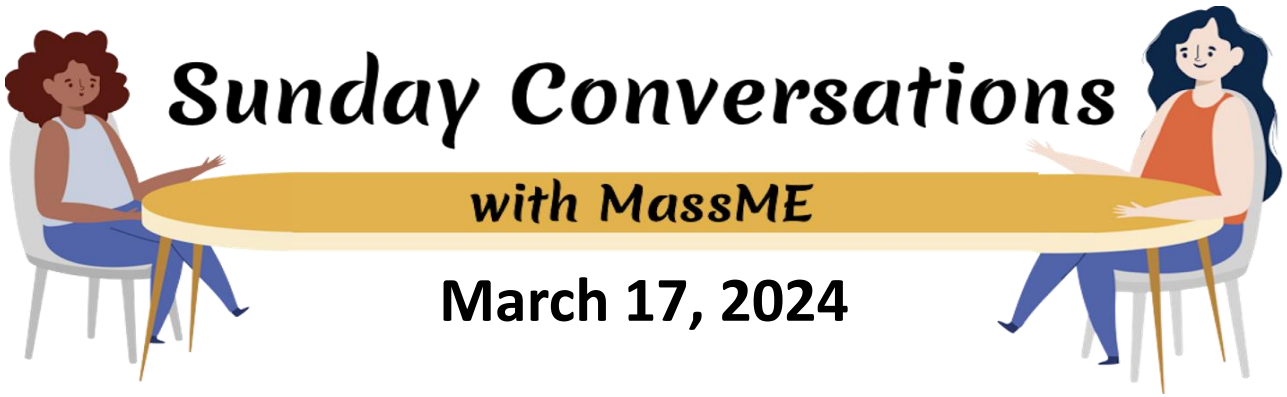
Massachusetts ME/CFS & FM
ASSOCIATION
EDUCATION, SUPPORT & ADVOCACY SINCE 1985

Dysautonomias 101: More than Just POTS

Peter Cariani, Ph.D.

Hayla Sluss, Ph.D.



March 17, 2024

Featured Speakers

Peter Cariani, Ph.D.

Hayla Sluss, Ph.D.

Housekeeping

- We respect your privacy
- Please stay muted
- Put questions/comments in the chat
- A recording of the main presentation and Q&A will be posted

We cannot answer questions related to your personal or any specific, medical condition.

The information in this presentation is for educational purposes only. Please consult with your physician or other healthcare provider in matters pertaining to your medical care.

The presenters' remarks are their own opinion, and do not represent the views or opinions of Massachusetts ME/CFS & FM Association.

Sunday Conversations with MassME

Please join us next month!

Got Mold?

Michael Rubino
Co-Founder and chair of Change the Air Foundation

Sunday, Apr 21, 2024, 4 p.m. EDT

Mass ME/CFS

Massachusetts ME/CFS & FM ASSOCIATION

"Dysautonomias 101: More Than Just POTS"

Sunday, March 17, 2024, 4 p.m. Eastern Time

Peter Cariani, Ph.D.

"Dysautonomias" refers to the generic term encompassing all disorders of the autonomic nervous system. In this edition of Sunday Conversations, Peter Cariani will give a brief overview of the autonomic nervous system and what can go wrong. He will also describe the role of dysautonomias in ME/CFS, FM, and other chronic conditions, what causes these conditions to be self-sustaining, what medical specialties treat dysautonomias, and add his own thoughts about diagnosis and treatment.

A recording will be available after the event.
A PDF of the slides will also be available.

Peter Cariani (B.S. MIT biology; M.S., Ph.D. SUNY-Binghamton, systems science) is a recently retired auditory and systems neuroscience researcher and teacher. His research has mainly involved understanding the neural codes that mediate perception of pitch, consonance, harmony, and rhythm. Over the last two decades he has taught undergraduate and graduate courses related to music perception and cognition, auditory neuroscience, and the neurobiology of consciousness at various Boston-area institutions (Tufts, Harvard, MIT, Boston Conservatory/Berklee, Boston University). He is currently co-authoring two books: a clinician's guide to music therapy and an outline of a new theory of brain function based on temporal codes. www.petercariani.com

Peter has two adult children who have been diagnosed with ME/CFS, and consequently has been studying the ME/CFS literature to help them find appropriate medical care and to try to understand the disease from a systems perspective. He is currently serving as a parent-caregiver person-with-lived-experience on the current NIH task force to formulate a roadmap for future ME/CFS research. No conflicts of interest.

My goal today is to provide you with a framework for thinking about dysautonomias in the context of ME/CFS

- How might they be related?
- Why do so many people with ME/CFS have dysautonomias?

DISCLAIMER: I am a neuroscientist, not a medical doctor, so I won't be dispensing medical advice. Please consult licensed medical professionals whenever possible.

First, we will discuss what neurologists mean when they use the term "dysautonomia"

Then, in order to understand this, we will need to look at some basic neuroscience that is related to the **Autonomic Nervous System (ANS)** and the **Hypothalamus.**

- **what it does -- functions**
- **what can go wrong -- dysfunctions**

Basic ME/CFS questions that (I think) we will need to answer in order to find a cure: Why the similar sets of symptoms? What causes ME/CFS to be self-sustaining?

I will also try to outline possible roles that autonomic dysfunctions might play in producing the major symptoms of ME/CFS: from isolated, separate, multiple disease processes (multiple causes) to a possible primary driver of major ME/CFS symptoms (unified causes).

Along the way, I will offer some lived-experiential advice re: dealing with our medical system and do a brief look at dysautonomia diagnostics & treatments.

Hayla Sluss will add additional points and give comments.

Then we will end with a brief Q &A segment.

I realize that there is a great deal of information on the slides. Don't panic! I will talk through all major points & a PDF will be posted online afterwards.

SOME RESOURCES
(that I've relied on)

Massachusetts ME/CFS & FM Association https://www.massmecfs.org

Solve M.E. (Solve ME/CFS Initiative) https://solvecfs.org

Open Medicine Foundation https://www.omf.ngo

Dysautonomia International http://dysautonomiainternational.org

American Autonomic Society https://americanautonomicsociety.org/resources/

International Assoc. for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME)

https://www.iacfsme.org.

See their ME/CFS: A Primer for Clinical Practitioners(2014, 50 pp.)
https://growthzonecmsprodeastus.azureedge.net/sites/451/2020/10/Primer_Post_2014_conference-8204127c-4e30-49b9-8ce5-39387edf4b99.pdf

Centers for DIsease Control & Prevention ME/CFS webpage https://www.cdc.gov/me-cfs/index.html

NIH Roadmap on ME/CFS Research

https://www.ninds.nih.gov/about-ninds/who-we-are/advisory-council/nandsc-mecfs-research-roadmap-working-group 4-hour webinars on Nervous System, Immune System, Metabolism, Genetics, Chronic Infections, Physiology, Lesser Studied Pathologies (e.g. connective tissue, mast cells, platelets) https://event.roseliassociates.com/me-cfs-research-roadmap/recordings/

YouTube videos on Dysautonomia by practicing clinicians

There are many primers and short videos by clinicians explaining a large array of issues related to dysautonomias. Search under "dysautonomia", POTS, ME/CFS, etc. and whatever aspect, symptom, diagnostic test, treatment you want to hear more about. This is often the fastest way of finding basic information. e.g. Drs. Hakim & Farhad on Autonomic Dysfunction, Dr. Rowe Managing Life with Autonomic Symptoms; Dr. Maitland- Mast Cell Activation Syndrome: More than "just allergies." Dr. Systrom on PEM.

Wikipedia https://www.wikipedia.org Reasonable, general source of basic information.

PubMed literature search. https://www.ncbi.nlm.nih.gov/pumed

NIH sponsored biomedical literature search engine/database that includes abstracts of papers, even those behind paywalls. Good for more in-depth and specific information.

Thanks also to Harvard University for access to their library system as a retired, corresponding member of the HMS faculty.

Medical diagnosis & treatment of ME/CFS is highly siloed by medical specialty.
Treatment almost always consists of treating individual symptoms.
Scientific understanding of ME/CFS is also highly siloed by medical specialty.
This can make it difficult to sort out the primary & secondary causes of ME/CFS symptoms.

For the past year, I have been participating in the current NIH effort to formulate a Roadmap for prospective research on ME/CFS in the capacity of a person-with-lived-experience (parent of two grown children with ME/CFS, of different types & severity).

The organization of the Roadmap project illustrates the various clinical and scientific perspectives through which ME/CFS is approached.

Working groups & associated public online webinars (highly recommended)
https://event.roseliassociates.com/me-cfs-research-roadmap/recordings/

Nervous system (brain fog, fatigue, neurogenic circulatory problems, sleep)
Immune system (inflammation, auto-immune disease, neuroimmunology)
Metabolism (mitochondrial dysfunctions, oxidative metabolism)
Physiology (physical activity, PEM)
Circulation (OI, POTS, insufficient cerebral blood flow/oxygenation)
Genomics/Genetic susceptibilities (incl. biomarkers, epigenetics)
Less studied Pathologies: Connective tissue, Spinal, Mast Cell, Reproductive, GI

Can we understand the inter-system causal links to connect the dots and find cures?

What does “dysautonomia” (DA) mean?

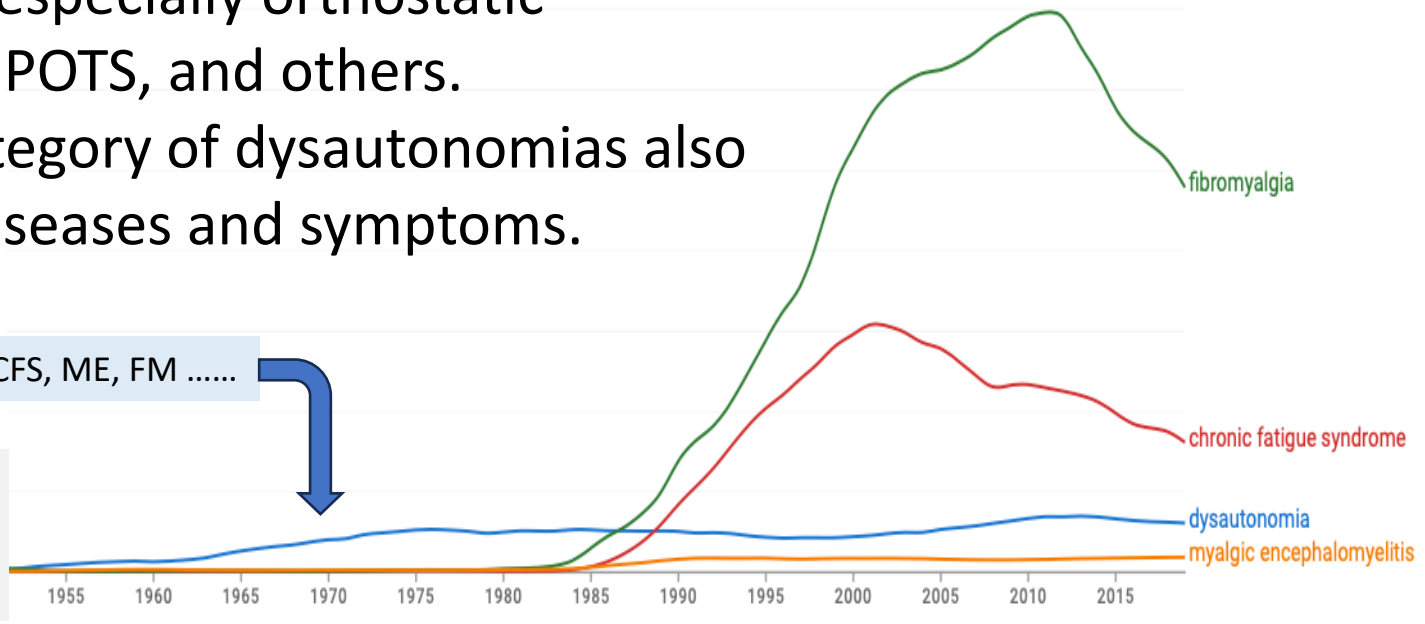
It’s a general umbrella term for disorders of the autonomic nervous system. Not a specific disease, syndrome, or diagnosis, but a blanket term that refers to the neural causes of functional impairments.

The term is mainly used by neurologists.

Many (up to 80%) ME/CFS patients have dysautonomias, especially orthostatic intolerance (OI), POTS, and others.
However, the category of dysautonomias also includes other diseases and symptoms.

What is dysautonomia?
Dysautonomia International website
Dysautonomia is an umbrella term used to describe several different medical conditions that cause a malfunction of the Autonomic Nervous System. The Autonomic Nervous System controls the "automatic" functions of the body that we do not consciously think about, such as heart rate, blood pressure, digestion, dilation and constriction of the pupils of the eye, kidney function, and temperature control. People living with various forms of dysautonomia have trouble regulating these systems, which can result in lightheadedness, fainting, unstable blood pressure, abnormal heart rates, malnutrition, and in severe cases, death.

The term predates CFS, ME, FM ……



Google Books Ngram Viewer
(incidence of words & phrases within Google Books database as a function of time)

10 Facts About Dysautonomia

DYSAUTONOMIA INTERNATIONAL

AWARENESS ADVOCACY ADVANCEMENT

1. Dysautonomia is pronounced dis'-oughta-know'-me-uh. Dysautonomia is a group of neurological conditions that impact over 70 million people around the world.

2. Dysautonomia means "dysfunction" of the "autonomic nervous system." The autonomic nervous system controls all of your involuntary bodily functions like your heart rate, breathing, maintaining proper blood pressure, digestion, sleep cycles, body temperature control, sweating and more.

3. There are many different types of dysautonomia, including, but not limited to, neurocardiogenic syncope, postural orthostatic tachycardia syndrome, inappropriate sinus tachycardia, orthostatic hypotension, autoimmune autonomic ganglionopathy, pure autonomic failure, and multiple system atrophy.

4. Dysautonomia can also occur secondary to other diseases. Diseases that commonly cause autonomic nervous system dysfunction include all types of diabetes, Sjögren's syndrome, celiac disease, multiple sclerosis, and Parkinson's.

5. Due to the malfunctioning of the autonomic nervous system in people with dysautonomia, symptoms can include tachycardia (a heart rate that is too fast), bradycardia (a heart rate that is too slow), poor blood flow to the heart, brain and other organs, chest pains, lightheadedness, fainting, nausea, a gastrointestinal tract that moves too fast or too slow, blood pooling in the extremities, shaking, too much or too little sweating, cognitive impairments ("brain fog"), headches, and much more.

6. Some, but not all, dysautonomia symptoms can be minimized by laying the patient down. This helps restore normal blood flow to the brain and chest area. This is why it can be so difficult for dysautonomia patients to stand sometimes.

7. Dysautonomia comes with a wide range of disability – from mild, to very disabling, to death in rare cases. While some dysautonomia patients can continue with work, school and social activities, many cannot, even with the best treatment currently available.

8. Some dysautonomia patients will get better over time, by either learning to manage their symptoms better, or by actually recovering from the illness. However, some remain sick with dysautonomia indefinitely, and some progressively get worse.

9. Many dysautonomia patients experience years of diagnostic delay, and have difficulty finding physicians to treat their dysautonomia once they are diagnosed, because most doctors have not received training on how to diagnose and treat autonomic nervous system disorders.

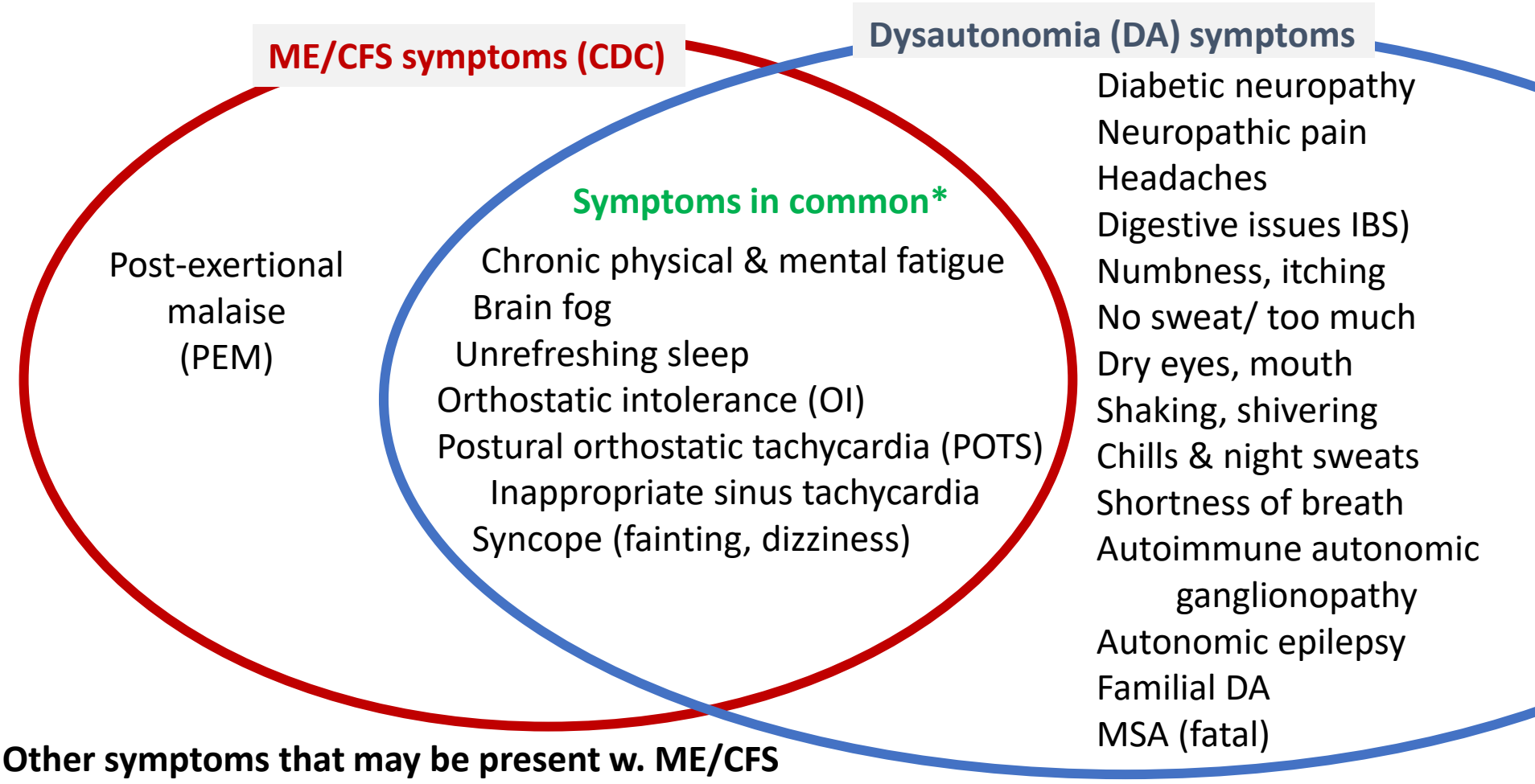
10. Dysautonomia International is the leading non-profit that advocates for individuals living with dysautonomia through research, physician education, public awareness, advocacy, and patient empowerment programs.

Working together, we can make a difference!

www.dysautonomiainternational.org

Many of these symptoms overlap with those of ME/CFS

OVERLAPS BETWEEN DYSAUTONOMIA AND ME/CFS SYMPTOMS



Other symptoms that may be present w. ME/CFS

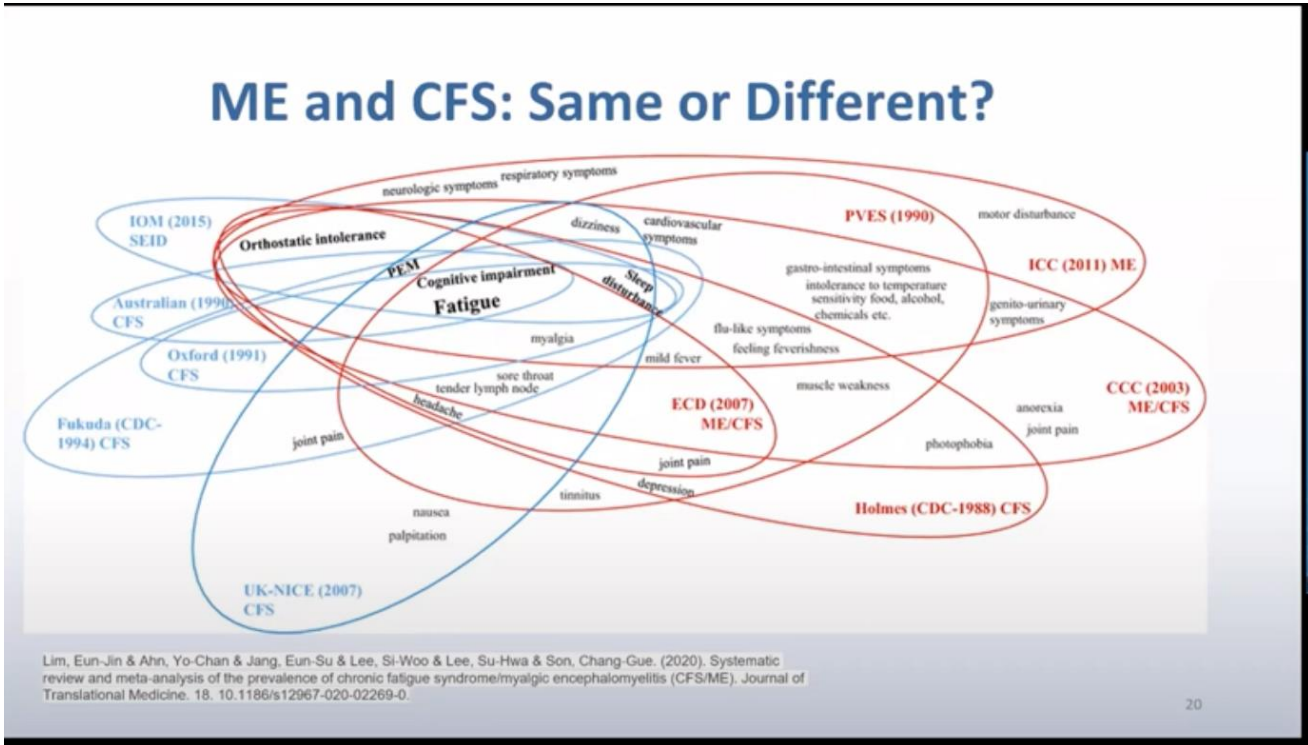
Muscle pain & aches, joint pain w/o swelling, redness
Hyperflexibility (connective tissue, E-D Syndrome)
Hypersensitivities: lights, sounds, foods, odors, chemicals
Immune dysfunctions & inflammation
Mast cell disorders, allergies, hives

30-80% of ME/CFS pts have dysautonomias (Komaroff)

Two poles of thought: separate vs. common causes

*Many symptom overlaps also with long-Covid, Lyme Disease, Gulf War Syndrome, chemotherapy, acute phases of viral infections

Symptomology & Terminology



16:39 / 1:00:51 • Decade 2 - Phil Chernin

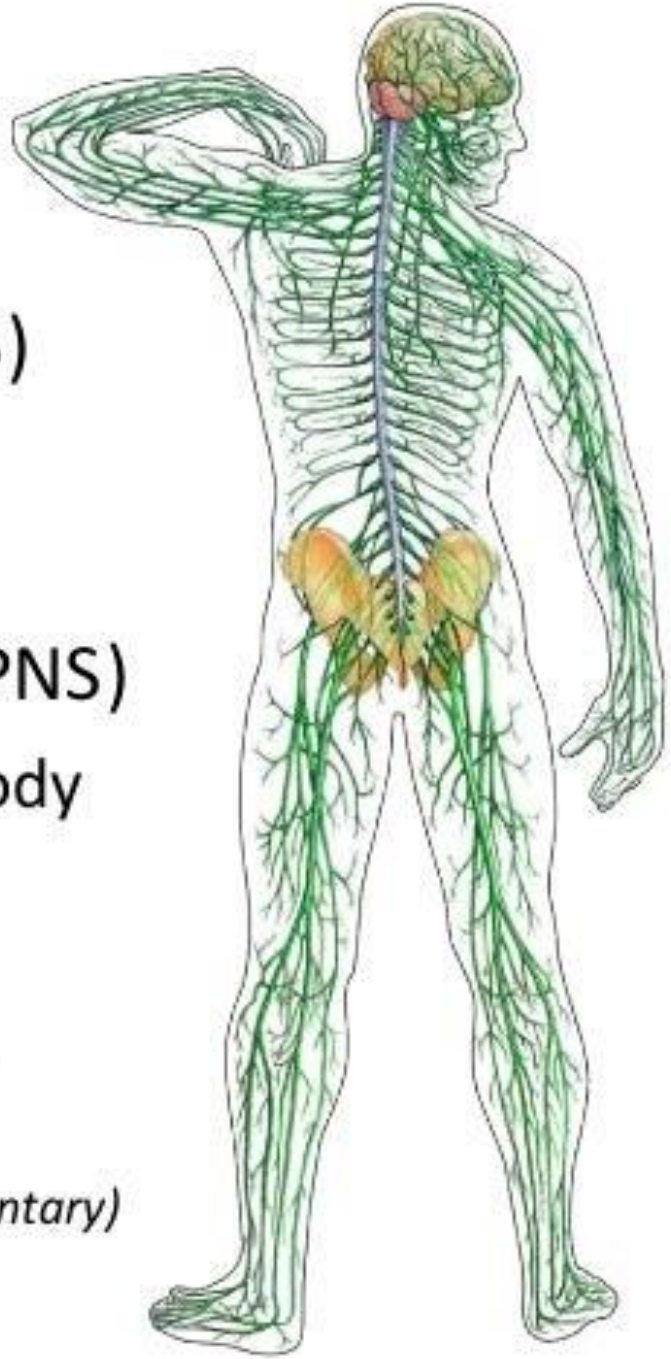
Sunday Conversations June 2023 - ZOOM through 40 years of ME/CFS with MassME!

Mass MECFS & FM Association
1.88K subscribers

Subscribed | 13 | Share | Clip

The Nervous System

- **Central Nervous System** (CNS)
  - Brain
  - Spinal Cord
- **Peripheral Nervous System** (PNS)
  - Nerves that connect all your body parts to the spinal cord
    - Somatic nerves *(voluntary)*
      - Motor (muscle) & sensory (senses)
    - Autonomic nerves
      - heart, respiration, digestion *(involuntary)*



https://image.slidesharecdn.com/24nervoussystemcnsandpns-180315192034/95/the-nervous-system-cns-pns-3-638.jpg?cb=1521142255

Autonomic nervous system

Functions: Bodily regulation, (feedback control → "homeostasis"
maintain system integrity & functions)

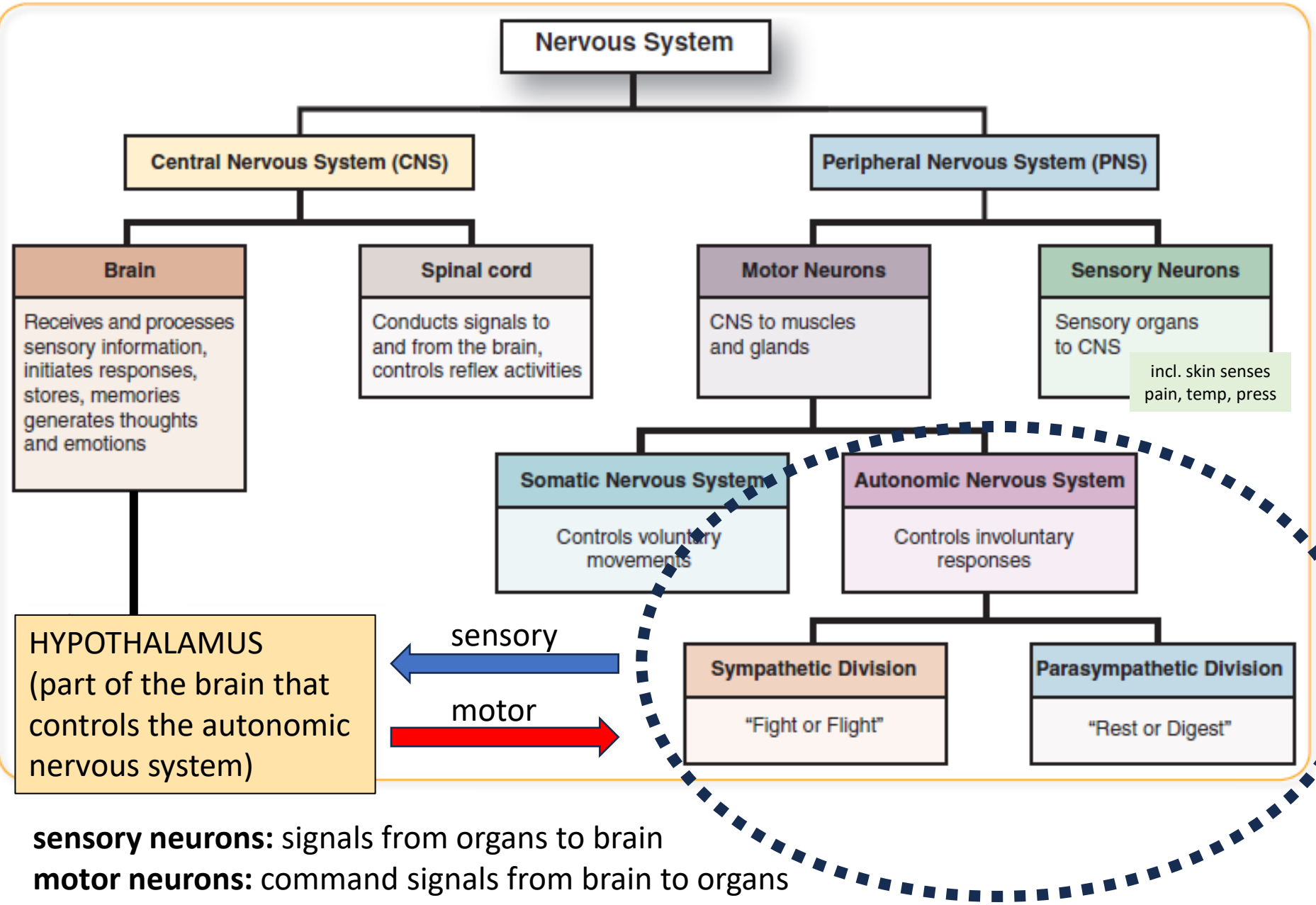
Sensory info from body organs & tissues → measure the current state of the body
(e.g. sense blood pressure)

Commands to bodily organs & tissues → change their actions
(e.g. speed up or slow down heart rate)

Sympathetic branch: **PREPARE FOR ACTION!!!!!** → increases arousal

Parasympathetic branch: **RELAX & REST. . . . . .** → decreases arousal

Enteric nervous system**:** senses & regulates GI system



sensory neurons: signals from organs to brain
motor neurons: command signals from brain to organs

Original figure (to which hypothalamus & add'l text was added)
https://socratic.org/questions/what-is-the-function-of-the-sensory-division-of-the-peripheral-nervous-system

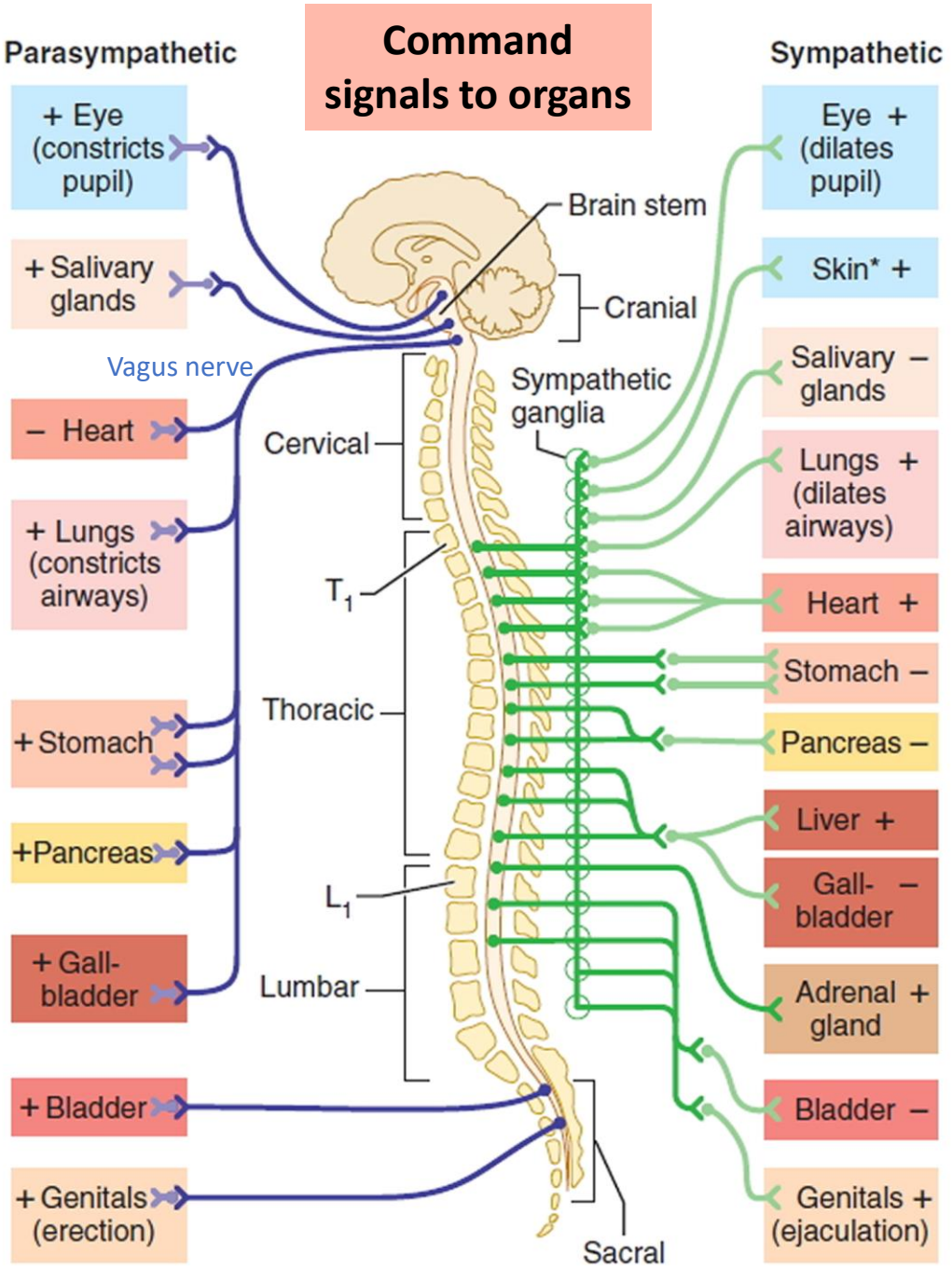
Central control circuits:
Hypothalamus (brain)

Relays:
Brainstem & spinal cord

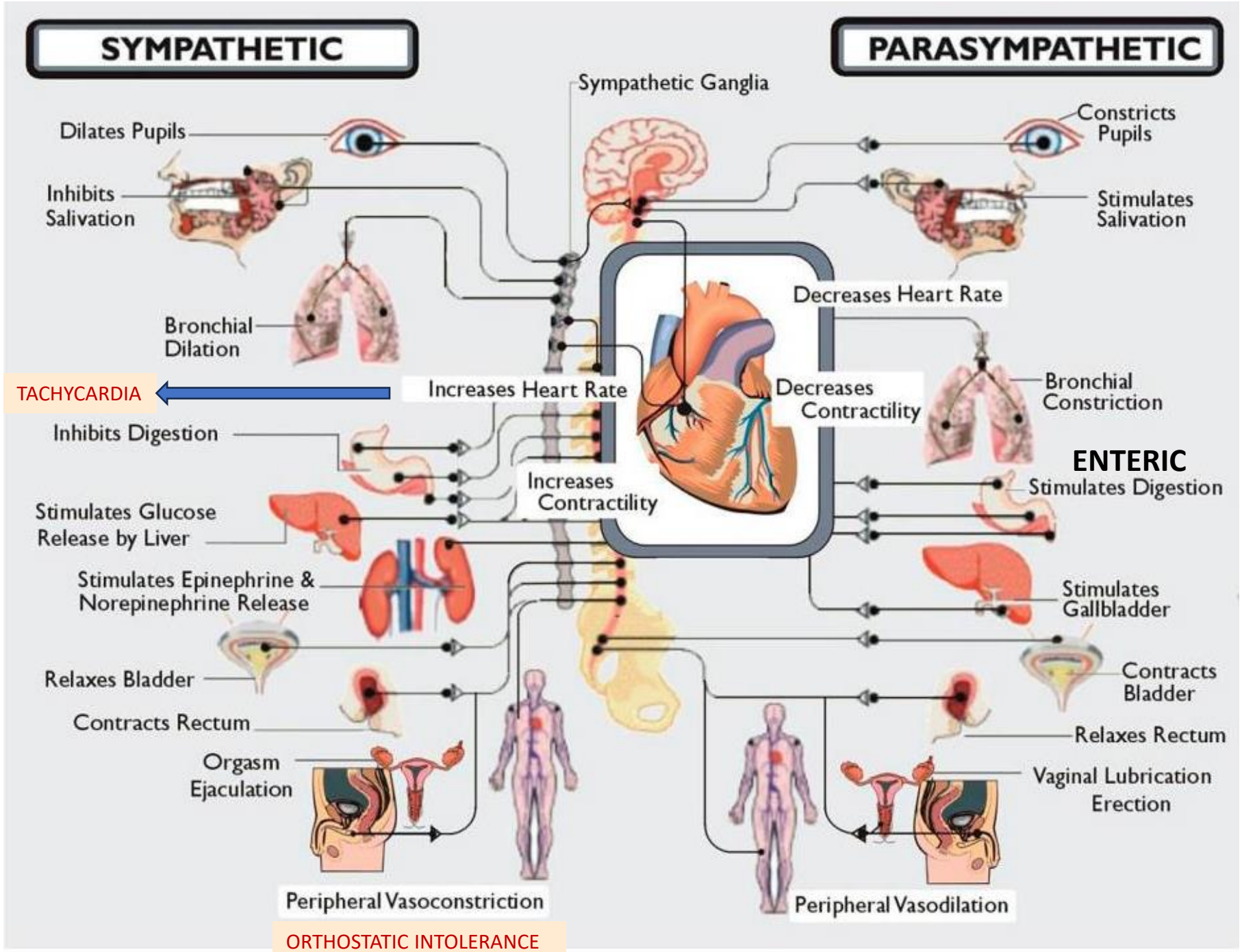
Autonomic system
Brainstem & spinal cord

Sympathetic & parsympathetic nerves

Bodily organs & tissues including blood vessels



https://healthjade.com/wp-content/uploads/2018/03/autonomic-nervous-system.jpg



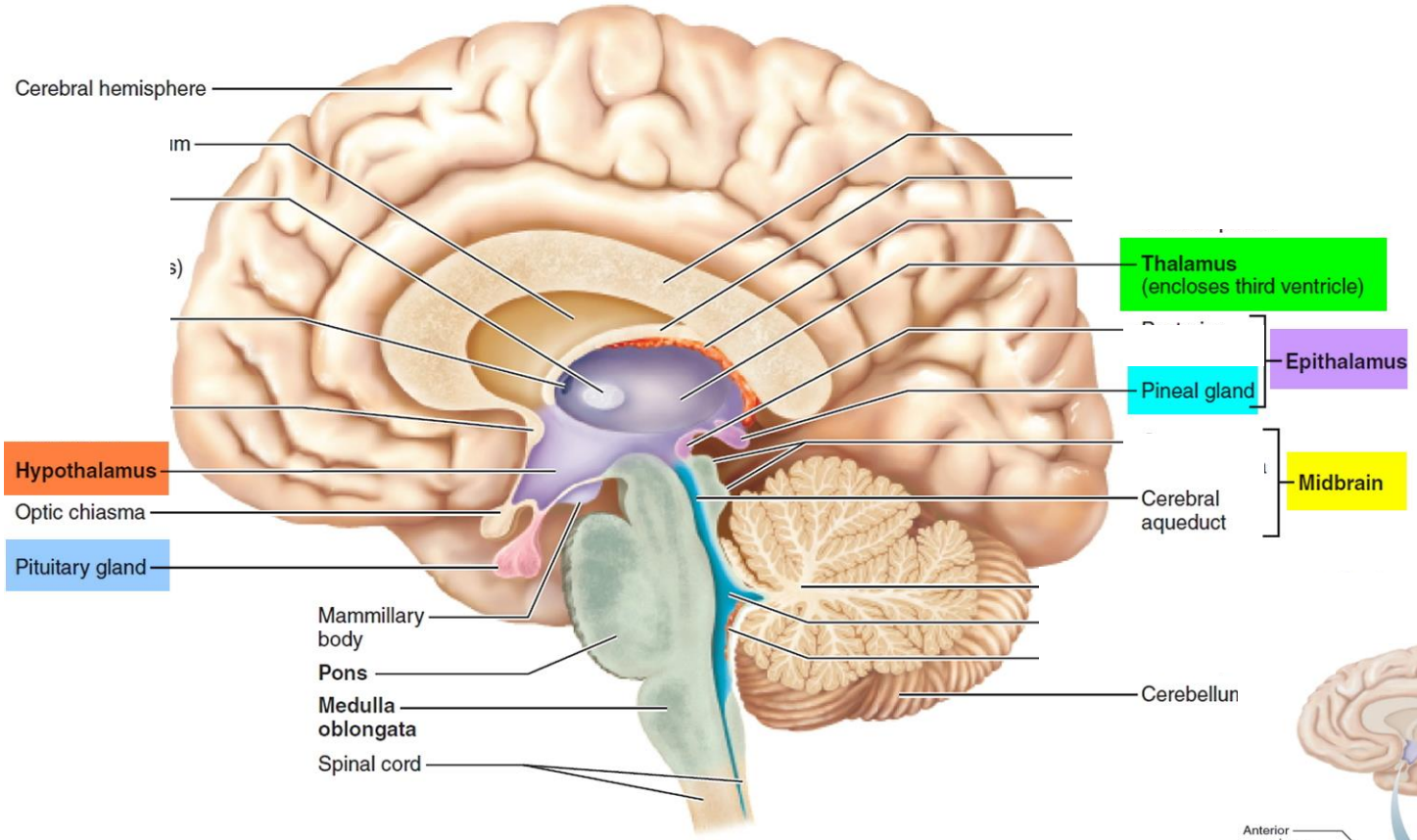
http://dysautonomiainternational.org/images/ANSchart.png

Hypothalamus: central control of bodily organs & systems – controls the autonomic system

Receives sensory information from organs & tissues from autonomic system

Sends commands to organs & tissues to maintain functions via autonomic system

[Functionally, the hypothalamus is the brain portion of the autonomic system.]

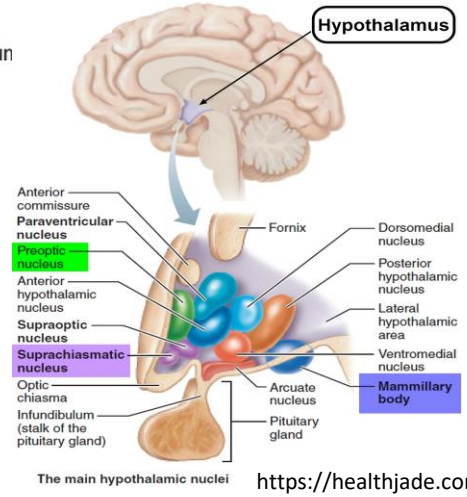


Blood-brain barrier

Brain also has mast cells (inflammatory molecules)

Brain has its own immune system (microglia)

HYPOTHALAMUS is not just one structure, but a collection of nuclei that contain cell bodies of different neurons with different functions.

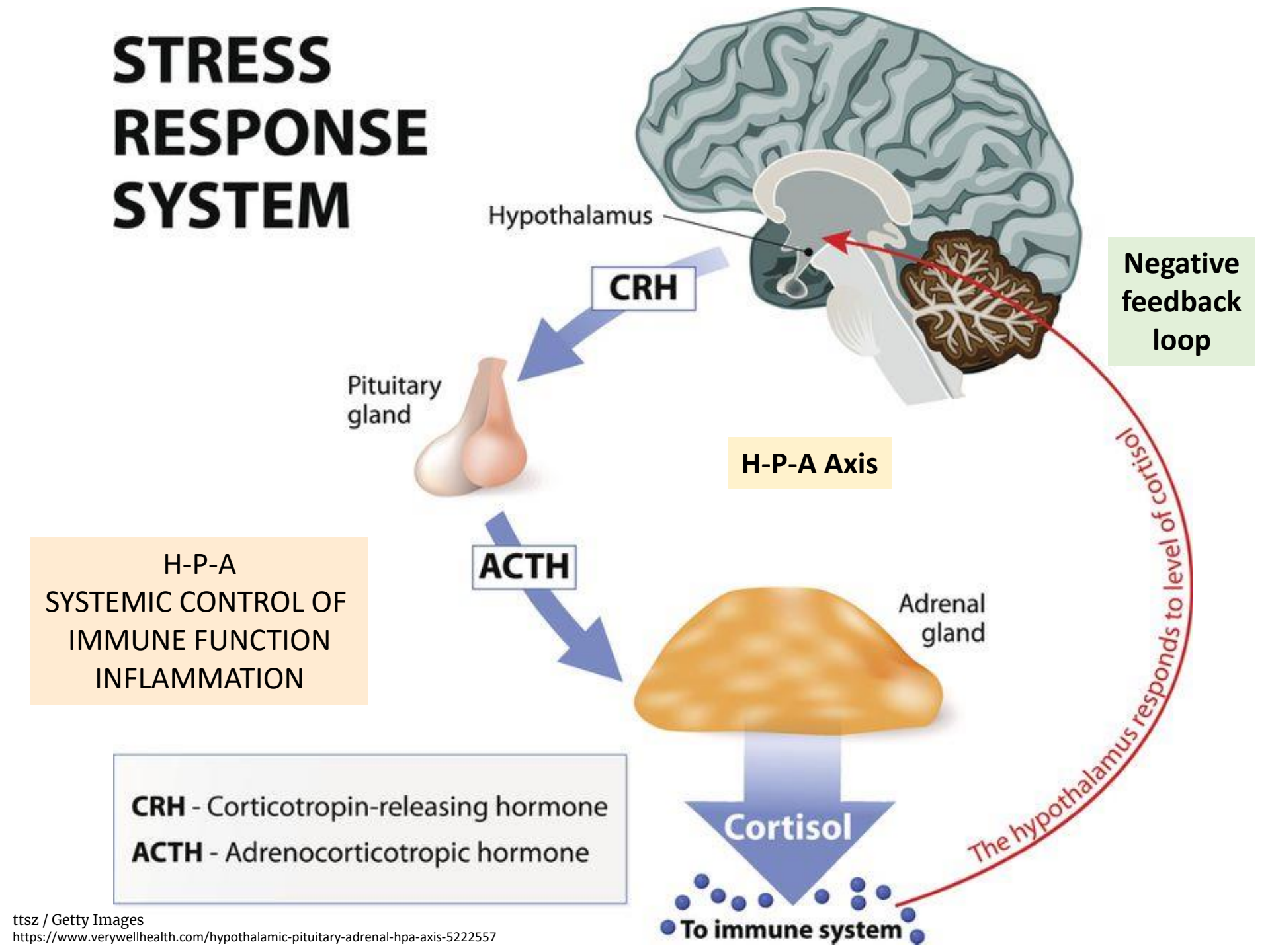


https://healthjade.com

Hypothalamic-autonomic functions and dysfunctions

Central control of autonomic system	**Disruptions (due to infection or inflammation)**
Blood pressure (vasopressin, etc.)	Orthostatic intolerance & lack of blood/O_2 brain
Heart rate	Tachycardia, brachycardia
Thermoregulation	Low body temperature, bad temp. regulation
Panting	
Sweating	No sweating or excessive sweating
Salivation	Salivation
Gastro-intestinal action	GI problems, gastroparesis
Feeding, appetite/satiety (orexin)	Increased appetite/hunger & weight gain
Energy & water balance	Increased urination & thirst
Metabolism (glucose, mitochondria)	Obesity, diabetes
Pupillary dilation & eye moisture	Blurred vision
Arousal, wakefulness	Drowsiness, stupor
Circadian rhythms & sleep regulation	Sleep disturbances (disruption of glymphatic clearance?)
Hormonal release (H & H-P-A axis)	
Corticotropin-releasing hormone (CRH)	Stress response, suppress inflammation
Gonadotropic sex hormones	
Prolactin (milk production)	
Oxytocin (bonding, reproduction, birth)	
Thyrotropin-releasing hormone	
Growth hormone & Somatostatin	

STRESS RESPONSE SYSTEM



Negative feedback loop

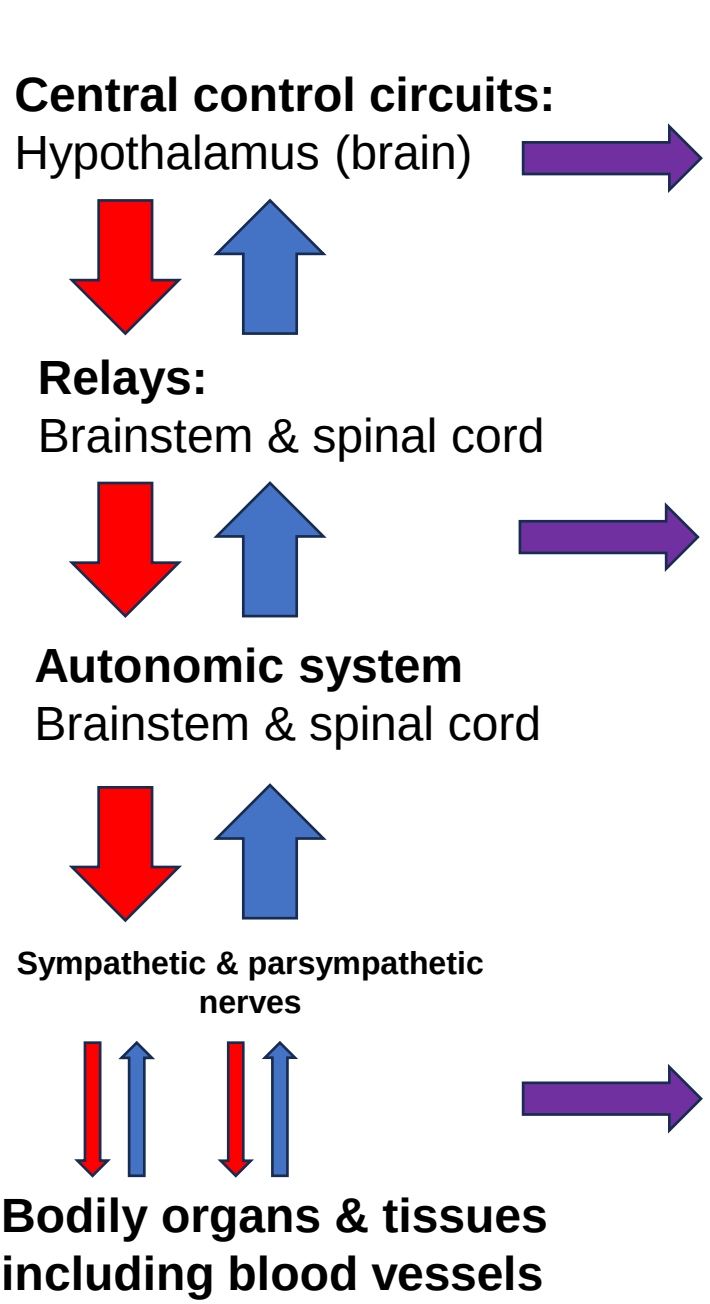
H-P-A Axis

H-P-A
SYSTEMIC CONTROL OF IMMUNE FUNCTION
INFLAMMATION

CRH - Corticotropin-releasing hormone
ACTH - Adrenocorticotropic hormone

ttsz / Getty Images
https://www.verywellhealth.com/hypothalamic-pituitary-adrenal-hpa-axis-5222557

FAILURE MODES: THINGS CAN GO AWRY IN DIFFERENT WAYS & AT SEVERAL LEVELS



Damage to central control circuits
Inadequate cerebral oxygen supply
Direct infection or injury (rare)
Reactivation of latent viruses (e.g. EBV)
Inflammation (cytokines) impairs functions
Auto-immune attack of hypothalamus
Mitochondrial dysfunctions

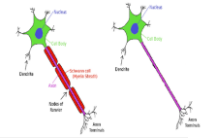
Impair neural signals in CNS
Direct infection or injury
Ongoing covert infection creates false signals
(e.g. vagus nerve ganglia)
Inflammation
Auto-immune attack of autonomic ganglia

Damage (peripheral) autonomic neurons
"Dysautonomias" & "small fiber neuropathies"
Diabetes produces peripheral neuropathies
Acute infection or ongoing covert infection
Reactivation of latent viruses (e.g. EBV, Herpes)
Inflammation
Auto-immune attack of autonomic synapses

“Small fiber neuropathy”

Diagnosis: impaired neuronal functions in the peripheral nervous system (15-20 million people in US, Wiki)

“Small fibers” are axons of neurons that are thin and/or don’t have a myelin sheath.
These fibers are slow-conducting – signals travel more slowly.


differencebetween.com

Afferents (covey sensory information → brain)
Small Aδ fibers (thinly myelinated) → touch, pressure, cold, acute pain
C fibers (unmyelinated, slow) → warm, slow pain & itching

Dysfunctions re: pain, touch, temp
Hypersensitivity
Chronic sensation
Insensitivity

Autonomic efferents (brain → skin, blood vessels & bodily organs)

- Orthostatic intolerance (OI): neurohumoral control of vascular tone – constriction/dilation
  hypotension → cerebral hypoperfusion → fainting, dizziness, fatigue, blurred vision
- Heart rate dysregulations: neurohumoral control of heart rate (via hypothalamus & A-P axis)
  tachycardia, POTS
- Sudomotor dysfunctions: neural control of skin pores
  increased or decreased sweating → Δ thermoregulation, wound healing
  diagnostics: sweat test (TST), axon reflex test (QSART), skin conductance (ESC),
  skin punch biopsy (axon density, invasive), spoon test, other tests
- Urinary, bowel, sexual dysfunctions: neural control of bladder, GI tract, sex organs
  e.g. inflam. bowel & celiac disease, ulcerative colitis, Crohn’s, G-B syndrome, ED

Things that can go awry: 1. Damage peripheral nerves in the autonomic system via infection, inflammation, auto-immune attack

Three ways neural functions can be disrupted:

1. Damage peripheral nerves ("dysautonomias")

2. Damage or impair neural relay stations (brainstem)

3. Impair neural control in the brain (hypothalamus)

1. Disruptions of peripheral nerves by pathogens, inflammation, autoimmune

- Unlike the Central Nervous System (brain + spinal cord), peripheral nerves are not as protected by the blood-brain barrier, ∴ may be more exposed to blood-borne pathogens, inflammatory agents, and other factors (high blood sugars)
- Disruptions of peripheral nerves can be caused by diabetes (most common). Other typical risk factors: dyslipidemia, obesity/BMI, smoking, hypertension
- Autoimmune responses can develop to peripheral nerves causing disruptions in their functions.
- Damage to autonomic sensory nerves from receptors (such as blood pressure receptors) disrupts feedback to control mechanisms
- Damage to autonomic efferent nerves impairs the ability of the system to command and control the activity of target organs

Things that can go awry: 2. Damage or impair relay stations (or send false signals to the hypothalamus)

Three ways neural functions can be disrupted:

1. Damage peripheral nerves (“dysautonomias”)

2. Damage or impair neural relay stations (brainstem)

3. Impair neural control in the brain (hypothalamus)

2. Disrupt proper action of relay stations (ganglia, brainstem nuclei)

- Neural damage from direct injury to or impairment of neuronal cell bodies in ganglia and brainstem nuclei that prevents transmission of sensory & control signals between hypothalamus & the targets of autonomic nerves (rare)
- Alarm signals can be sent to the relay station via sensory afferents of the autonomic nervous system. van Elzakker and others have proposed that infections and injuries to the gut send alarm signals via the vagus nerve to the hypothalamus that put it into a “sickness response mode” that shuts down multiple systems (van Elzakker, 2013; Komaroff MassMECFS&FM YouTube, 2023)
- Ongoing occult infections in relay stations send unrelenting alarm signals to hypothalamus (viruses often hang out in neuronal axons, e.g. herpes)
- Inflammatory cytokine molecules can travel up the vagus nerve to brainstem relay stations where they provoke “mirror responses” in hypothalamus immune cells (microglia) that cause inflammation that impairs its function.

VAGUS NERVE

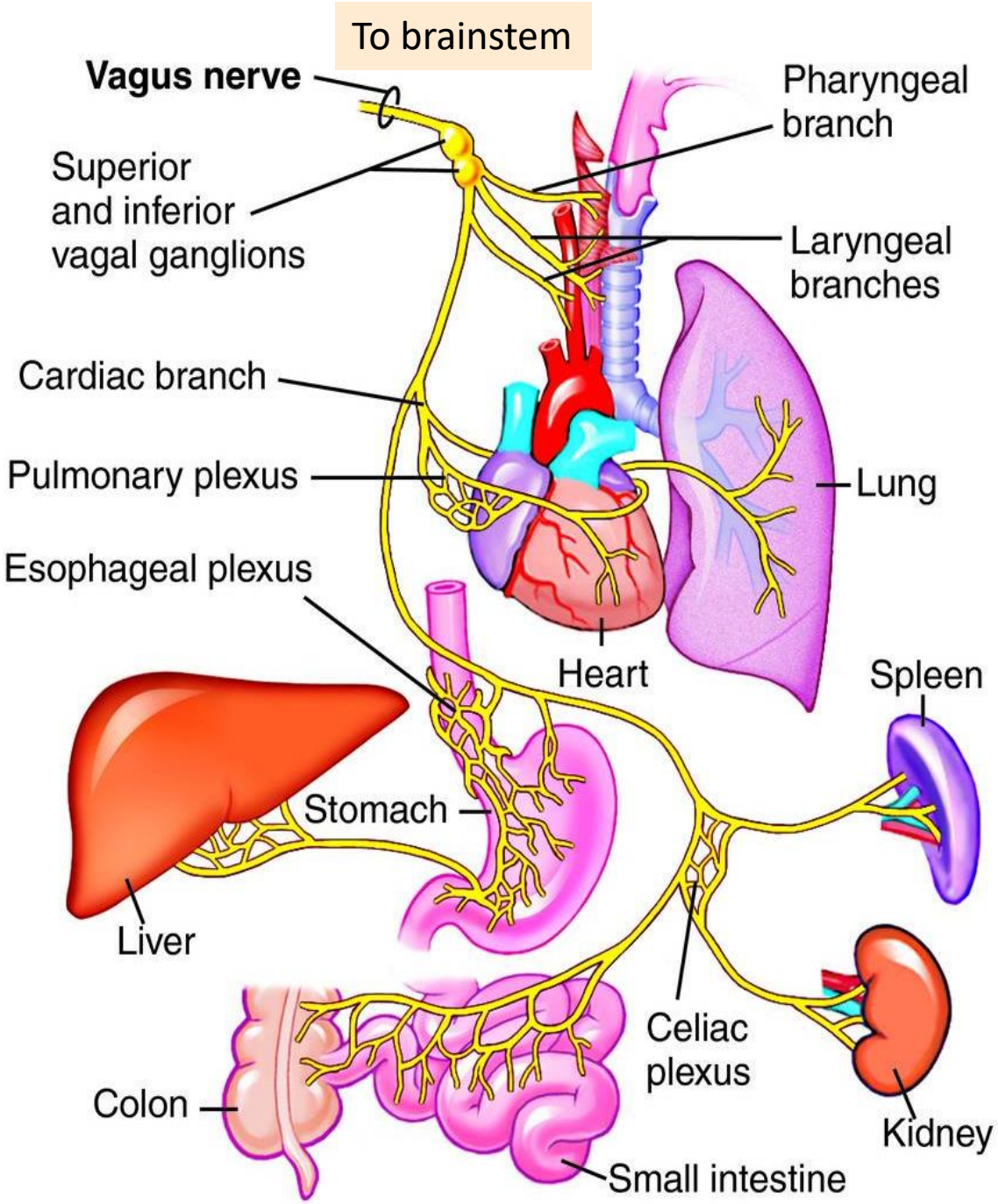
Longest cranial nerve
"wandering nerve"

Sympathetic
autonomic nerve
(RELAX)

Cottage industry of vagus nerve stimulators for relaxation

Mostly motor commands,
but some sensory afferents
that detect pathogens & toxins
in the gut

May be a conduit from
gut to brainstem
for proinflammatory cytokines
(Goehler et al, 1999),
which in turn sends alarm signals
to hypothalamus



https://socratic.org/questions/does-the-vagus-nerve-belong-to-the-sensory-somatic-or-autonomic-system

Chronic fatigue syndrome from vagus nerve infection: A psychoneuroimmunological hypothesis

(2013)

Michael B. VanElzakker *

M.B. VanElzakker / Medical Hypotheses 81 (2013) 414–423

A B S T R A C T

Chronic fatigue syndrome (CFS) is an often-debilitating condition of unknown origin. There is a general consensus among CFS researchers that the symptoms seem to reflect an ongoing immune response, perhaps due to viral infection. Thus, most CFS research has focused upon trying to uncover that putative immune system dysfunction or specific pathogenic agent. However, no single causative agent has been found. In this speculative article, I describe a new hypothesis for the etiology of CFS: infection of the vagus nerve. When immune cells of otherwise healthy individuals detect any peripheral infection, they release proinflammatory cytokines. Chemoreceptors of the sensory vagus nerve detect these localized proinflammatory cytokines, and send a signal to the brain to initiate sickness behavior. Sickness behavior is an involuntary response that includes fatigue, fever, myalgia, depression, and other symptoms that overlap with CFS. The vagus nerve infection hypothesis of CFS contends that CFS symptoms are a pathologically exaggerated version of normal sickness behavior that can occur when sensory vagal ganglia or paraganglia are themselves infected with any virus or bacteria. Drawing upon relevant findings from the neuropathic pain literature, I explain how pathogen-activated glial cells can bombard the sensory vagus nerve with proinflammatory cytokines and other neuroexcitatory substances, initiating an exaggerated and intractable sickness behavior signal. According to this hypothesis, any pathogenic infection of the vagus nerve can cause CFS, which resolves the ongoing controversy about finding a single pathogen. The vagus nerve infection hypothesis offers testable hypotheses for researchers, animal models, and specific treatment strategies.

Vagus nerve infection → proinflammatory cytokines → vagus nerve activation → "sickness response" → fatigue, sleep disruption, dysautonomias, etc.

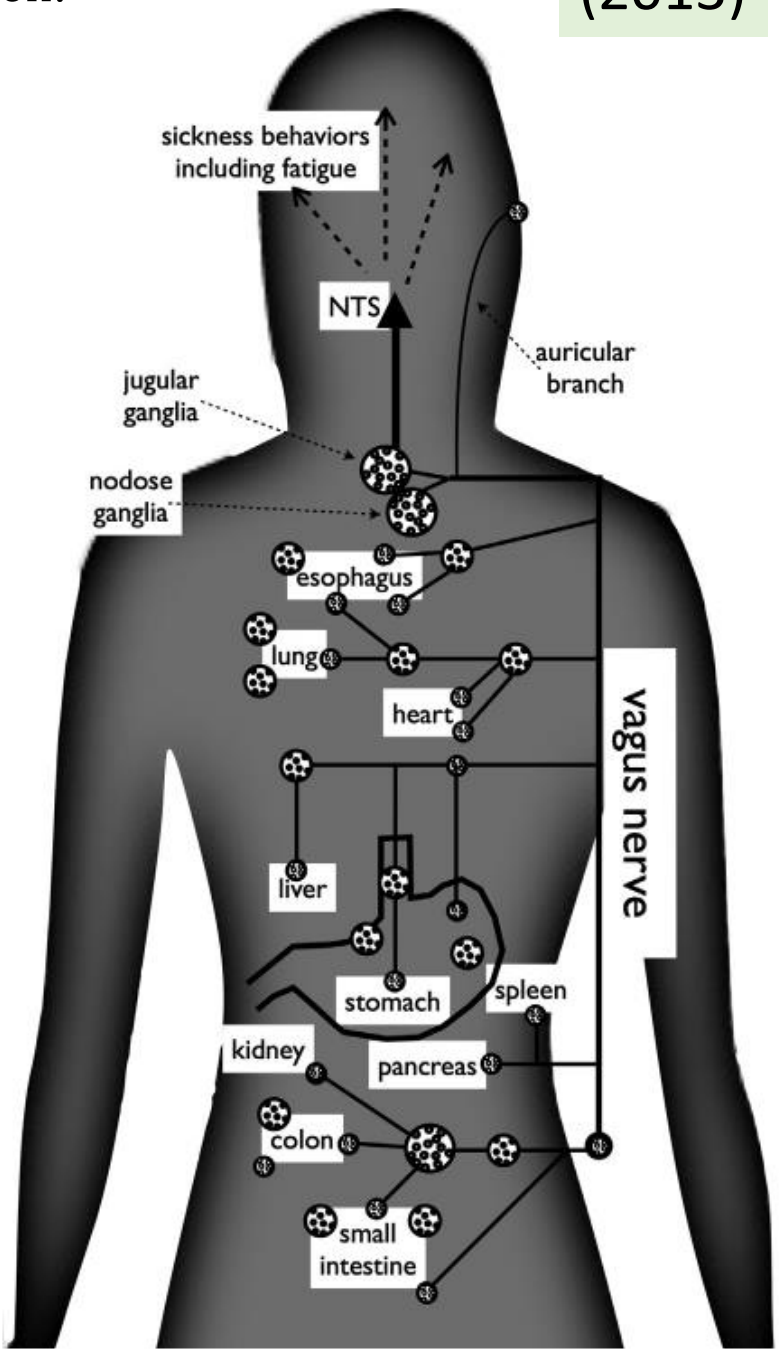


Fig. 1. A highly simplified schematic of vagus nerve anatomy. Circles represent ganglia and paraganglia, which contain both glial cells and sensory vagus nerve chemoreceptors. A viral or bacterial infection within any ganglia or paraganglia causes glial activation, leading to the release of proinflammatory cytokines and other neuroexcitatory mediators. The resulting afferent signal enters the brain at the nucleus tractus solitarius (NTS), and triggers sickness behaviors. When normal glial cell activation becomes pathological as it does in neuropathic pain conditions, the signal is intensified and intractable, leading to CFS.

Things that can go awry: 3. Damage or impair relay stations (or send false signals to the hypothalamus)

Three ways neural functions can be disrupted:

1. Damage peripheral nerves ("dysautonomias")

2. Damage or impair neural relay stations (brainstem)

3. Impair neural control in the brain (hypothalamus)

3. Impair central neural control (hypothalamus)

- Hypothalamus regulates sleep cycles, metabolism, immune response
- HPA axis regulates inflammation & stress adaptation via cortisol, which reduces inflammation (CRH→ACTH→ cortisol)
- Parts of the hypothalamus & pituitary (neurosecretory organs) may not be as well protected by blood-brain barrier (BBB) as other brain regions. Also, the BBB is more permeable than was previously thought. More like a pump system.
- ∴ HPA is susceptible to inflammation (cytokines from mast cells/microglia) & autoimmune responses. There are extensive communications between neural & immune systems (Skaper et al, 2012). There is a theory of ME/CFS based on interactions between neural and immune systems.
- Incoming false alarm signals that don't shut off. Occult, chronic infections in gut or brainstem → ongoing hypothalamus "sickness response" (van Elzakker, 2013; Komaroff MassMECFS&FM YouTube talk 2023)

Vulnerability of Peripheral Nerves and Autonomic CNS to infection and inflammation

Two ways neural functions can be disrupted:

1. Damage peripheral nerves (efferents or sensory afferents)

2. Impair neural control in the brain (Hypothalamic-Pituitary-Adrenal (HPA) Axis)

3. Impair central neural control

- Hypothalamus regulates sleep cycles, metabolism, immune response, stress adaptation,
- HPA axis regulates inflammation & stress adaptation via cortisol, which reduces inflammation (CRH→ACTH→ cortisol)
- Parts of the hypothalamus & pituitary (neurosecretory organs) are not as well protected by blood-brain barrier as other brain regions. Also the blood-brain barrier is more permeable than was previously thought. More like a pump system.
- ∴ HPA is susceptible to inflammation (cytokines) & autoimmune responses
- Covert, chronic infections in gut or brainstem → hypothalamus "sickness response" (van Elzakker, 2013; Komaroff MassMECFS&FM YouTube talk 2023)

For more information on the vagus nerve theory and mechanisms of the generation of the major symptoms of ME/CFS, I highly recommend Michael van Elzakker's talk for Mass ME/CFS & FM on October 19, 2019 that is available on YouTube.

https://www.youtube.com/watch?v=rIUccEITT6E

ME/CFS at the Intersection of the Nervous & Immune Systems (Lecture) - Michael VanElzakker, PhD

Mass MECFS & FM Association
1.88K subscribers
Subscribe
317
Share
Save

Review
FASEB J
. 2012 Aug;26(8):3103-17.
doi: 10.1096/fj.11-197194. Epub 2012 Apr 19.

Microglia and mast cells: two tracks on the road to neuroinflammation

Stephen D Skaper[1], Pietro Giusti, Laura Facci

Abstract

One of the more important recent advances in neuroscience research is the understanding that there is extensive communication between the immune system and the central nervous system (CNS). Proinflammatory cytokines play a key role in this communication. The emerging realization is that glia and microglia, in particular, (which are the brain's resident macrophages), constitute an important source of inflammatory mediators and may have fundamental roles in CNS disorders from neuropathic pain and epilepsy to neurodegenerative diseases. Microglia respond also to proinflammatory signals released from other non-neuronal cells, principally those of immune origin. Mast cells are of particular relevance in this context. These immunity-related cells, while resident in the CNS, are capable of migrating across the blood-spinal cord and blood-brain barriers in situations where the barrier is compromised as a result of CNS pathology. Emerging evidence suggests the possibility of mast cell-glia communications and opens exciting new perspectives for designing therapies to target neuroinflammation by differentially modulating the activation of non-neuronal cells normally controlling neuronal sensitization, both peripherally and centrally. This review aims to provide an overview of recent progress relating to the pathobiology of neuroinflammation, the role of microglia, neuroimmune interactions involving mast cells, in particular, and the possibility that mast cell-microglia crosstalk may contribute to the exacerbation of acute symptoms of chronic neurodegenerative disease and accelerate disease progression, as well as promote pain transmission pathways. We conclude by considering the therapeutic potential of treating systemic inflammation or blockade of signaling pathways from the periphery to the brain in such settings.

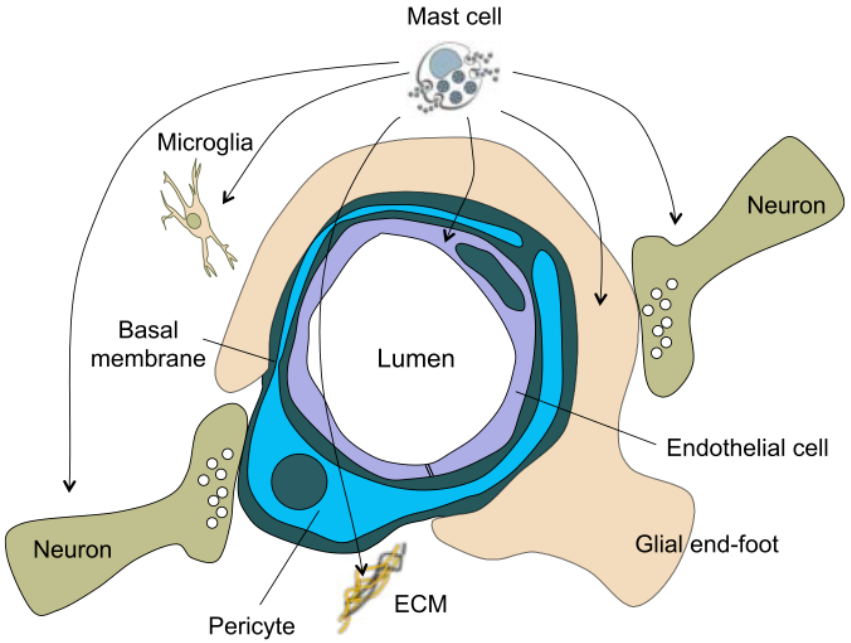


Figure 1. Schematic illustration of the cellular elements of the neurovascular unit comprising an intracerebral arteriole or capillary. ECM, extracellular matrix.

Mast cells secrete inflammatory factors
(general nonspecific immune mobilization signals)

Mast cells exist everywhere in body & brain

Microglia are the macrophages of the brain

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome—Metabolic Disease or Disturbed Homeostasis due to Focal Inflammation in the Hypothalamus?

J Pharmacol Exp Ther 367:155–167, October 2018

Hatziagelaki, Adamaki, Tsilioni, Dimitriadis, Theoharides

Inflammation Hypothesis: mast cells and microglia disrupt hypothalamus

Autoimmune Hypothesis: immune attack of mitochrondria disrupt hypothalamus

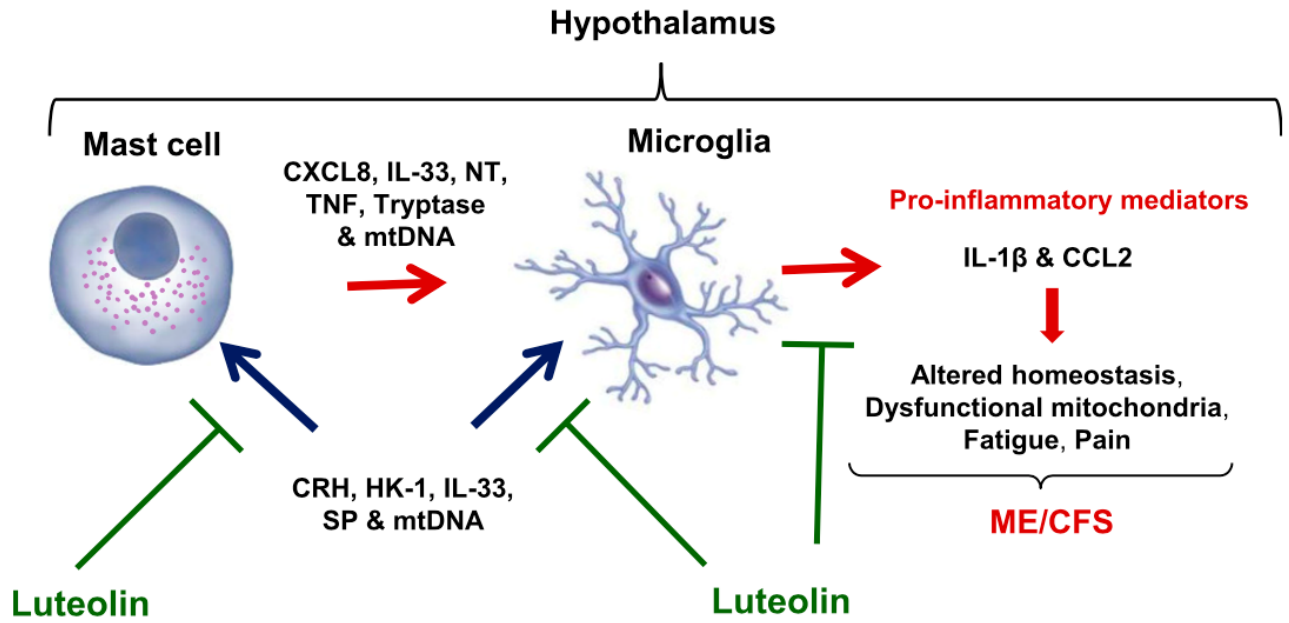


Fig. 1. Diagrammatic representation of the proposed mast cell/microglia interactions in the hypothalamus contributing to the pathogenesis of ME/CFS, which could serve as targets for treatment. Hypothalamic mast cells are stimulated by stress-associated triggers such as CRH, HK-1, and SP, along with mtDNA and IL-33; some derive from the nasal cavity, while others may reach the area through a disrupted blood-brain barrier or through lymphatics. Stimulated mast cells then secrete molecules such as CXCL8, neurotensin (NT), TNF, tryptase, and mtDNA (CXCL), which activate microglia to secrete more inflammatory molecules (especially, IL-1β, IL-6, and CXCL8) that further disrupt homeostasis, causing mitochondrial dysfunction and contributing to symptoms of ME/CFS. Luteolin could inhibit these processes at different steps, as shown.

Journal of Pharmacology & Experimental Therapeutics 367:155–167, October 2018

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome—Metabolic Disease or Disturbed Homeostasis due to Focal Inflammation in the Hypothalamus?

Erifili Hatziagelaki, Maria Adamaki, Irene Tsilioni, George Dimitriadis, & Theoharis C. Theoharides

ABSTRACT

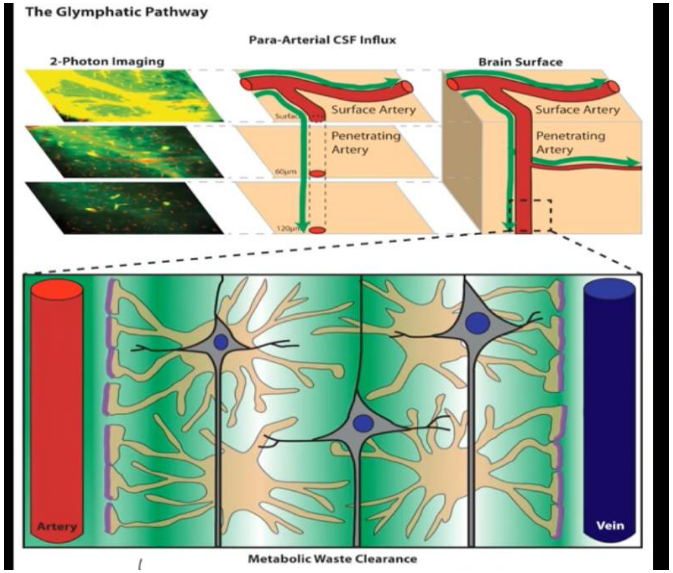
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex disease characterized by debilitating fatigue, lasting for at least 6 months, with associated malaise, headaches, sleep disturbance, and cognitive impairment, which severely impacts quality of life. A significant percentage of ME/CFS patients remain undiagnosed, mainly due to the complexity of the disease and the lack of reliable objective biomarkers. ME/CFS patients display decreased metabolism and the severity of symptoms appears to be directly correlated to the degree of metabolic reduction that may be unique to each individual patient. However, the precise pathogenesis is still unknown, preventing the devel- opment of effective treatments. The ME/CFS phenotype has been associated with abnormalities in energy metabolism, which are apparently due to mitochondrial dysfunction in the absence of mitochondrial diseases, resulting in reduced oxidative metabolism. Such mitochondria may be further contributing to the ME/CFS symptomatology by extracellular secretion of mitochondrial DNA, which could act as an innate pathogen and create an autoinflammatory state in the hypothalamus. We pro- pose that stimulation of hypothalamic mast cells by environmental, neuroimmune, pathogenic and stress triggers activates microglia, leading to focal inflammation in the brain and disturbed homeostasis. This process could be targeted for the development of novel effective treatments.

Glyphatic system (disc. ~2012):

- A "waste clearance system" in the brain
  (like the brain's lymphatic system)
- Activated during deep slow-wave sleep

What role does the hypothalamus play
in producing slow-wave sleep cycles
and activation of glymphatic clearance?

- Impairment of glymphatic → ME/CFS?
- Possible consequent symptoms similar to
  sleep deprivation:
  fatigue, brain fog, drowsiness
  inflammation ↑, immune response ↓



Video, Wikipedia, "Glymphatic System"

The putative glymphatic signature of chronic fatigue syndrome: A new view on the disease pathogenesis and therapy

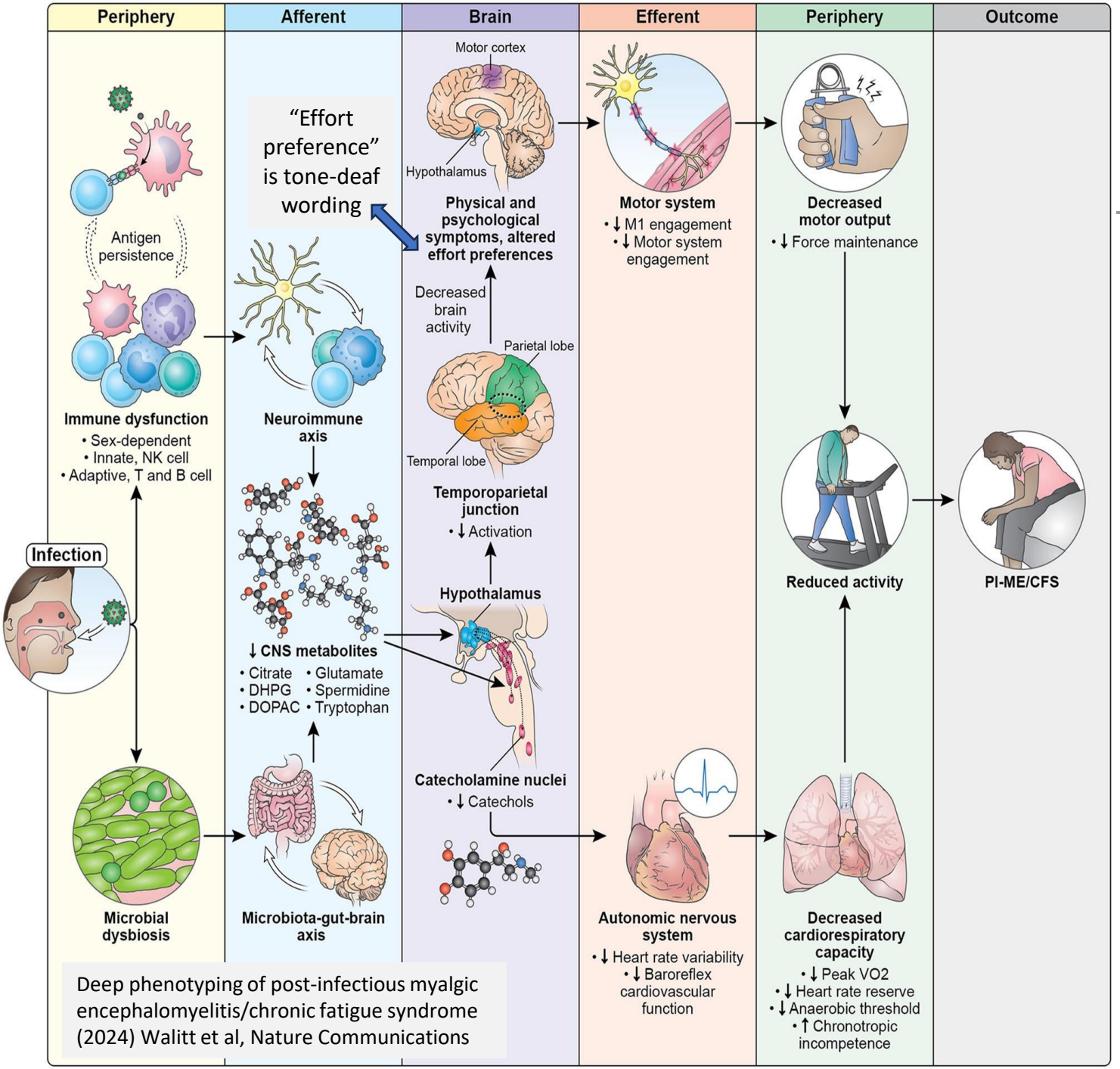
Peter Wostyn, Peter Paul De Deyn

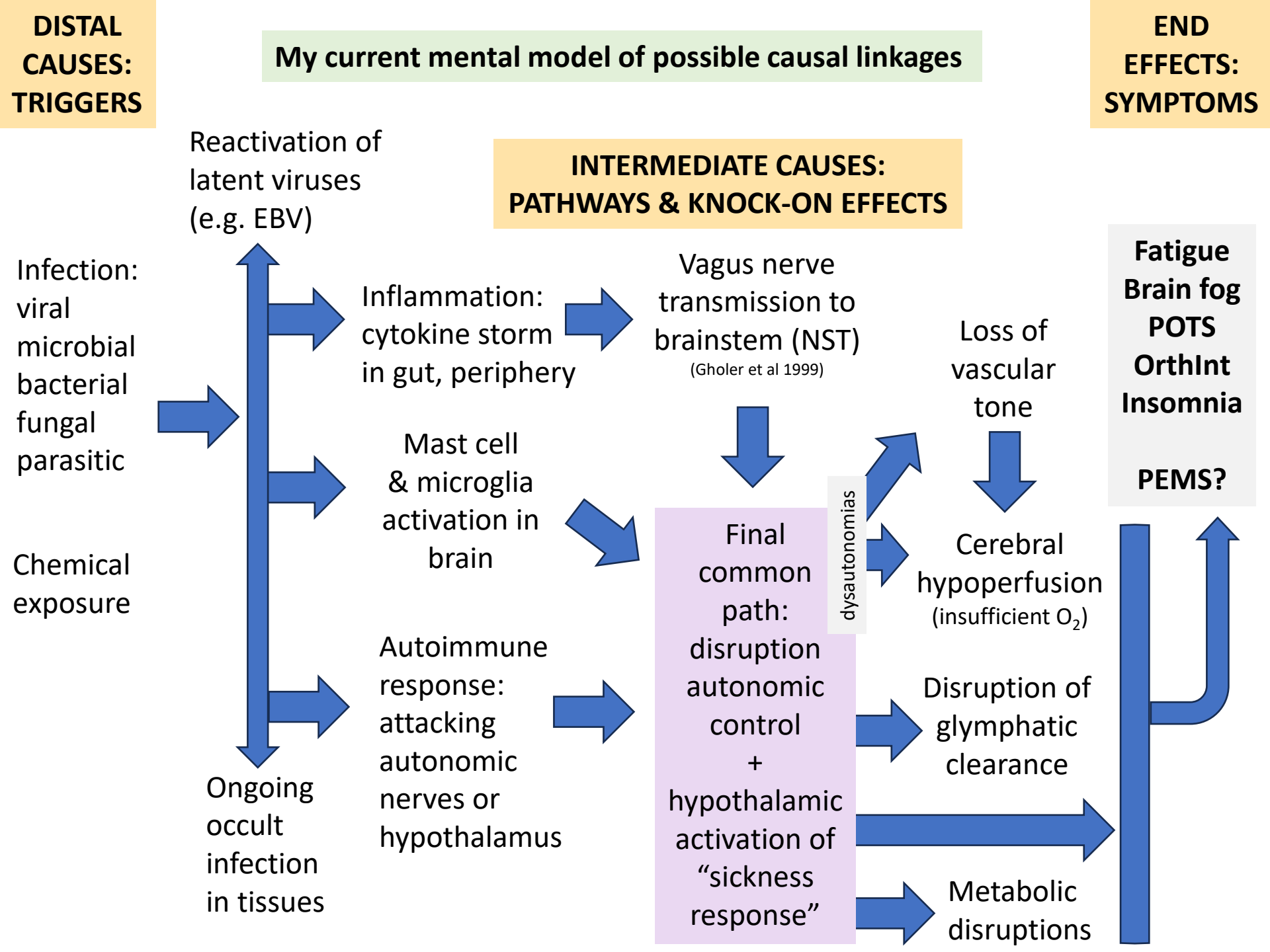
Medical Hypotheses 118 (2018) 142–145

ABSTRACT

The underlying pathophysiology of chronic fatigue syndrome remains incompletely understood and there are no curative treatments for this disorder at present. However, increasing neuroimaging evidence indicates that functional and structural abnormalities exist in the brains of chronic fatigue syndrome patients, suggesting that the central nervous system is involved in this disorder and that at least some chronic fatigue syndrome patients may have an underlying neurological basis for their illness. In the present paper, we speculate that glymphatic dysfunction, causing toxic build up within the central nervous system, may be responsible for at least some cases of chronic fatigue syndrome. We further postulate that cerebrospinal fluid diversion such as lumboperitoneal shunting may be beneficial to this subgroup of patients by restoring glymphatic transport and waste removal from the brain. Although recent evidence indicates that at least some chronic fatigue syndrome patients may benefit from cerebrospinal fluid drainage, further studies are needed to confirm this finding and to determine whether this can be attributed to enhancement of glymphatic fluid flow and interstitial fluid clearance. If confirmed, this could offer promising avenues for the future treatment of chronic fatigue syndrome. Clearly, given the relative invasive nature of cerebrospinal fluid diversion, such procedures should be reserved for chronic fatigue syndrome patients who are severely debilitated, or for those with severe headaches. Anyhow, it seems worthwhile to make every effort to identify new therapies for patients who suffer from this devastating disease, especially given that there are currently no effective treatments for this condition.

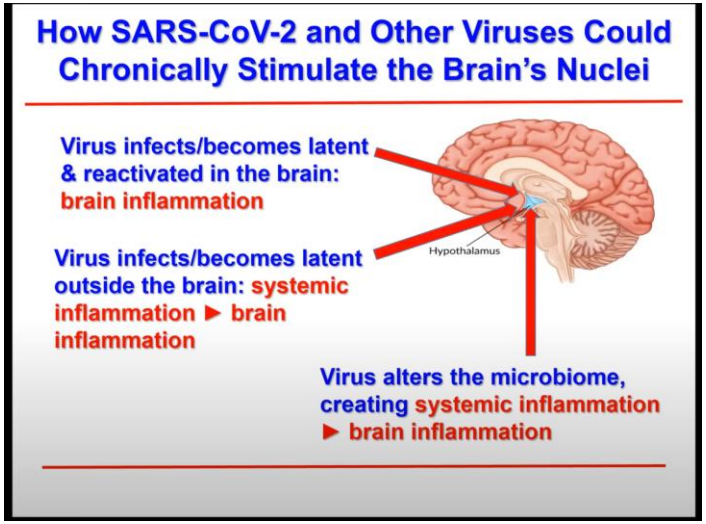
Fig. 10 | Pathophysiology of PI-ME/CFS. Diagram illustrates potential mechanisms and a cascade of events that lead to the development of ME/CFS after an infection. Exposure to an infection leads to concomitant and persistent immune dysfunction and changes in gut microbiome. Immune dysfunction affects both innate and adaptive immune systems that are sex dependent. We hypothesize that these changes are driven by antigen persistence of the infectious pathogen. These immune and microbial alterations impact the brain, leading to decreased concentrations of metabolites which impacts brain function. The catecholamine nuclei release lower levels of catechols, which impacts the autonomic nervous system and manifests with decreased heart rate variability and decreased baroreflex cardiovascular function, with downstream effects on cardiopulmonary capacity. Altered hypothalamic function leads to decreased activation of the temporoparietal junction during motor tasks, suggesting a failure of the integrative brain regions necessary to drive the motor cortex. This decreased brain activity is experienced as physical and psychological symptoms and impacts effort pre- ferences, leading to decreased engagement of the motor system and decreases in maintaining force output during motor tasks. Both the autonomic and central motor dysfunction result in a reduction in physical activity. With time, the reduc- tion in physical activity leads to muscular and cardiovascular deconditioning, and functional disability. All these features make up the PI-ME/CFS phenotype.

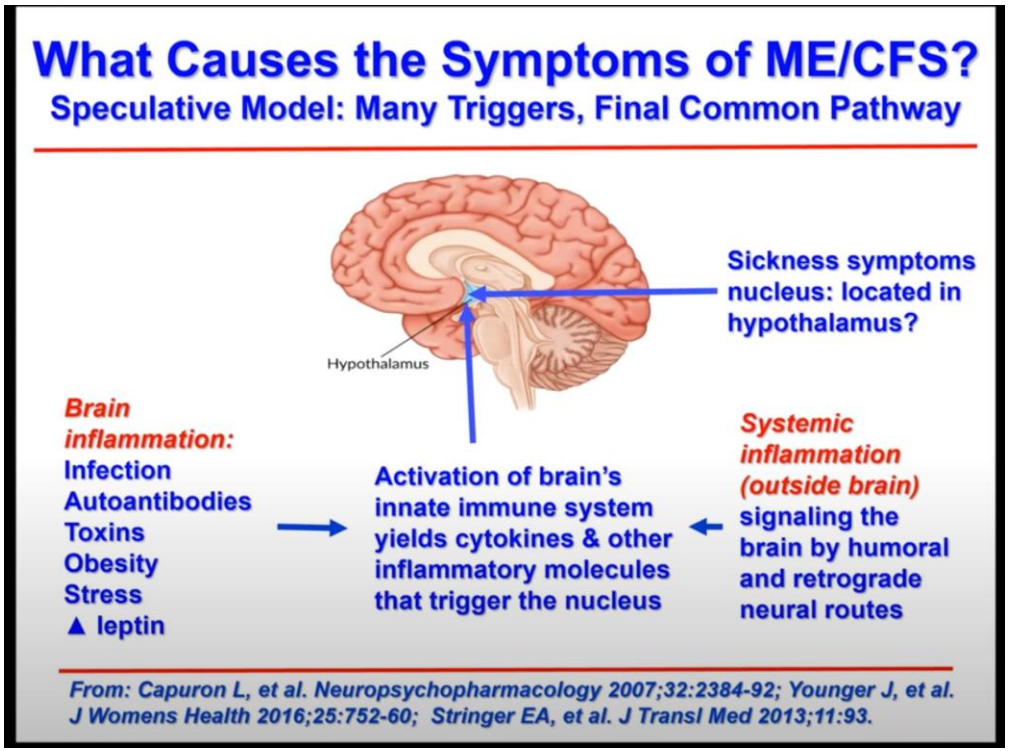



DISTAL CAUSES: TRIGGERS
My current mental model of possible causal linkages
END EFFECTS: SYMPTOMS
INTERMEDIATE CAUSES: PATHWAYS & KNOCK-ON EFFECTS
Reactivation of latent viruses (e.g. EBV)
Infection: viral microbial bacterial fungal parasitic
Chemical exposure
Ongoing occult infection in tissues
Inflammation: cytokine storm in gut, periphery
Vagus nerve transmission to brainstem (NST)
(Gholer et al 1999)
Mast cell & microglia activation in brain
Autoimmune response: attacking autonomic nerves or hypothalamus
Final common path: disruption autonomic control + hypothalamic activation of "sickness response"
dysautonomias
Loss of vascular tone
Cerebral hypoperfusion
(insufficient O_2)
Disruption of glymphatic clearance
Metabolic disruptions
Fatigue
Brain fog
POTS
OrthInt
Insomnia
PEMS?

For more discussion of symptom commonalities between various post-infection syndromes (ME/CFS, Long Covid, others) and the various inter-system linkages, I highly recommend Dr. Anthonv Komaroff's October 22, 2022 talk for Mass ME/CFS & FM that is available on YouTube.

https://www.youtube.com/watch?v=AbVMvRS-a7Y





In Summary

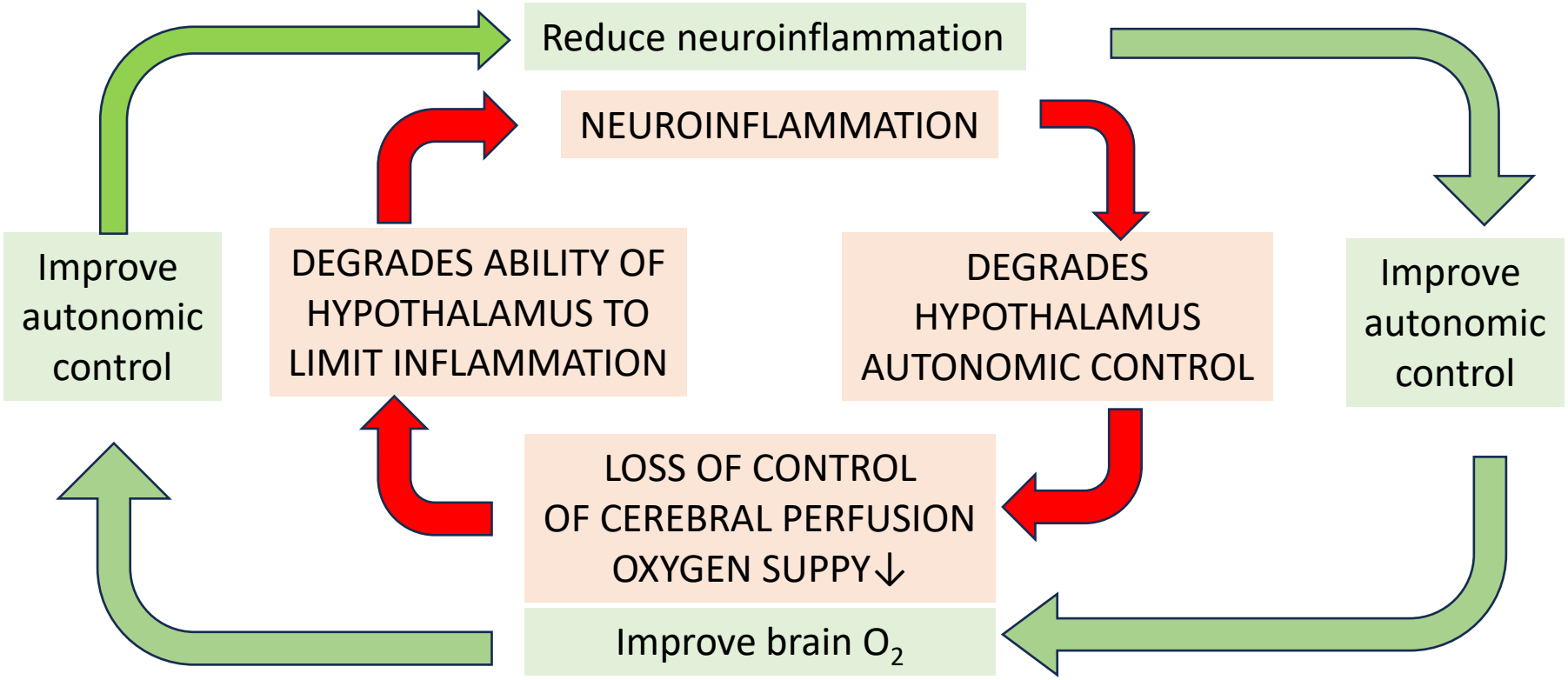
- ME/CFS and Long COVID have underlying biological causes, including an infectious trigger (in many), immune activation and neuroinflammation, autoantibodies, dysautonomia, oxidative stress, defective energy metabolism, hypometabolic state, and a pro-inflammatory gut microbiome
- These abnormalities 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.

What makes the ME/CFS state self-sustaining?

Normally the acute sickness state is temporary and resolves itself. This is the question we need to answer in order to find a cure rather than treating each symptom one by one.

It may be the case that there are mutually reinforcing processes that form a **vicious cycle** – each step makes all the others worse. However, for every vicious cycle there is a **virtuous cycle**, where any improvement in one step improves all the others.

Reversing the process anywhere in the cycle turns a vicious cycle into a virtuous one.



MORE PRACTICAL MATTERS

Some practical advice re: navigating our medical system

- I am a neuroscientist, not a medical doctor, so I won't be dispensing medical advice — please consult licensed medical professionals whenever possible.
- However, finding appropriate medical specialists who are familiar with dysautonomias and ME/CFS can be/most often is quite difficult. ME/CFS patient advocacy organizations can be extremely helpful here. Mass ME/CFS & FM helped my family enormously early on when we had not yet found informed doctors.
- Finding competent specialists is complicated by widespread ignorance of ME/CFS by first-line medical providers (primary care physicians).
- New patients face long wait times to see such specialists, and simply getting an appointment can itself be difficult, requiring various tests (that need to be ordered by one's PCP). A cooperative, open-minded PCP is essential.
- I think it's important to find specialists familiar with symptoms and treatments particular to ME/CFS: e.g. neurologists → dysautonomias & proper tilt table tests; cardiologists → OI & POTS; sleep doctors → chronic insomnia; immunologists → specifics of ME/CFS
- Many ME/CFS patients don't get proper diagnoses for several years.
- The situation may have improved since the abatement of the Covid pandemic and increased awareness of Long Covid. Because of their similarities, you may be able to find competent specialists in clinics for Long Covid.

Diagnostic tests re: dysautonomias

Wide array of tests to determine where autonomic impairments exist

Resources:

Dysautonomia International http://dysautonomiainternational.org
Dysautotonomia Project https://autonomiceducation.com/patient-courses
YouTube clinician videos: e.g. Dr. Khosro Farhad on small fiber polyneuropathy
Wikipedia: good for quick definitions, basic information

Clinical tests (quantiative, "objective" physiological measurements):

Orthostatic blood pressure response:

NASA Lean Test (simple, 10', can be done at home if you need to convince your PCP)

Tilt table (gold standard, find a specialist familiar with dysautonomias, OI, or POTS, important for documenting dysautonomias and chronic fatigue syndrome)

Heart rate variation to standing (vagal afferent and efferent limbs)
Baroflex sensivity (slowing of heart rate w. blood pressure Δ)
Isometric exercises (increase in diastolic BPto test efferent limbs);
Valsava Maneuver tests (BP & HR, noninvasive or invasive arterial catheter)
Sweat - sudomotor (Skin conductance @ diff. body locations via electrical skin conductance)
Pupillary response (use drugs to test for dilation)
Quantitative Sudomotor Axon Reflex Test (QSART, local piloerection, sweating)
Infusion of pressor drugs (test adrenergic response)
Response to thermal changes (hot or cold water, radiant heating)
Tearing (lacrimal function, Schirmer test for detecting dry eyes in Sjögren syndrome)
Various tests of GI and genito-urinary functions

Source: Principles of Neurology, Victor & Ropper, 7th ed. (2001)

Therapies re: dysautonomias

Wide array of tests to determine where autonomic impairments exist

Resources:

Dysautonomia International http://dysautonomiainternational.org
Dysautotonomia Project https://autonomiceducation.com/patient-courses
Dysautonomia Information Network https://www.dinet.org/info
YouTube clinician videos
Wikipedia: good for quick definitions, basic information

Orthostatic intolerance (OI): Methods to expand blood volume

Self care: Increase salt intake, better hydration, compression garments
Drugs: midodrine, droxidopa, fludrocortisone, pyridostigmine
Self-care: Eat small meals, raise head of bed

Per Dr. Komaroff, if you have ME/CFS and PEM, be wary of exercise (pace yourself, don't over-exert). Awareness of PEM may be less prevalent in the non-ME/CFS medical community. Opinions differ among medical practitioners – not a simple issue. If you do exercise, do it in a incremental, graded manner, monitor your responses to it in the following days, adjust your level accordingly, consult w. your doctors.

Postural tachycardia syndrome (POTS) https://www.standinguptopots.org/

Many of the same therapies as for OI that differ according to POTS subtype.
Neuropathic POTS (HR↑BP = on standing): sympathetic underactivation in legs vasoconstriction↓
Hyperadrenergic POTS (HR↑BP↑ on standing): sympathetic overactivation
Beta blockers (propanolol) & other off-label meds
Hypovolemic POTS (low blood volume)

Source: Principles of Neurology, Victor & Ropper, 7th ed. (2001)

Massachusetts ME/CFS & FM
ASSOCIATION
EDUCATION, SUPPORT & ADVOCACY SINCE 1985

Symptoms and Accomodations for Dysautonomia

Hayla Sluss, PhD

March 17, 2024

Hayla Sluss, Ph.D.
Discussing symptoms and accommodations.

Hayla Sluss (Ph.D. molecular medicine) is a researcher and Assistant Professor at UMass Chan Medical School, and a Board member of MassME.

Dysautonomia

Key takeaway:

- Different for each person
- Can occur at different times/unpredictable:
  - Transition from lying to standing
  - Prolonged standing
  - Prolonged sitting
  - Walking

Generalized symptoms- previously reviewed:

- rapid heartbeat/tachycardia >100bpm
- hypovolemia: HR increase 30 bpm (40 adolescents)
  10 min after standing (POTS) JH
- Low BP upon standing (Orthostatic Hypotension/ Neurally mediated)
  - drop 20 mm Hg top/systolic with 2-5 min standing (Mayo)
  - drop 10 mm Hg bottom/diastolic within 2-5 min standing (Mayo)
- Chronic Orthostatic Intolerance (may not have change in HR)

ME/CFS and Dysautonomia: Overlapping and Non-Overlapping Symptoms

SYMPTOM	ME/CFS	DYSAUTONOMIA
PEM	✓	
Disrupted sleep	✓	✓
Fatigue	✓	✓
Difficulty thinking/ Concentrating/recall	✓	✓
Temperature disregulation	✓	✓
Rapid Heartbeat	✓	✓
Low BP upon standing	✓	✓
Chronic OI	✓	✓
Heart Palpitations	✓	✓
Lightheadedness	✓	✓
Dizziness	✓	✓
Intolerance of exercise	✓	✓
Sensitivity sound/light	✓	✓
GI/Urinary	✓	✓

SYMPTOM	ME/CFS	DYSAUTONOMIA
Headache/ migraine	✓	✓
Blurry Vision	✓	✓
tremors	✓	✓
Nausea	✓	✓
Syncope/Fainting	✓	✓
Weakness	✓	✓
Pale complexion	✓	✓
Giddiness	✓	✓
Anxiety	✓	✓ less common
Chest Pain	✓	✓ less common
Neck Pain	✓	✓ less common
Shoulder Pain	✓	✓ less common
Dsynepea/diff breathing	✓	✓ less common

Students		
Provide notes (if missed or low concentration), anonymously better	Hardcopy book at house/room	Allowing for snacks and water, and breaks if needed
Extension on tests, reduction material due (concept v busy work)	Info about future assignments	Testing quiet place if needed
Virtual classes	Help manage timing if needed	No penalty for missing class or leaving if needed
Dorm- living near classes	Tutor for info missed or helping with brain fog	No calling out student, especially in front of other students

Workplace		
Provide best ergonomic situation	Material for projects provided	Allow for food or snacks close by if needed
Allow for workload extension or reduction workday	Heads up on assignments	Quiet or private place, allow to put feet up
Virtual meetings if needed	Help manage timing if needed	Allowance for missing meetings
Mindful of length of meeting room to office/workroom if in person	Work buddy to help with updating meetings	Provide supportive environment

Dysautonomia Youth Network of America, Inc.

Dysautonomia International

HKS 2024

QUESTIONS
&
ANSWERS

Please join us next month!

Got Mold?

Michael Rubino
Co-Founder and chair of Change the Air Foundation

Sunday, Apr 21, 2024, 4 p.m. EDT

Please join us next month!

We are only able to produce this speaker series through your membership and generous donations. Thank you!

massmecfs.org/**join** massmecfs.org/**donate**

To join the Sunday Conversations team: volunteer@massmecfs.org