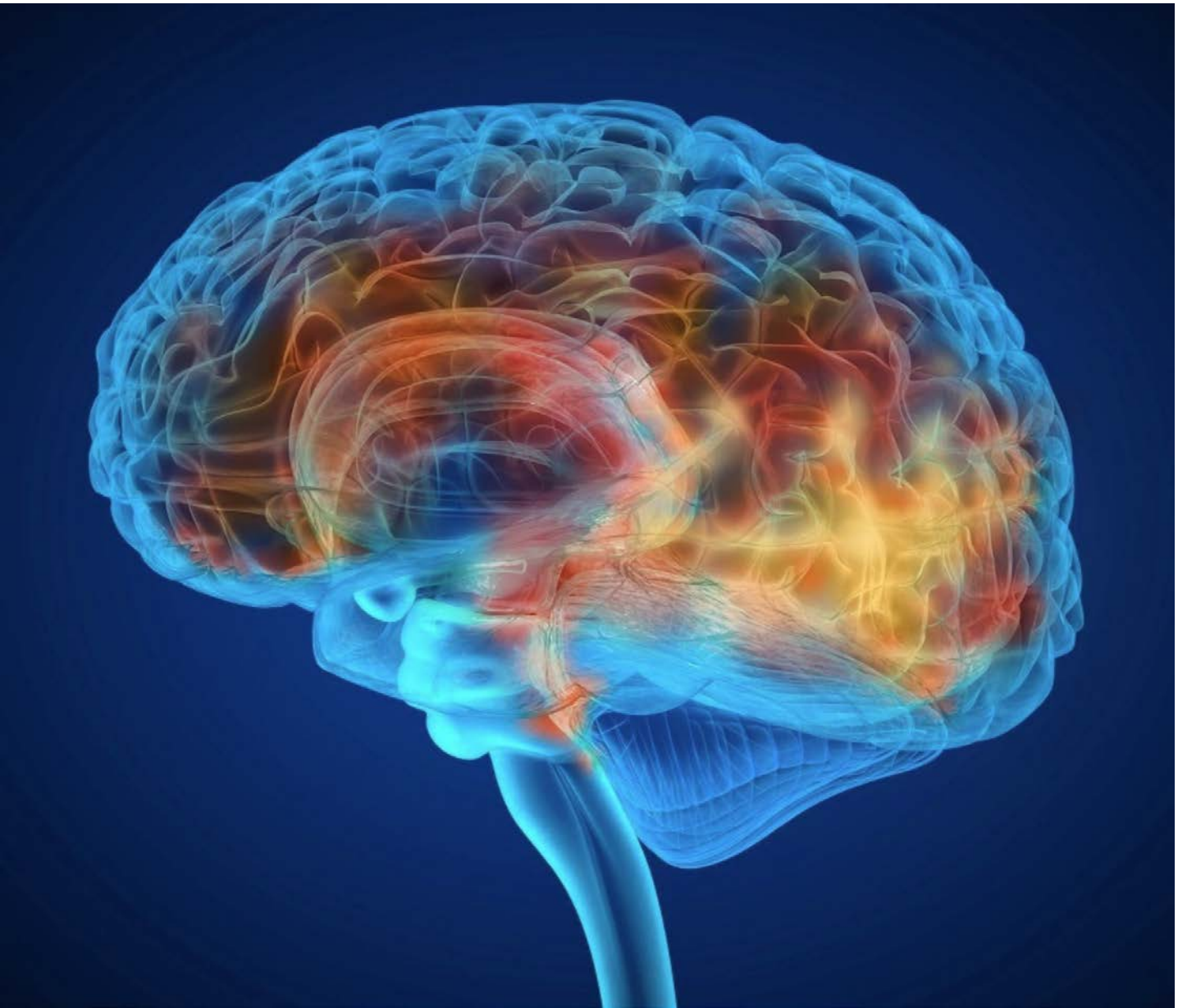
## What do we feel like when we're sick?

# Sickness Behavior

- **Seen in most animals, even invertebrates**
- **A *temporary* response to injury and infection: to focus body's energy stores on fighting infection & healing injury (*acute* inflammation & fever) the brain decreases energy-consuming activities: lethargy, social withdrawal, achiness, sleepiness, loss of libido, difficulty thinking, depression, anorexia**
- **Are there circumstances in which this acute physiology could become *chronic,* with sickness symptoms becoming chronic?**

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

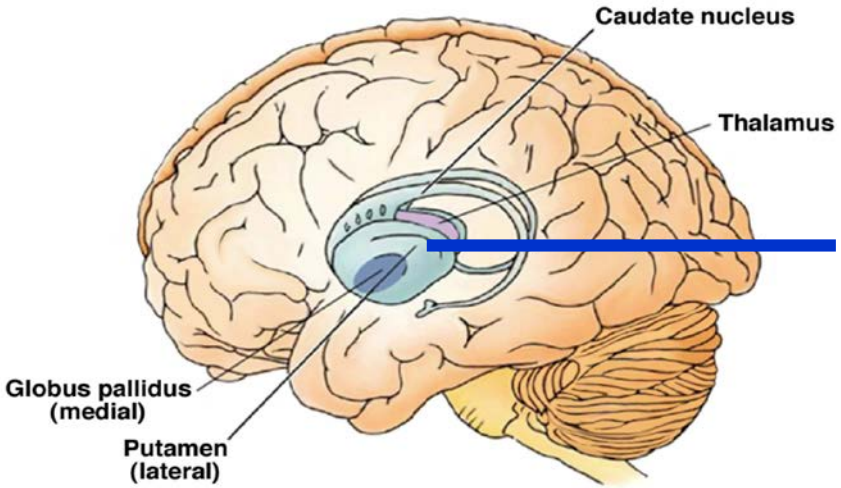
# Neuroinflammation in ME/CFS



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

# What Causes the Symptoms of ME/CFS?

## Speculative Model: Many Triggers, Final Common Pathway

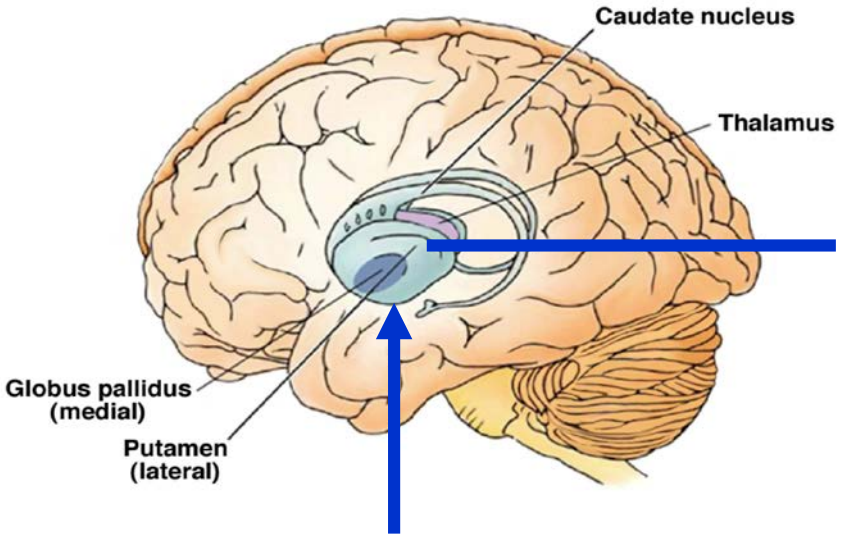



**Fatigue nucleus: in basal ganglia/ prefrontal cortex/ ant. cingulate?**

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

# What Causes the Symptoms of ME/CFS?

## Speculative Model: Many Triggers, Final Common Pathway



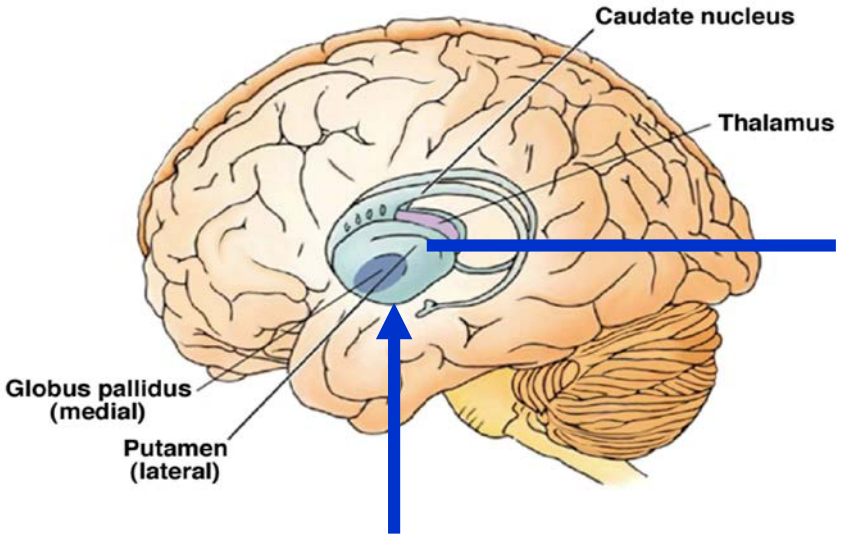

**Fatigue nucleus: in basal ganglia/ prefrontal cortex/ ant. cingulate?**

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

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

# What Causes the Symptoms of ME/CFS?

## Speculative Model: Many Triggers, Final Common Pathway




- 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**

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

← **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.*

# How Can Inflammation *Outside* the Brain Activate the Innate Immune System *Inside* the Brain?-part 1

**Innate immune system in the brain can be activated by infection elsewhere in the body due to:**

- ***Humoral:*** **A blood-brain barrier made "porous" by inflammation, allowing entry into the brain of circulating immune cells and molecules (via circumventricular organs and brain endothelial cells)**

***From: Poon DC-H, et al. Neuroscience and Biobehavioral Reviews 2015;57:30–45***

# How Can Inflammation *Outside* the Brain Activate the Innate Immune System *Inside* the Brain?-part 2

**Innate immune system in the brain can be activated by infection elsewhere in the body due to:**

- ***Humoral:*** **A blood-brain barrier made "porous" by inflammation, allowing entry into the brain of circulating immune cells and molecules (via circumventricular organs and brain endothelial cells)**

➡ ***Neural:*** **Peripheral inflammation triggers retrograde signals up the vagus nerve to the brain**

***From: Poon DC-H, et al. Neuroscience and Biobehavioral Reviews 2015;57:30–45***

# What Triggers Neuroinflammation?

**Chronic, low-grade infection of the brain**

**Inflammation elsewhere in the body, such as caused by the gut microbiome**

# Metagenomic Gut Microbiome Study

- **50 ME/CFS and 50 matched healthy controls**
- **Relative abundance of several genera were significantly associated with ME/CFS: pro-inflammatory bacteria *increased* anti-inflammatory bacteria were decreased.**
- **Several bacterial metabolic pathways also were significantly associated with ME/CFS**
- **The relative abundance of those bacterial taxa, and those same bacterial metabolic pathways, not only were associated with ME/CFS: they also were positively correlated with the severity of symptoms —particularly fatigue and pain**

***From: Nagy-Szakal D…Lipkin WI. Microbiome 2017;5:44***

# Gut Barrier Damage May Trigger Innate Immunity

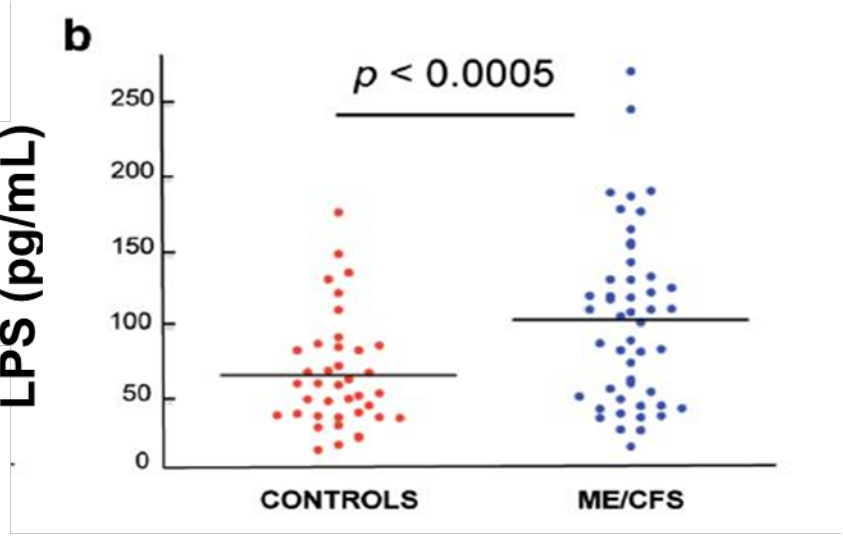
**Breach in gut barrier**

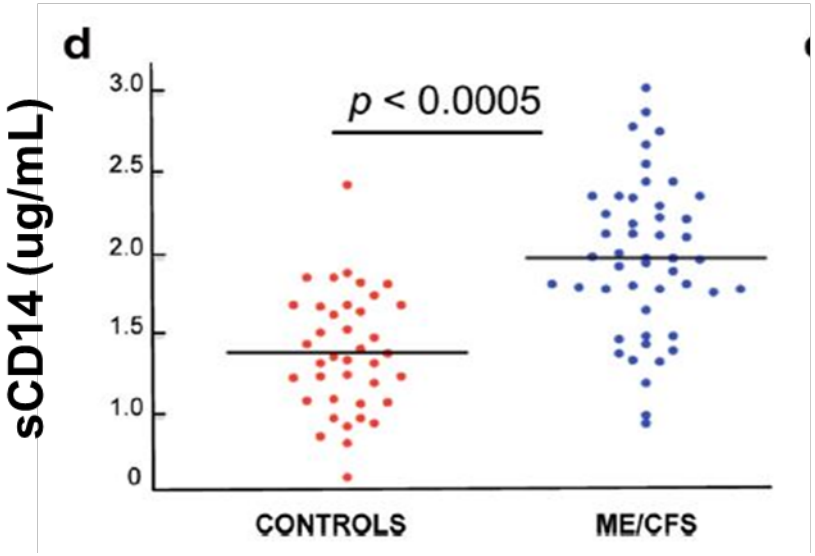
**LPS translocate to blood**

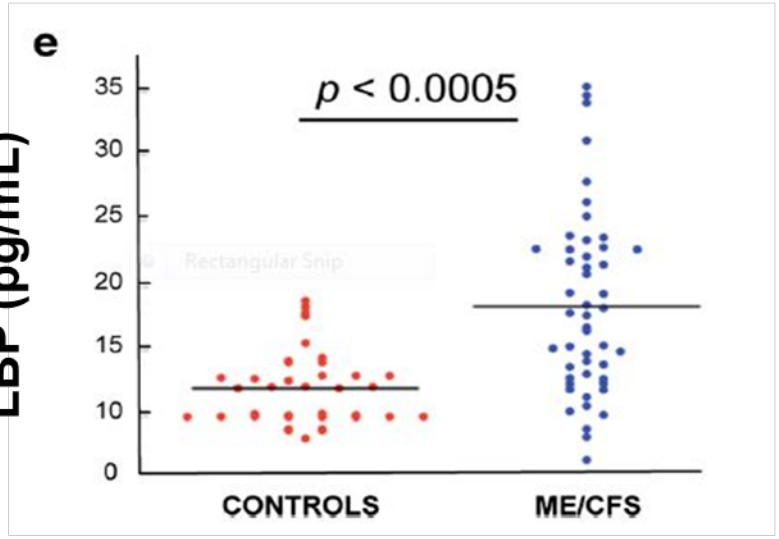
**LPS binding protein (LBP) up +**

**sCD14 (LPS-LBP receptor) up:**

**Triggering innate immunity**




*From: Giloteaux L, et al. Microbiome 2016 4:30, doi 10.1186/s40168-016-0171-4*

# Depressed Metabolism:

## The Hibernation-Torpor/Dauer Model for ME/CFS

# What Purpose is Served by Dauer and Hibernation/Torpor?

- **Worms can enter a state called dauer, and larger animals (including mammals) can enter a state called hibernation/torpor–a *temporary* state prompted by harsh environmental conditions that helps an animal survive, but at the expense of considerably reduced functional capacity**
- **Energy-requiring reactions, and the need for oxygen as a source of energy, are reduced to a bare minimum**

# Similarities: Dauer and Hibernation/Torpor

**Both states**

- **Are regulated by genes that also are involved in oxidative stress & innate immunity[1]**
- **Involve increased glycolysis and decreased aerobic respiration[2]**
- **May involve alterations in the microbiome[3]**
- **Allow only essential energy-requiring functions: hypometabolic[4]**
- **Are reversible, and controlled by autonomic NS[5]**


*[1] Lin XX. Nat Commun 2018;9/10.1038/s41467-018-06624-0.*
*[2]Fielenbach N. Genes & Development 2008;22:2149.*
*[3]Carey HV, Annu Rev Nutr 2017;37:477.*
*[4]Drew KL, J. Neurochem 2007;102:1713.*
*[5]Bargmann C, Horvitz HR. Neuron. 1991;7:729.*

# Can the Different Models Be United?

# Uniting These ME/CFS Disease Models

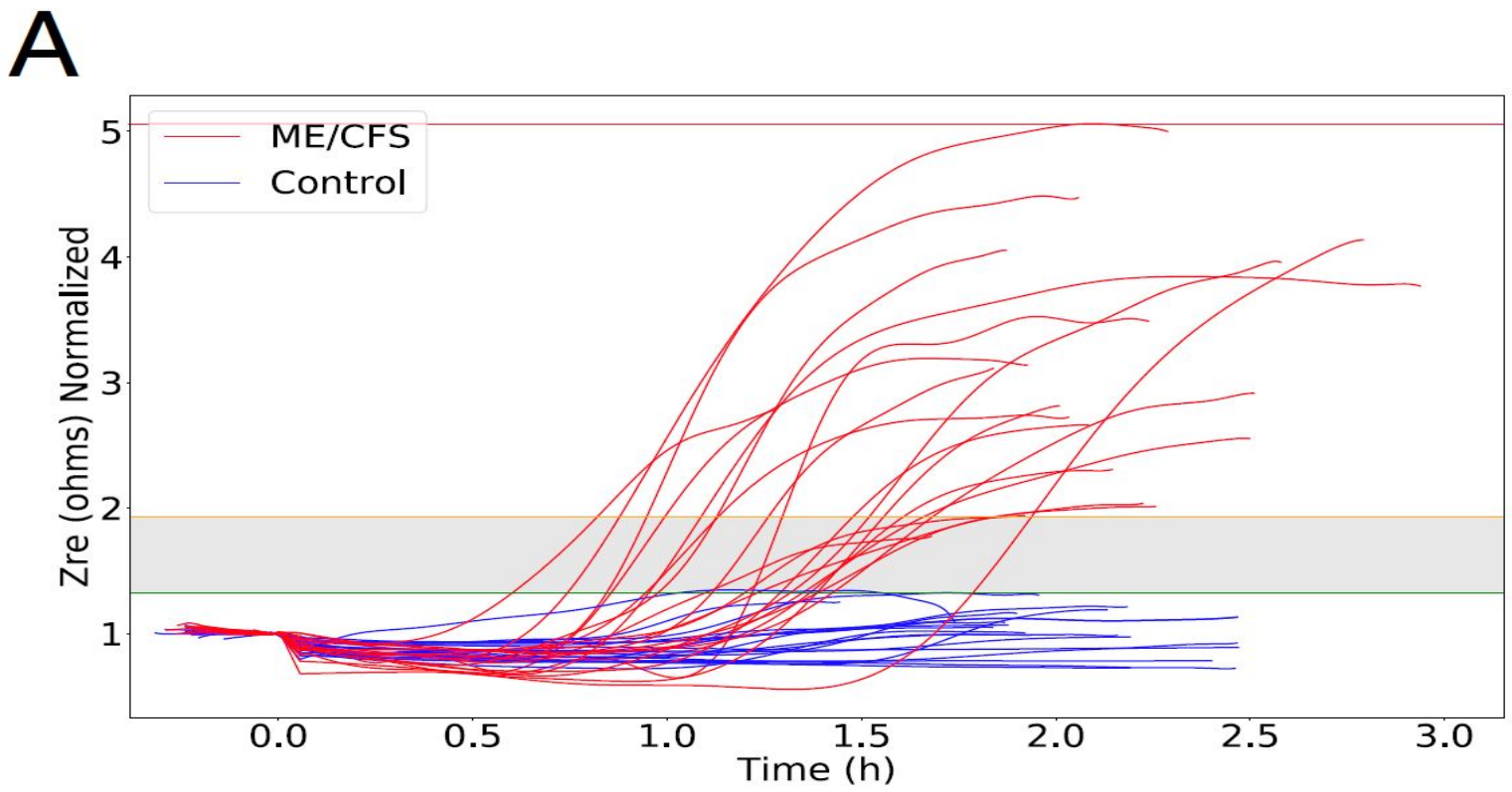
- Sickness behavior from neuroinflammation and dauer/hibernation-torpor involve ancient biological mechanisms that preserve energy in order to prevent or heal injury, but at the expense of temporarily impaired function
- The microbiome may be causing inflammation/ injury in some patients
- Do the symptoms of ME/CFS result from activation of these ancient mechanisms, and a pathological inability to turn them off?

# In Summary...

- There is robust evidence of underlying abnormalities in patients with ME/CFS
- Those abnormalities have considerable overlap with several well documented models of disease
- More needs to be done to solidify and expand our understanding of each of these abnormalities, and of their relationship with each other...and of the triggers that set them all in motion

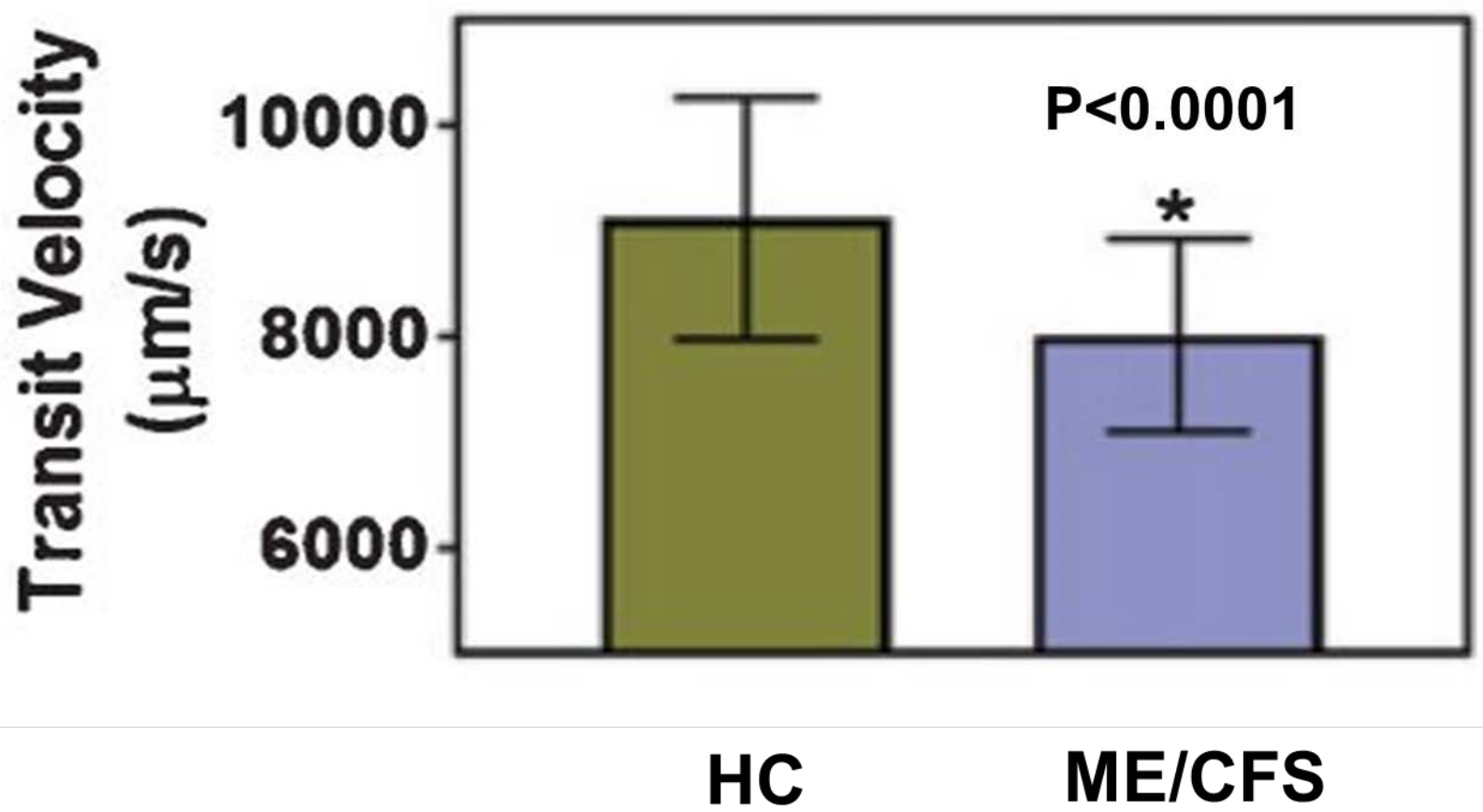
# A Possible Diagnostic Test for ME/CFS

**Mononuclear white blood cells from 20 people with ME/CFS, but not from 20 healthy controls, develop increased electrical impedance with osmotic stress.**




*From: Esfandyarpour R...Davis RW. PNAS 2019;116:10250-7*

# RBCs Are Stiffer and Transit Microcirculation More Slowly in ME/CFS

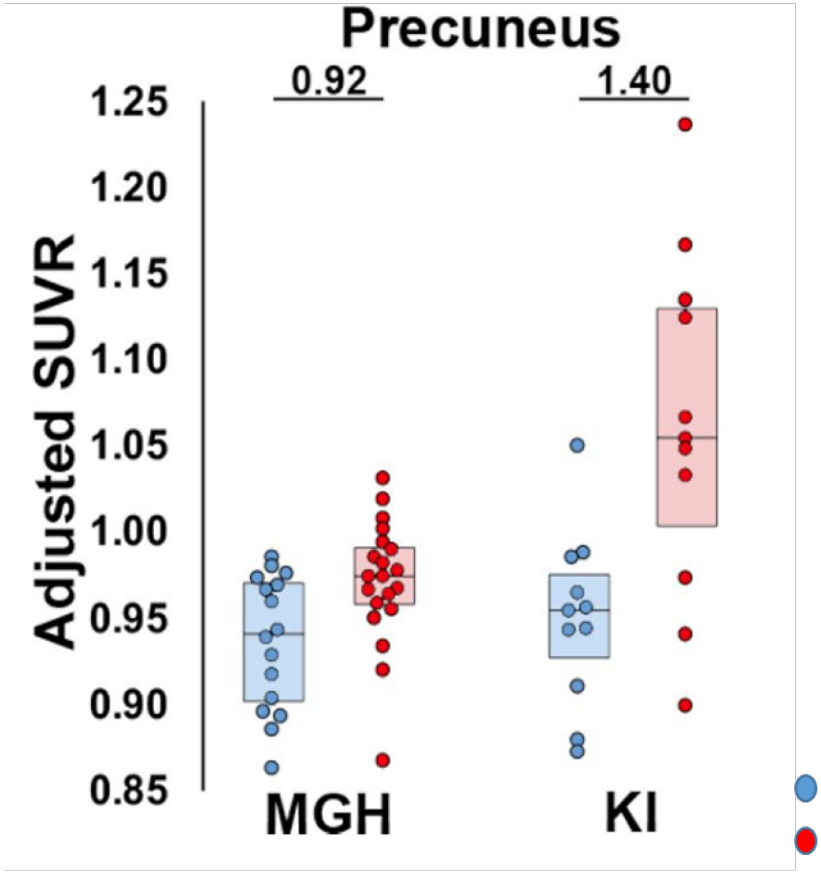


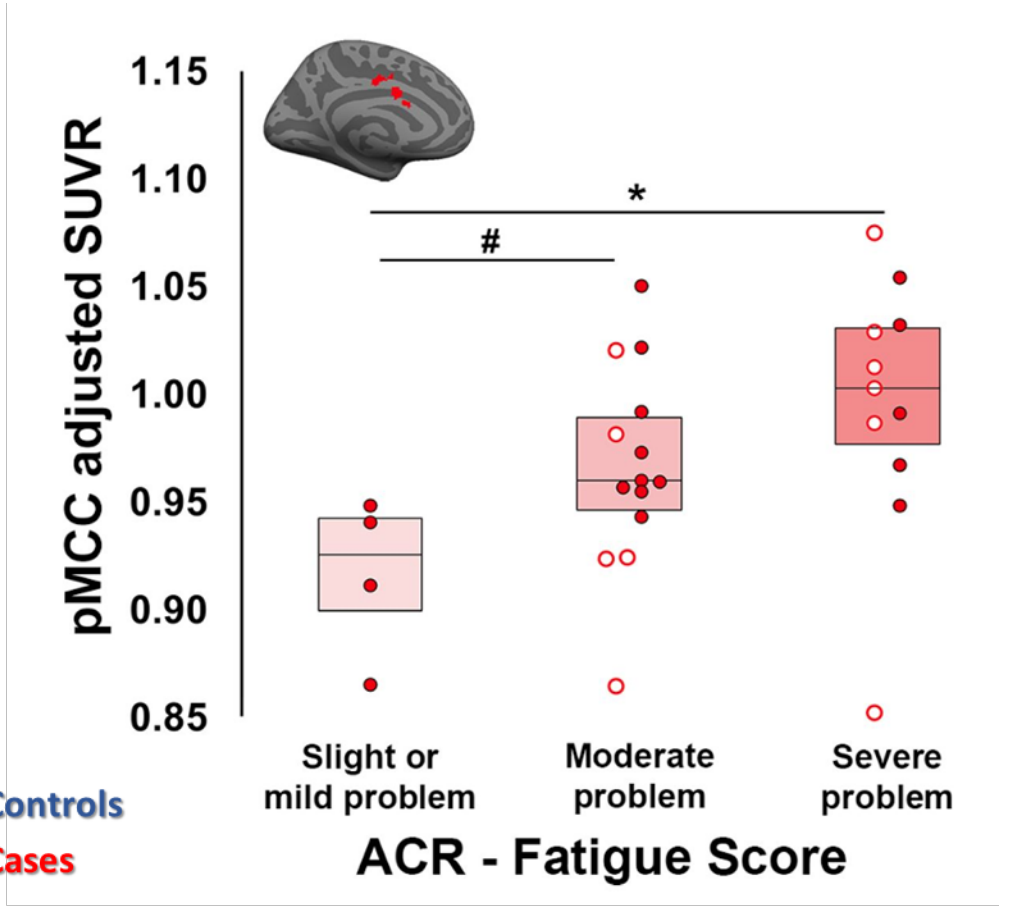

*From: Saha AK, et al. Clin Hemorheology and Microcirc 2019;71:113*

# Neuroinflammation in Fibromyalgia

## Diffuse Activation of Glial Cells by PET Scan, Especially Frontal and Parietal Lobes, Correlating with Fatigue

*MGH & Karolinska Institute*




*From: Albrecht DS, et al. Brain, Behavior & Immunity. 2019;75:72*