

‘Fatigue’ in Myalgic Encephalomyelitis (ME)

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Disclaimer and Disclosures

Disclaimer

This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure

This certifies that I, Betsy Keller, have a financial relationship that is relevant to the subject matter of this presentation.

I conduct cardiopulmonary exercise tests (CPET) for research and as a fee-based assessment for evidence of impairment.

'Fatigue' ... according to Google

(https://www.skybrary.aero/index.php/Fatigue#Fatigue_Types)

- **Physical**

- Inability to exert muscular force to extent intended

- **Mental**

- Including sleepiness
- General decrease of attention and ability to perform complex, or even simple tasks, with customary efficiency
- Often due to loss of or interrupted sleep pattern

- **Types of Fatigue (3)**

- **Transient**

- Acute – due to extreme sleep restriction or prolonged wakefulness within 1-2 days

- **Cumulative**

- due to mild sleep restriction or prolonged wakefulness

- **Circadian**

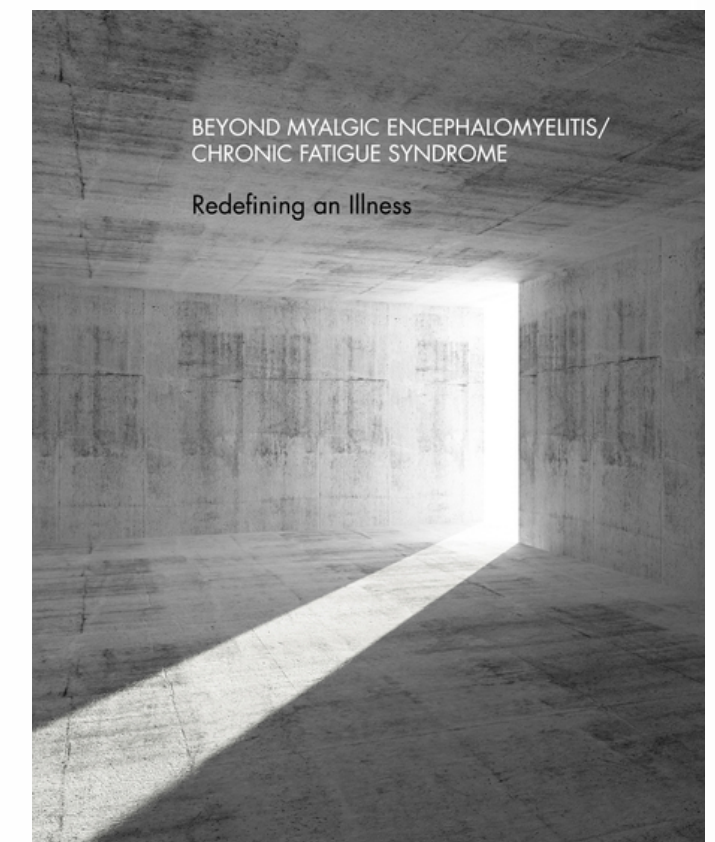
- due to reduced performance during nighttime hours, esp. during window of circadian low (WOCL) between 2-6 am

Clinical diagnostic criteria requires the patient have:

1. **A substantial reduction or impairment in the ability to engage in pre-illness levels** of occupational, educational, social, or personal activities that persists for more than 6 months and is **accompanied by fatigue**, which is often profound, is of new or definite onset (not lifelong), is **not the result of ongoing excessive exertion**, and is **not substantially alleviated by rest**,
2. **Post-exertional malaise**,* and
3. **Unrefreshing sleep***

At least one of two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance



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* Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

Post Exertional Malaise

“the illness within the illness” (Komaroff, 2011)

ME/CFS Canadian Consensus Definition:

***“Physical or mental exertion often causes debilitating malaise and/or **fatigue**, generalized pain, deterioration of cognitive functions, and worsening of other symptoms that may occur immediately after activity or be delayed.*”**

ME International Consensus Criteria

***“Postexertional neuroimmune **exhaustion** is the hallmark feature. This cardinal feature is a pathological **inability to produce sufficient energy** on demand with prominent symptoms primarily in the neuroimmune regions”*”**

IOM (NAM) Report

***“Worsening of symptoms after physical, cognitive, or emotional effort”*”**

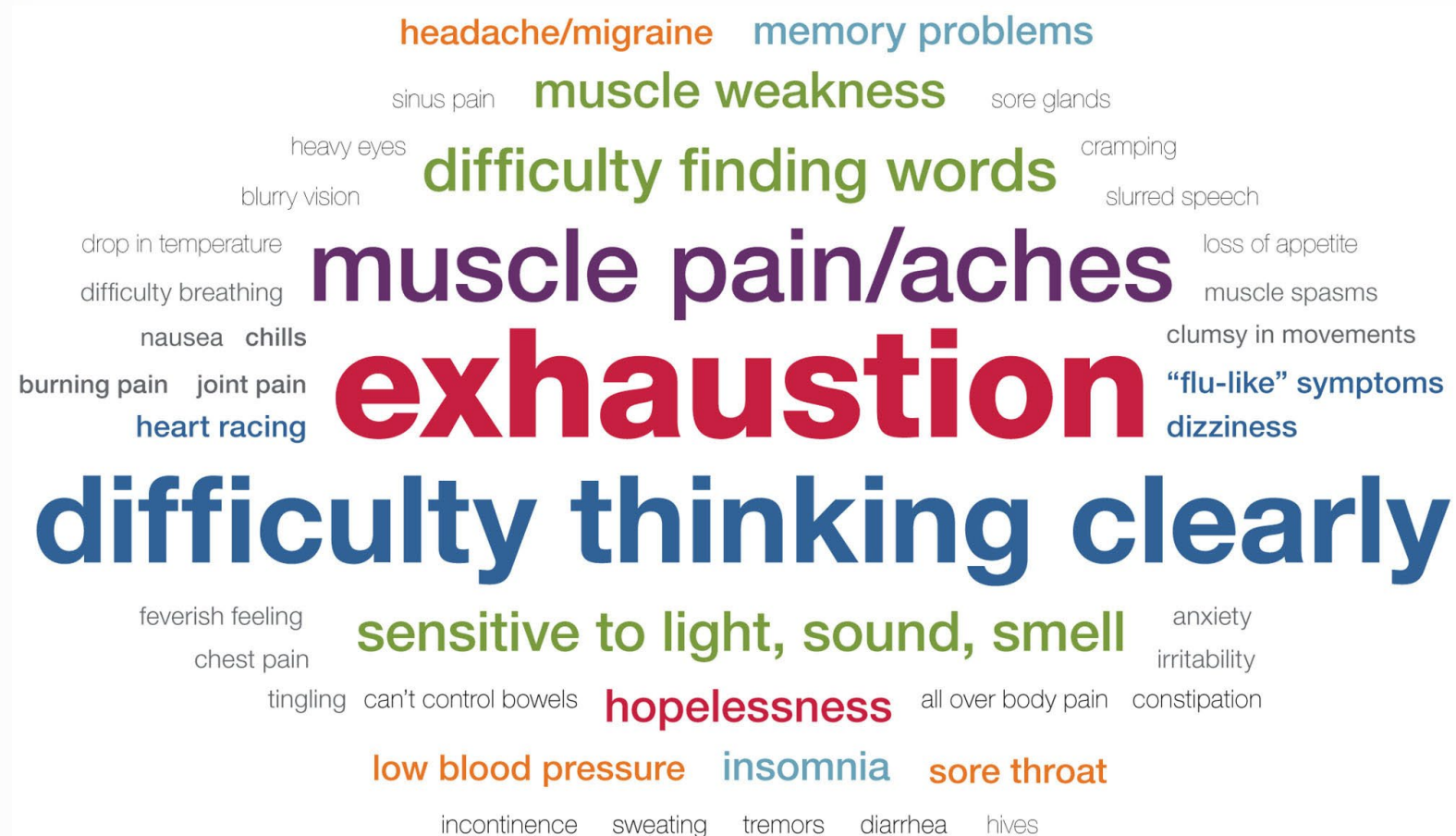


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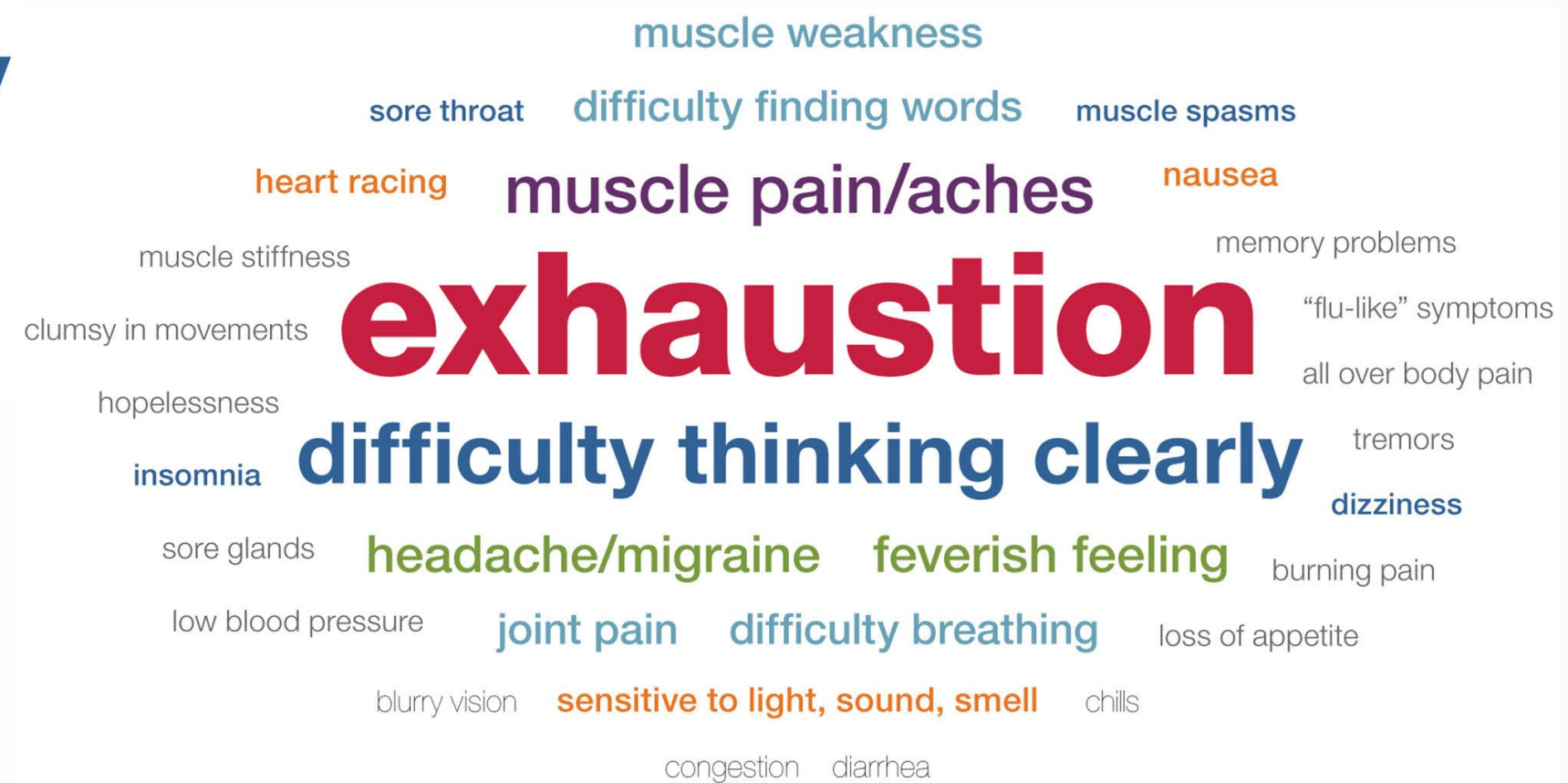
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Symptoms of PEM

Symptoms of daily PEM



Symptoms of PEM following CPET



Stussman B et al. (2020) Front. Neurol.
11:1025. doi: 10.3389/fneur.2020.01025

What is a cardiopulmonary exercise test (CPET)?



CPET measures effectiveness of **heart, lungs & muscles** to deliver and use oxygen to produce energy



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Aerobic capacity (VO_2max): **predicts mortality, index of impairment,** **measure of energy production**

Exercise capacity most powerful predictor of mortality

- 6213 Clinically referred subjects
- Myers et al (2002)

Exercise capacity an independent predictor of mortality in women, higher than previously established in men

- 5721 Asymptomatic women in the St. James Women Take Heart Project
- Gulati et al (2003)



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Why a 2-day CPET for ME/CFS?

1 CPET does not assess ability to recover normally



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Why 2 CPETs?

Stevens S. et al. (2018), Front Pediatr, vol. 6



CPET-1

Baseline VO_2 peak

Anaerobic threshold

Post Exertional Malaise (PEM)

CPET-2

PEM compromised VO_2 peak

Anaerobic threshold



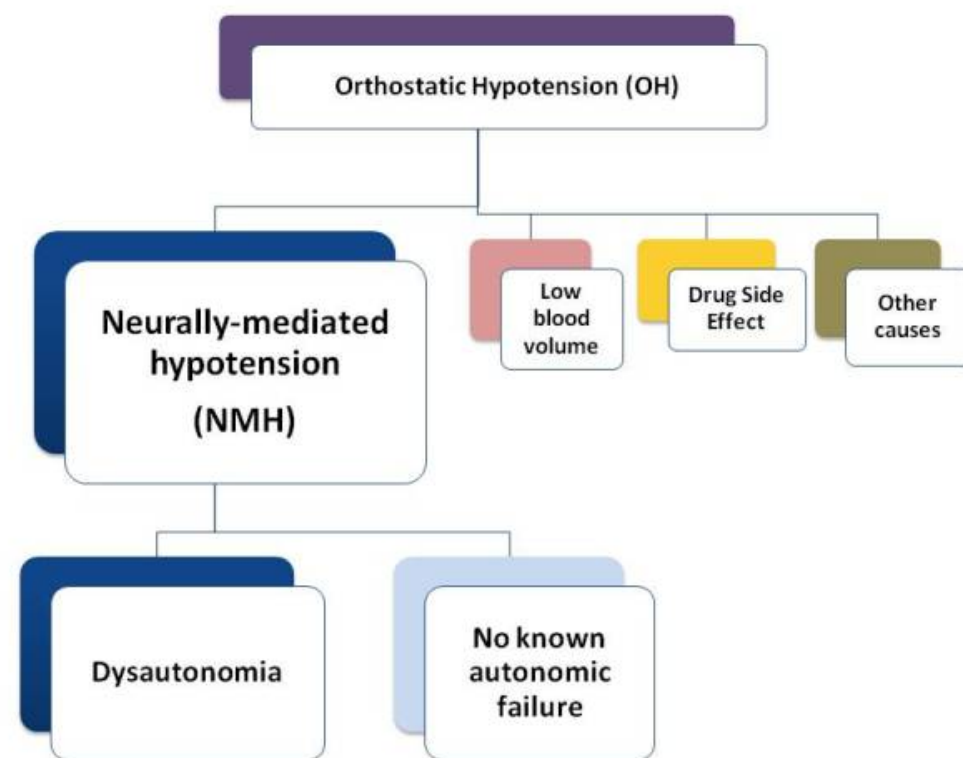
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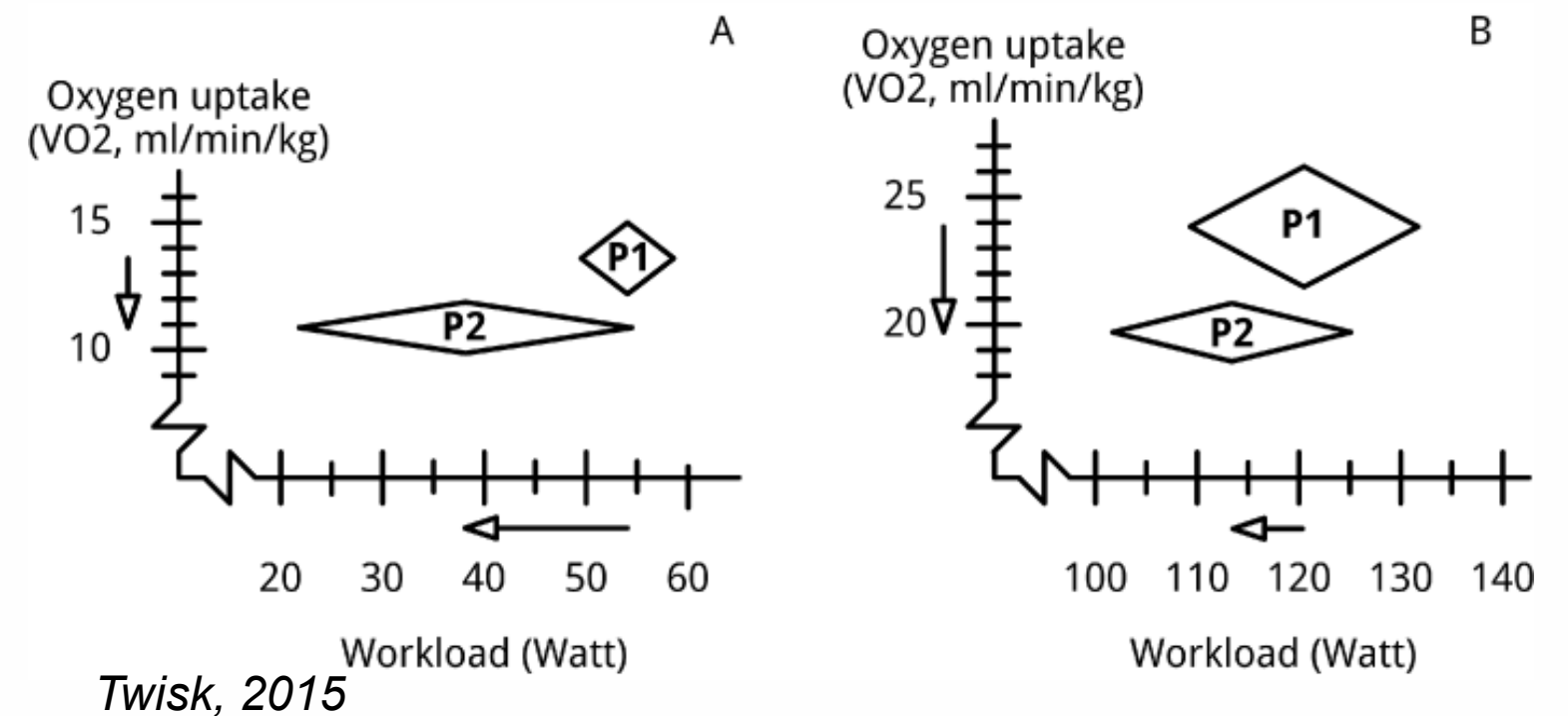
SUBSETS of abnormal responses to 2-day CPET, N=97 ME/CFS

Keller, IACFS/ME, 2016

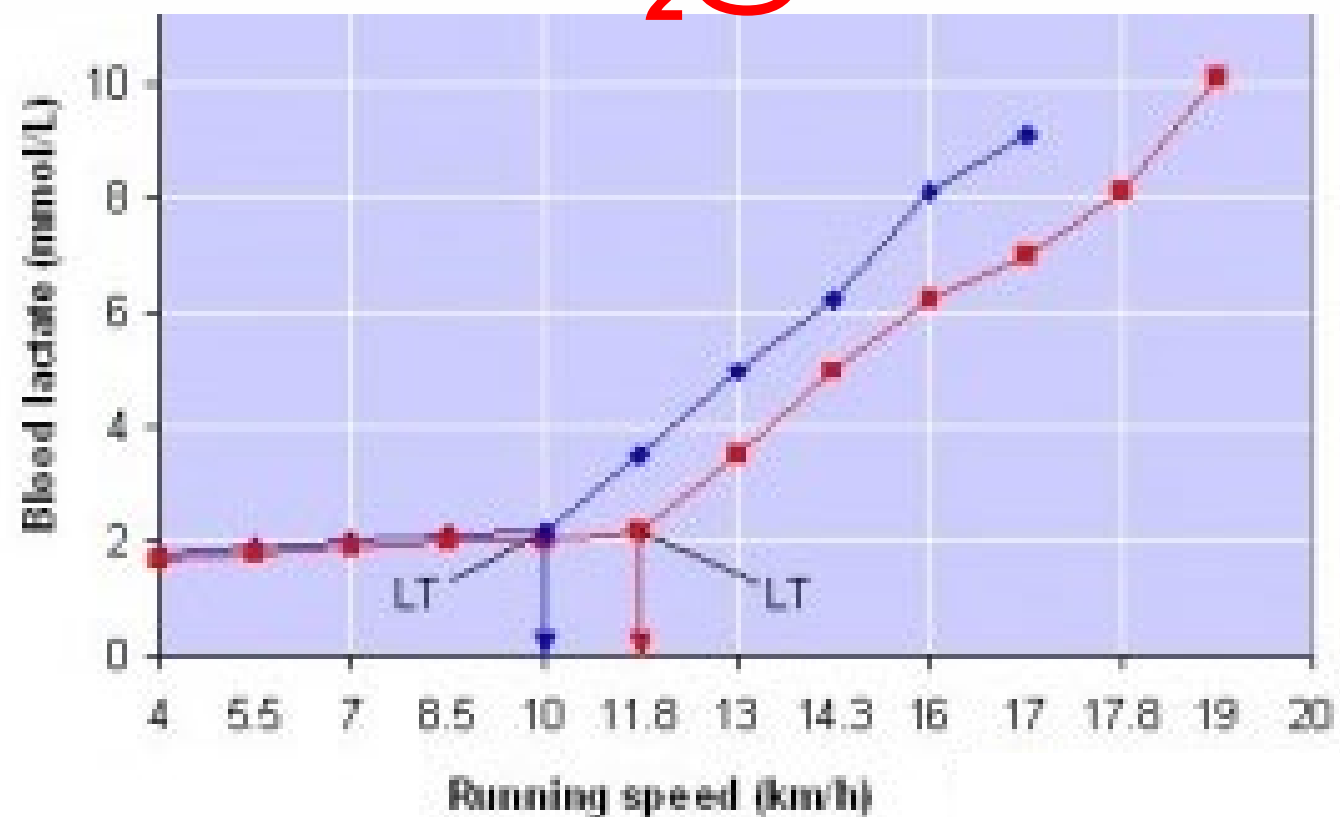
HR/BP and/or Ventilatory



VO₂peak



VO₂@VAT



Low Functional Capacity



PERSPECTIVE

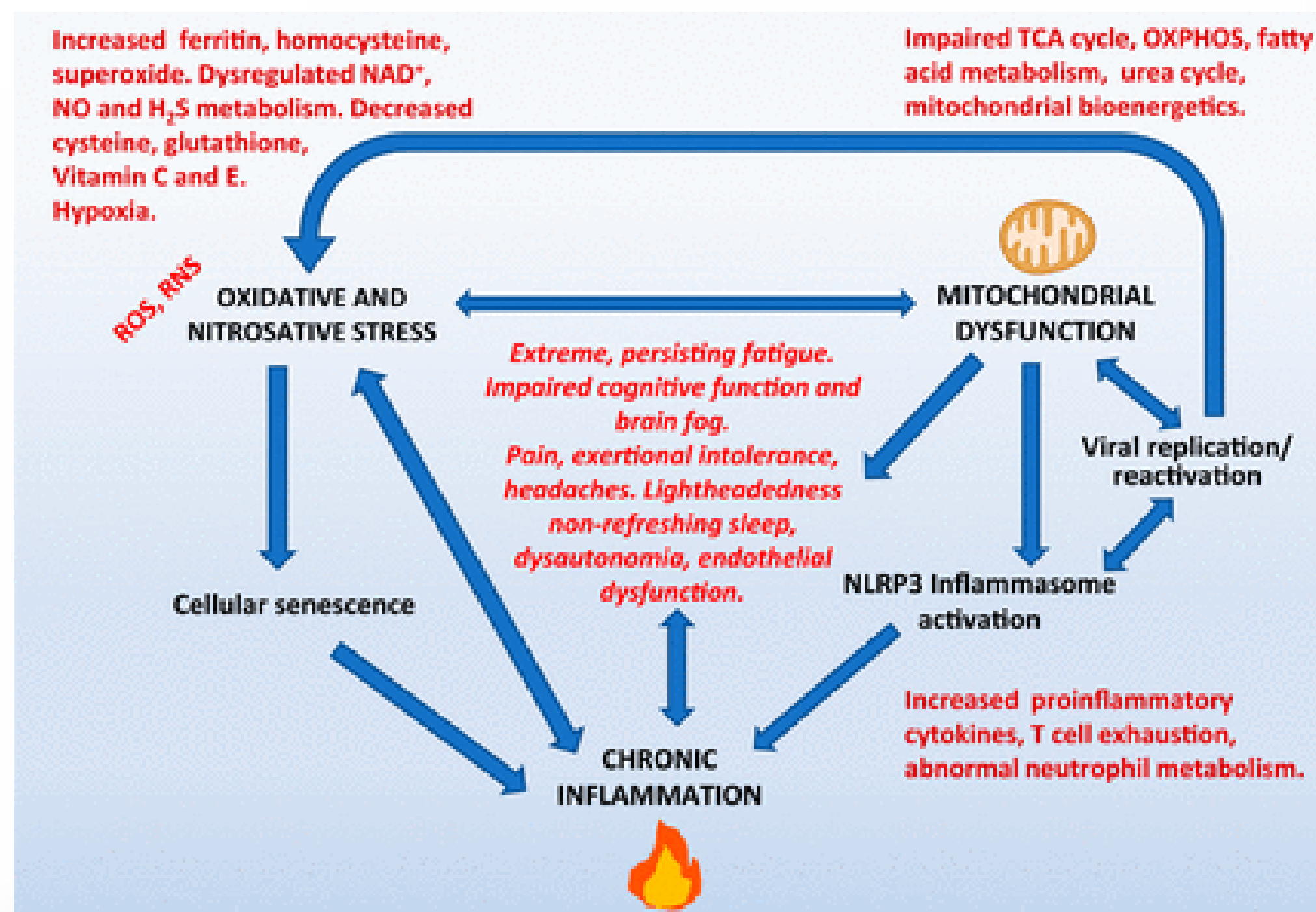


Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome

Bindu D. Paul, Marian D. Lemle, Anthony L. Komaroff, and Solomon H. Snyder

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PNAS August 24, 2021 118 (34) e2024358118; <https://doi.org/10.1073/pnas.2024358118>

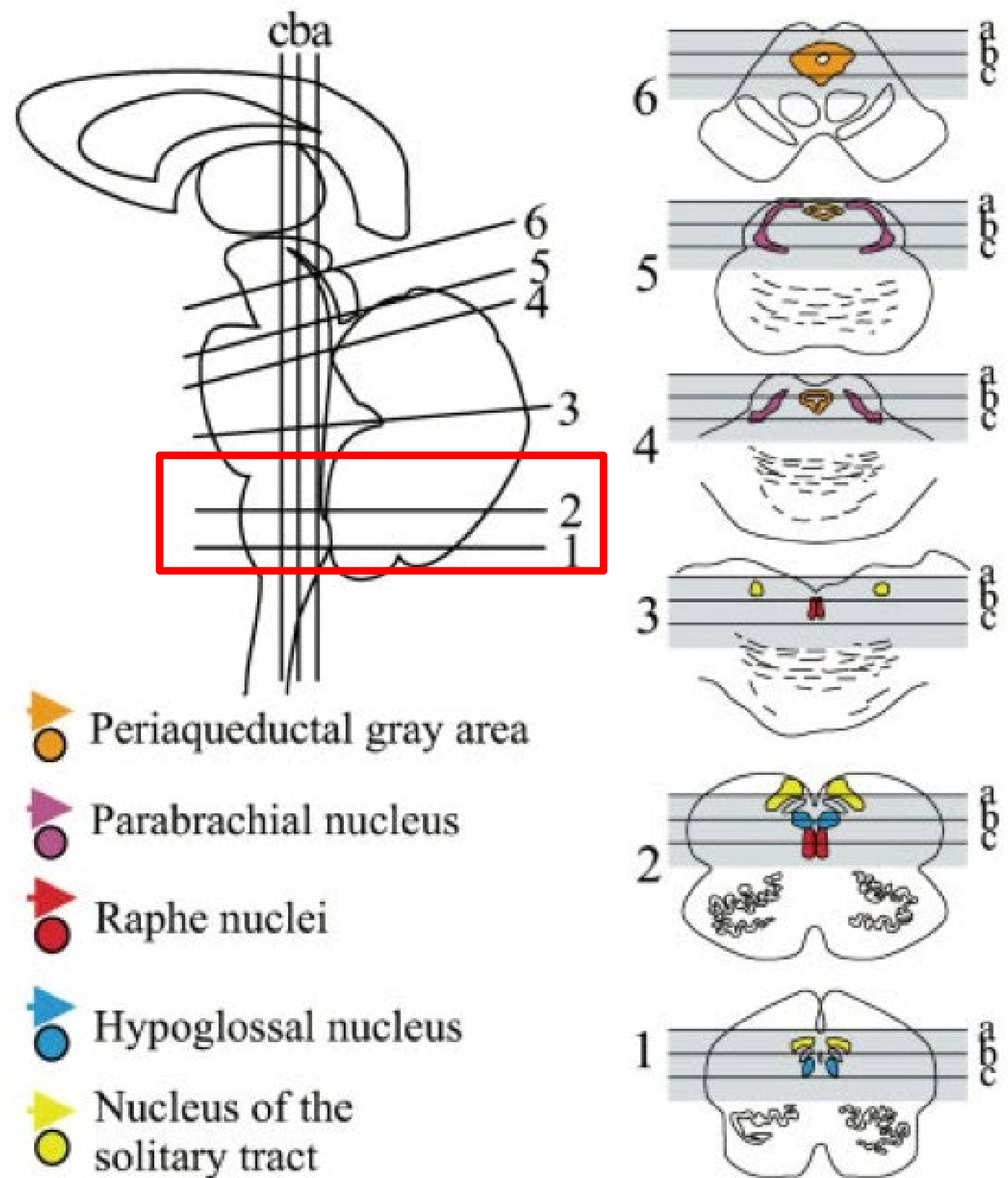


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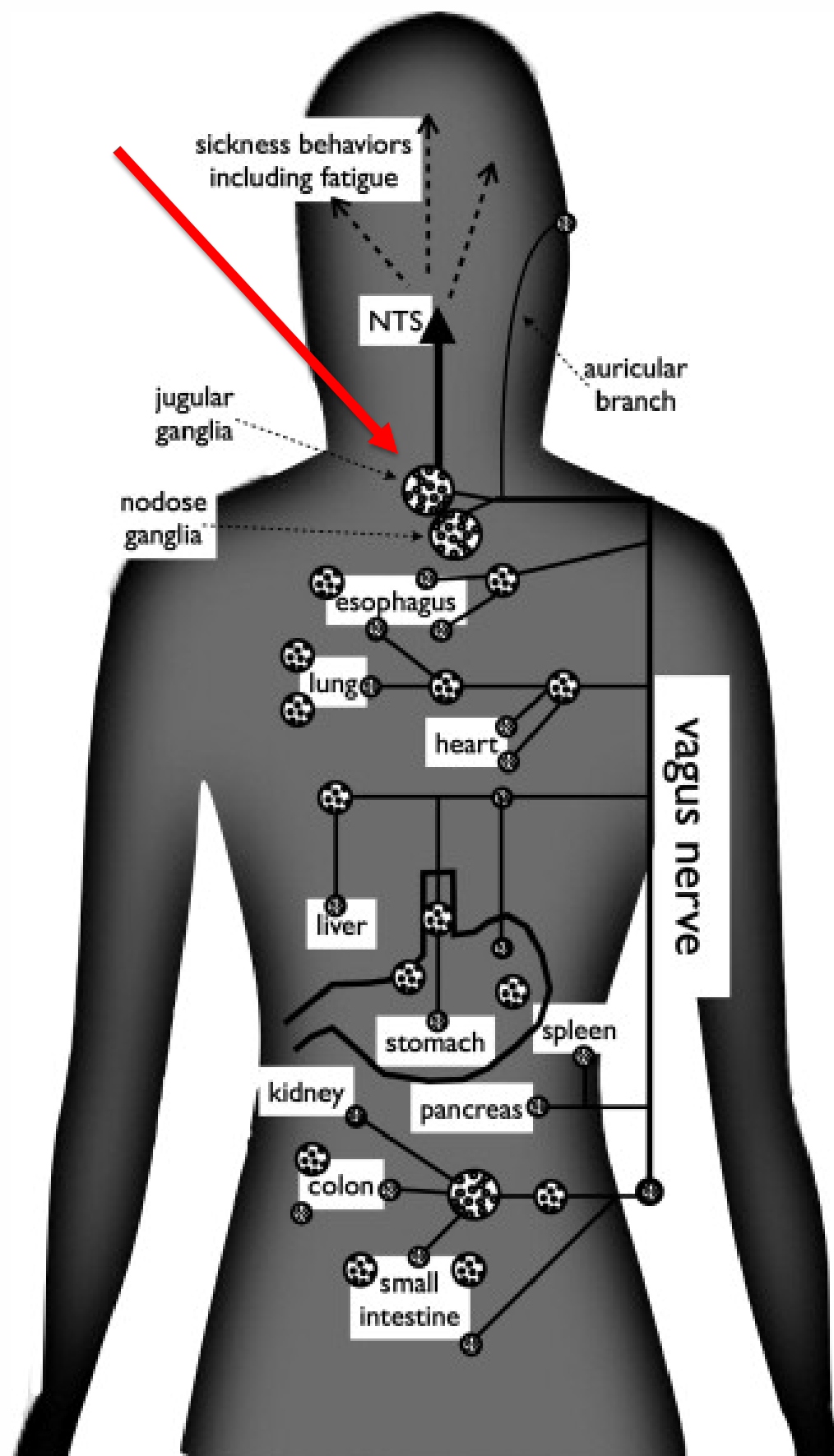
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Nucleus Tractus Solitarius (NTS)

- In medulla
- carries afferent taste information
- major processing station for ascending visceral info from body
- important role in neuro-immune loops and autonomic reflexes
- Major functions include taste and cardiac control



Simplified vagus nerve anatomy



- Circles = ganglia/paraganglia with glial cells & sensory VN chemoreceptors
- Infection in ganglia/paraganglia causes glial activation
- Release of PROINFLAMMATORY cytokines & neuroexcitatory mediators
- Vagus nerve afferent signal to brain at NTS causes 'sickness behavior'
- Once normal glial cell activation is pathological (e.g., neuropathic pain), signal intensifies and becomes intractable (as with ME/CFS)

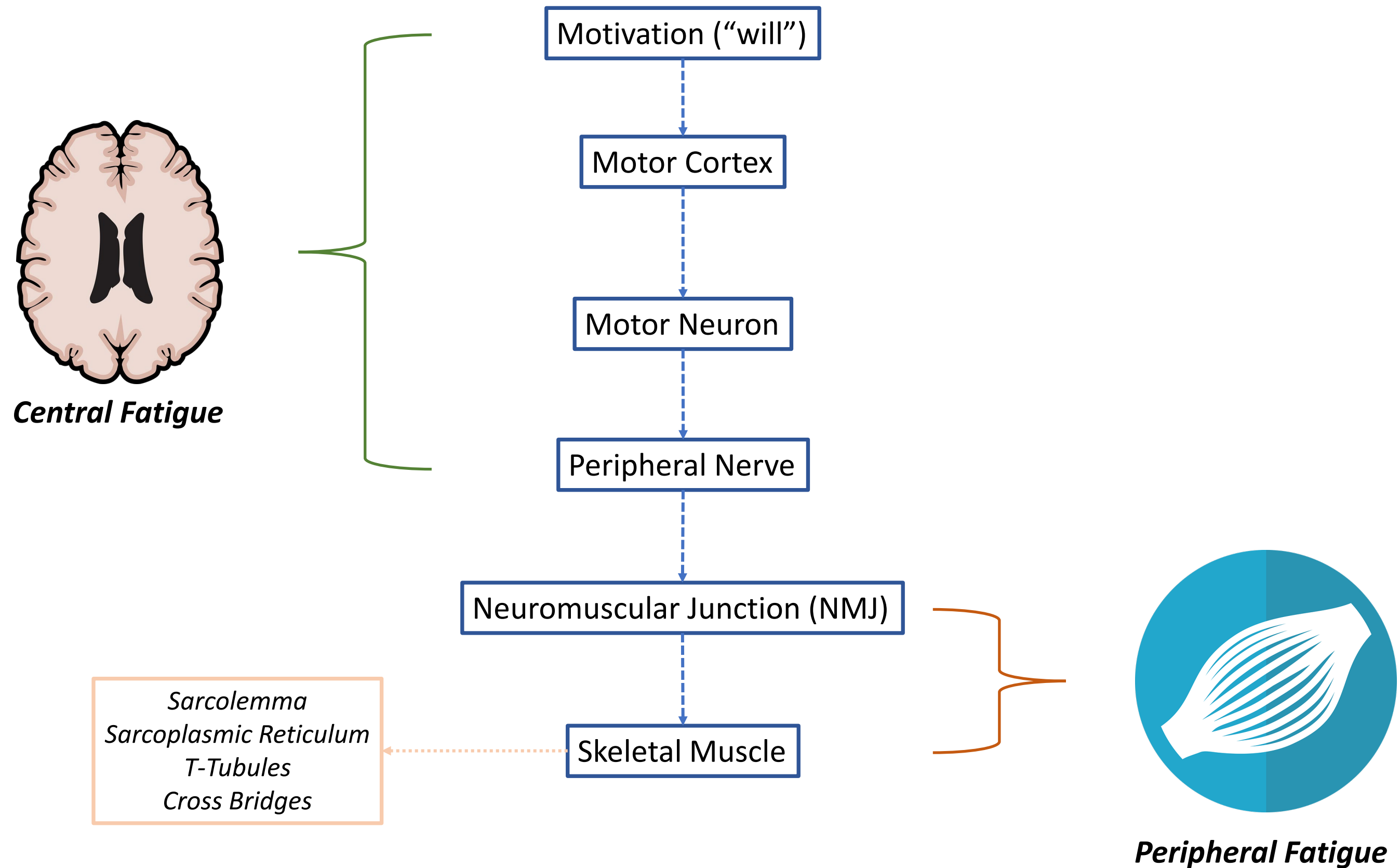
From: VanElzakker (2013) *Med Hyp*, vol. 81

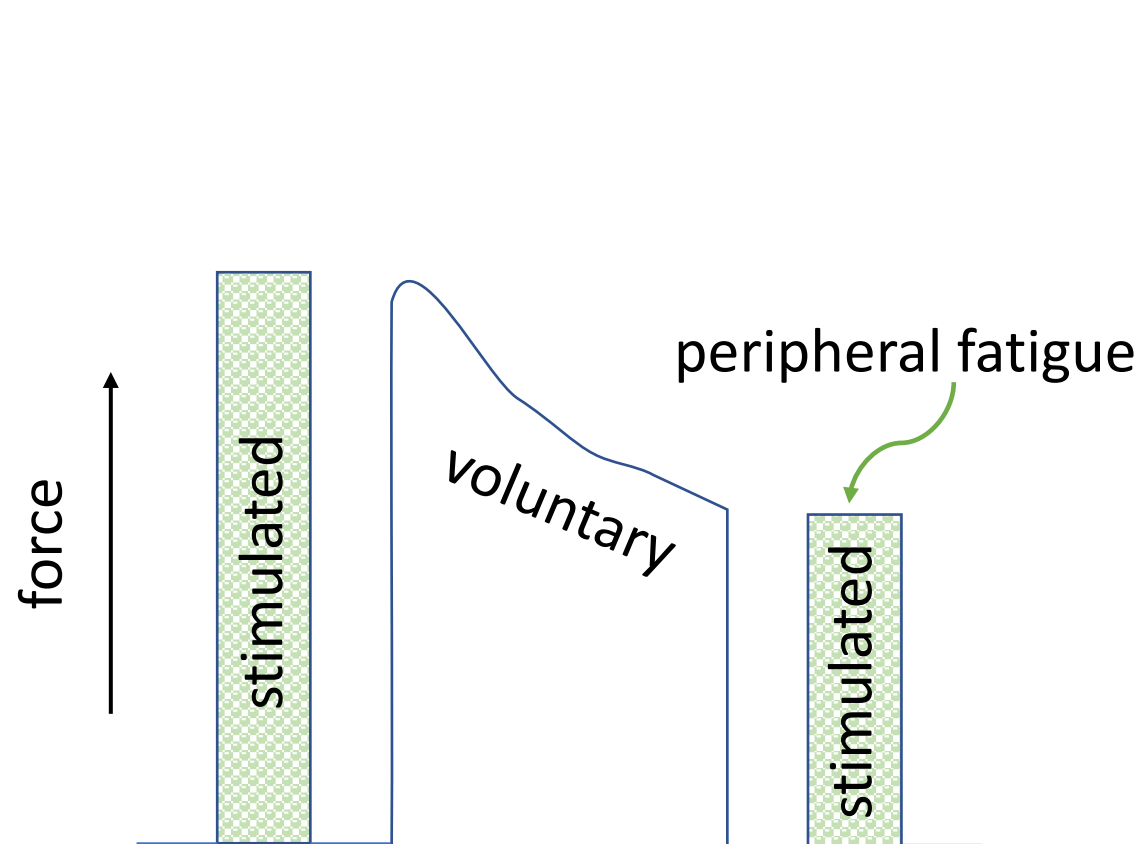


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Possible sites of fatigue from exercise science perspective





Motivation ("will")

Motor Cortex

Motor Neuron

Peripheral Nerve

Neuromuscular Junction (NMJ)

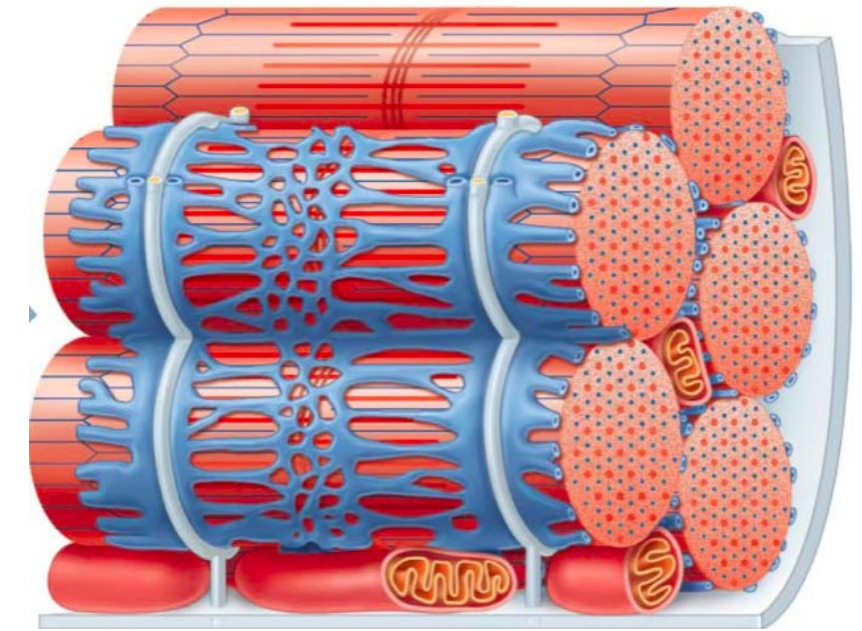
Skeletal Muscle

Sarcolemma
Sarcoplasmic Reticulum
T-Tubules
Cross Bridges



Peripheral Fatigue

Sources of peripheral fatigue



Impaired Calcium Release:

- Accumulation of K^+
- Accumulation of Mg^{2+}
- Accumulation of H^+
- Accumulation of P_i
- Accumulation of ROS
- ↓ SR calcium channel opening

Depression in E-C coupling:

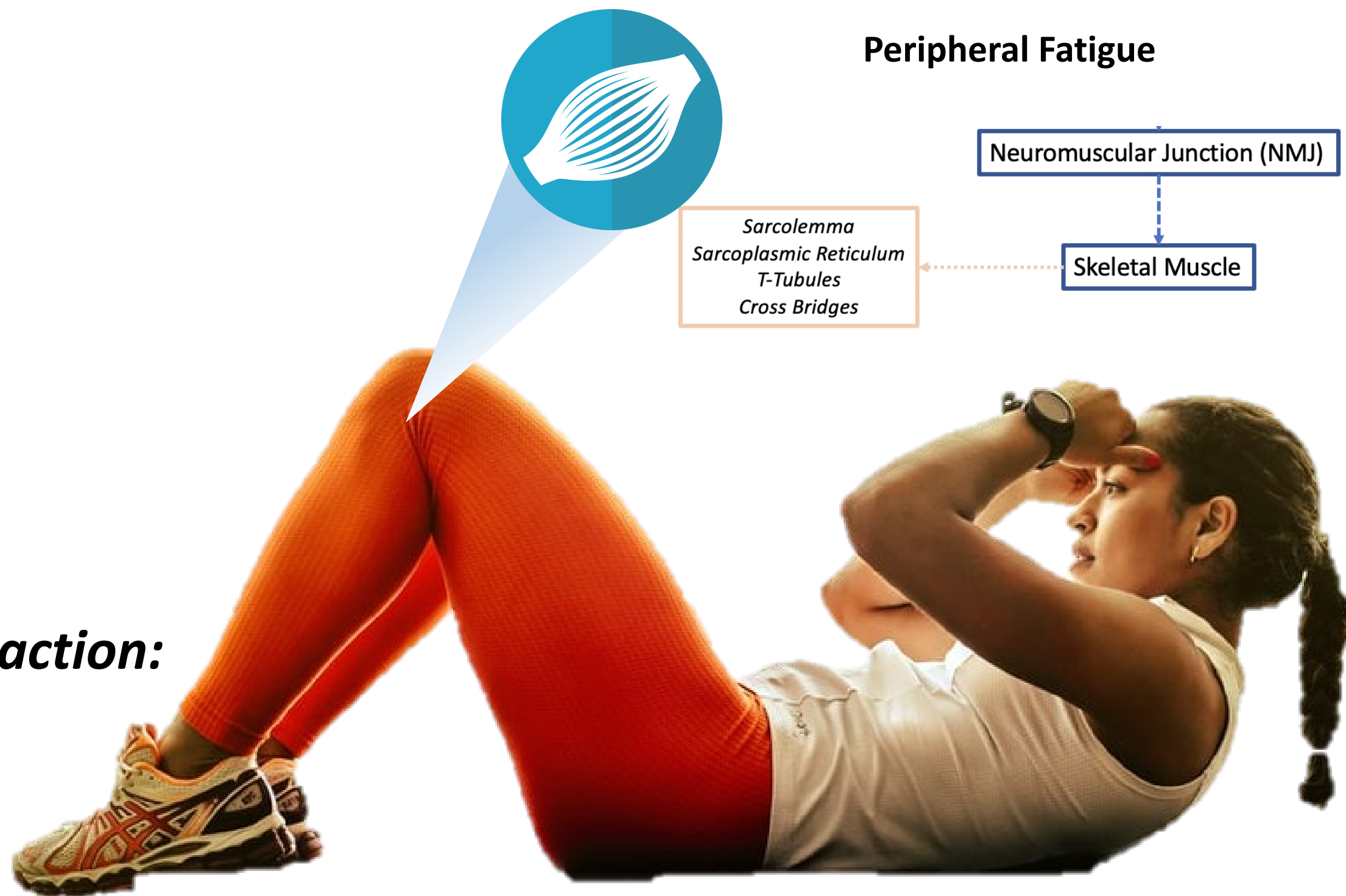
- ↑ efflux of K^+

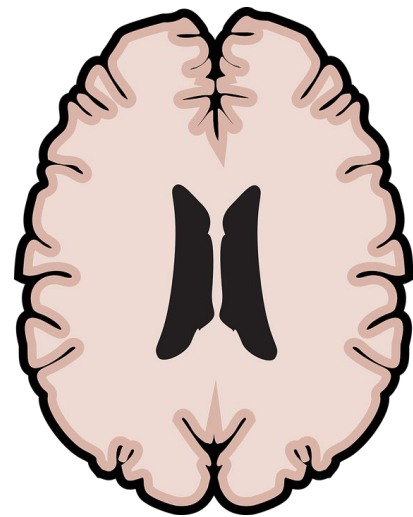
Inhibited cross-bridge interaction:

- Accumulation of P_i
- Accumulation of H^+

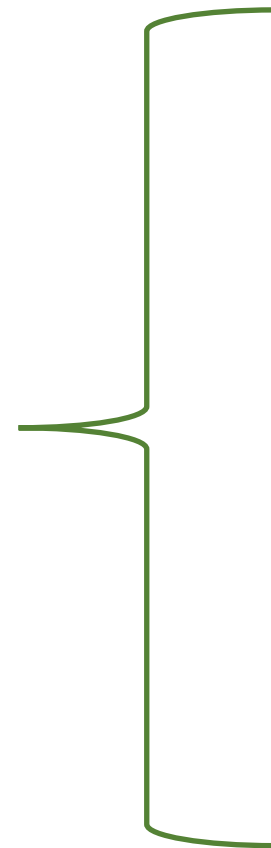
Low muscle glycogen:

Associated with impaired SR Ca^{2+} release & reuptake and Na^+/K^+ pump function





Central Fatigue



Motivation (“will”)

Motor Cortex

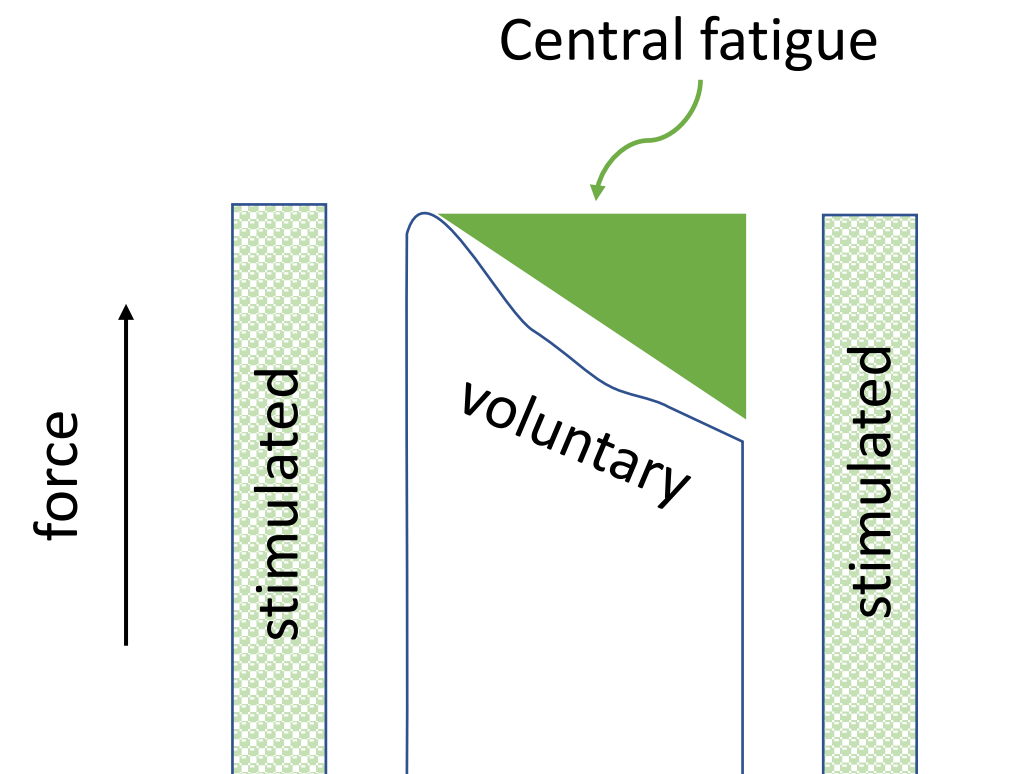
Motor Neuron

Peripheral Nerve

Neuromuscular Junction (NMJ)

Skeletal Muscle

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Cross Bridges



Sources of central fatigue

Altered motor unit firing rates via:

- ↓ excitability to synaptic input
- Lowered excitatory drive from motor cortex
- ↑ firing of **III/IV** muscle afferents
- ↓ firing of muscle spindles → presynaptic inhibition

Impaired excitability of motor cortex cells

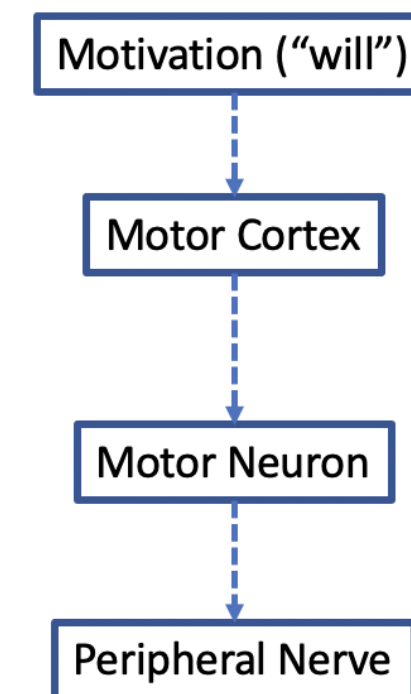
Enhancement of serotonergic neurons via:

- ↑ influx of tryptophan from ↓ blood BCAAs

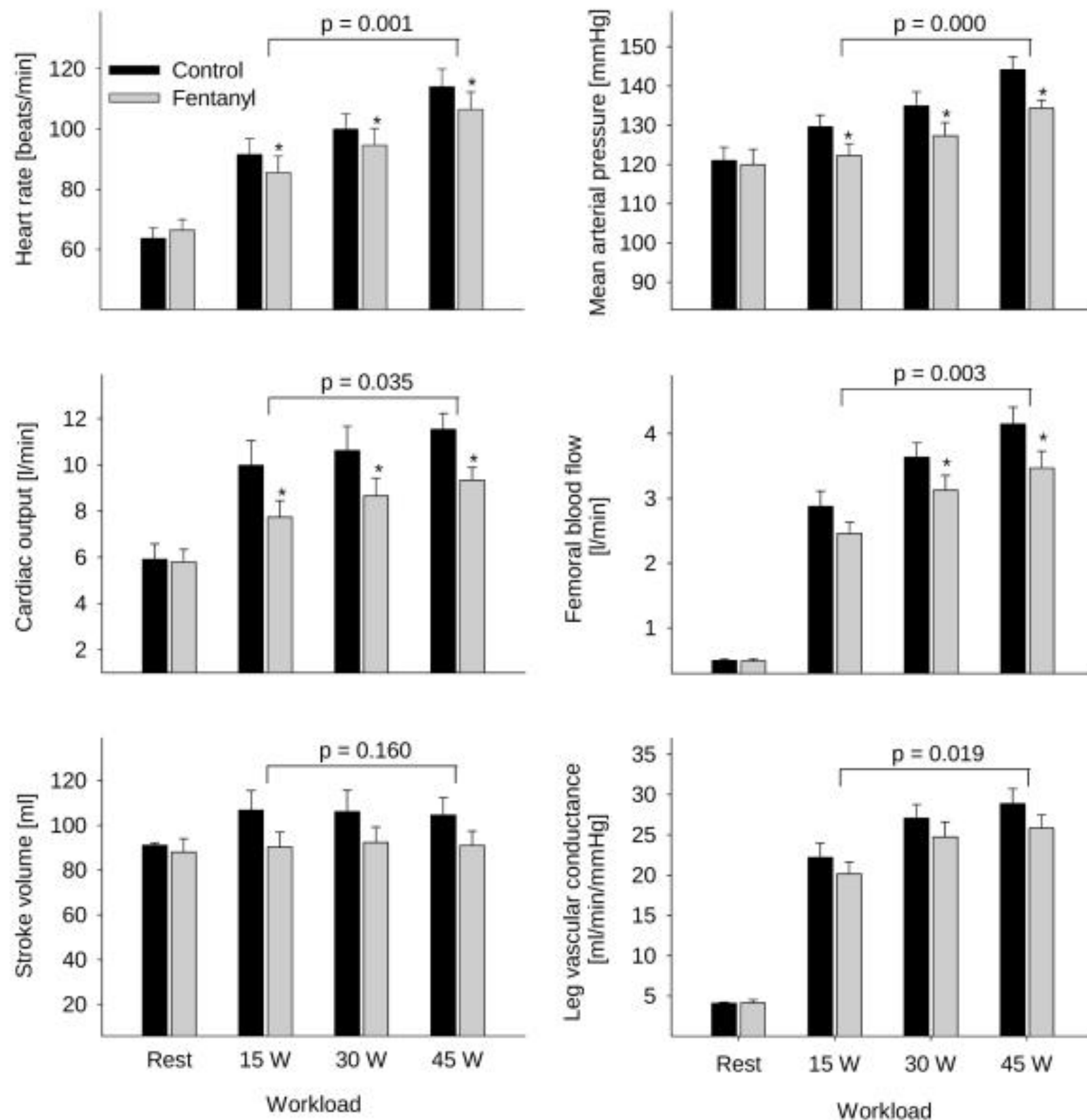
Exercise-induced cytokine release



Central Fatigue



Significance of group III and IV muscle afferents for the endurance exercising human

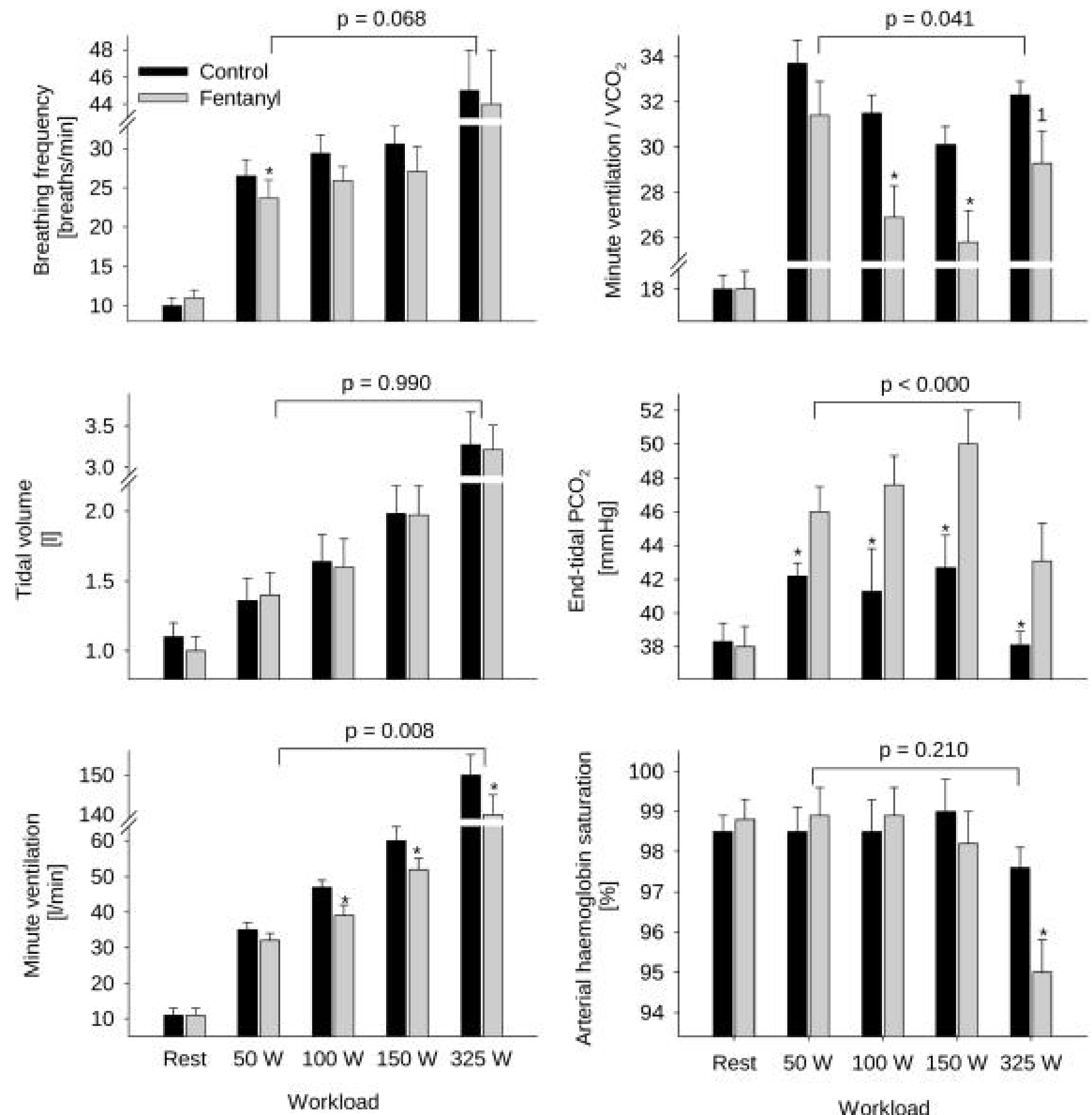


- Group III/IV muscle afferents from the lower limbs *blocked* during endurance exercise:
 - Reduced circulation
 - Reduced ventilation
 - Arterial hypoxemia
 - Reduced perfusion pressure
 - Reduced blood flow/O₂ delivery
 - Facilitated ventilatory & metabolic acidosis
- **All contribute to peripheral muscle fatigue**

Significance of group III and IV muscle afferents for the endurance exercising human

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Summary

In ME/CFS:

- **FATIGUE and PEM are not mutually exclusive**
- **Feedback and feedforward loops that ultimately govern autonomic nervous system function are disrupted**
- **Disruption of the 'sickness circuitry' (from gut, enterovirus, injury, inflammation, trauma, etc.) contribute to systems-level derangement in exercise test responses in ME/CFS**
- **Similar patterns of autonomic dysfunction are observed in 'stressed' organisms – e.g., COVID-19 long haulers, Lyme, injury...**
- ***Thank you for your attention***



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