
Post-Exertional Malaise



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Post-Exertional Malaise



- Unique and **PATHOGNOMONIC** finding in ME/CFS
- Not known to exist in **ANY** other illnesses, including those suffering from post-chemotherapy complications or in the most decompensated of individuals
- Now being recognized in those with post-acute sequelae of COVID (PASC) as well

Post-Exertional Malaise

“**inability to recover** normally following physical, cognitive, or emotional exertion [resulting in] a level of **fatigue** that is more profound, more devastating, and longer lasting than is observed in patients with other fatiguing disorders”

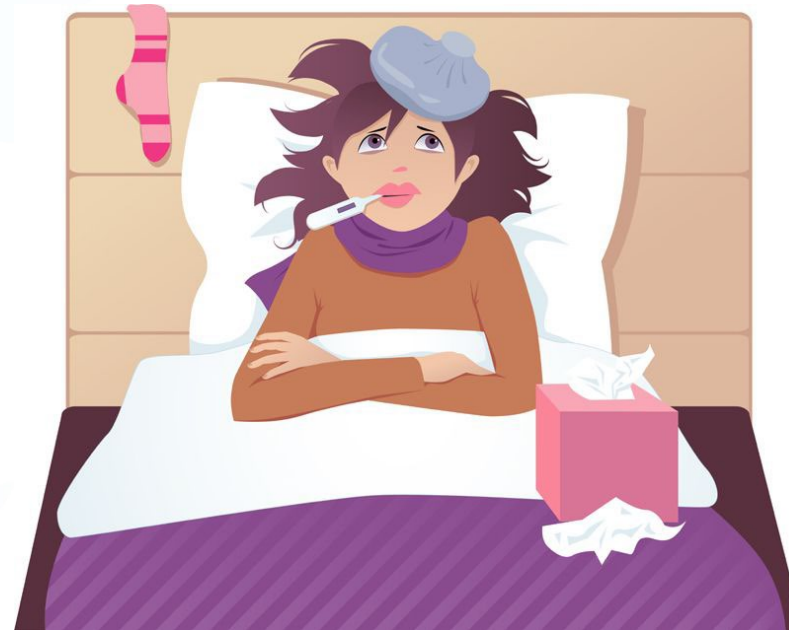
Post-Exertional Malaise

Fatigue is accompanied by:

- Profound loss in stamina
- Reduction in functional capacity
- Augmented symptoms of one's usual ME/CFS or PASC pathology
 - Worsening autonomic dysfunction
 - Reduced metabolic efficiency
 - Immune dysfunction
 - Perturbations in the HPA axis

Augmented Symptoms in PEM

- “Flu-like symptoms” (subjective fevers, sore throats, arthralgia, myalgia)
- Cognitive symptoms (brain fog, word-finding difficulties, reduced concentration)
- Insomnia
- Headaches
- Sensory sensitivity
- Orthostatic intolerance



The PEM Experience....

- Not uncommon for people experiencing PEM to remain confined to bed for much of the duration of their episode
- May struggle to complete basic ADL's including toileting or preparing food



“If there was a fire in the house, I am not sure I would be able to make it out in time”

Triggers for PEM

- Exercise
- Orthostatic stress
- Cognitive or mental activities
- Environmental stressors
 - Bright lights
 - Loud sounds
 - Multiple visual inputs
 - Chemical exposures
- Emotional Responses



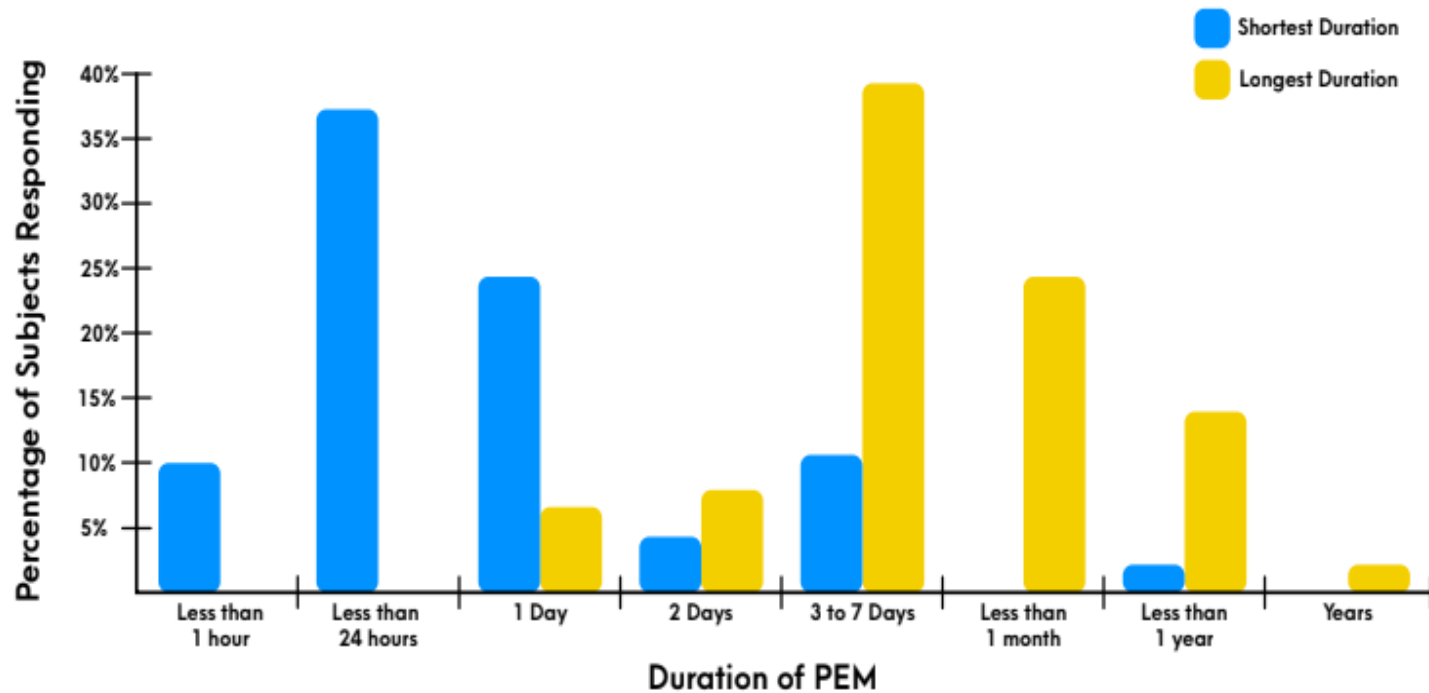
Examples of PEM Triggers in More Severely Ill



- Reading a book
- Using a computer
- Having an improvisational conversation
- Showering
- Sitting up to eat a meal



Range of Duration of PEM

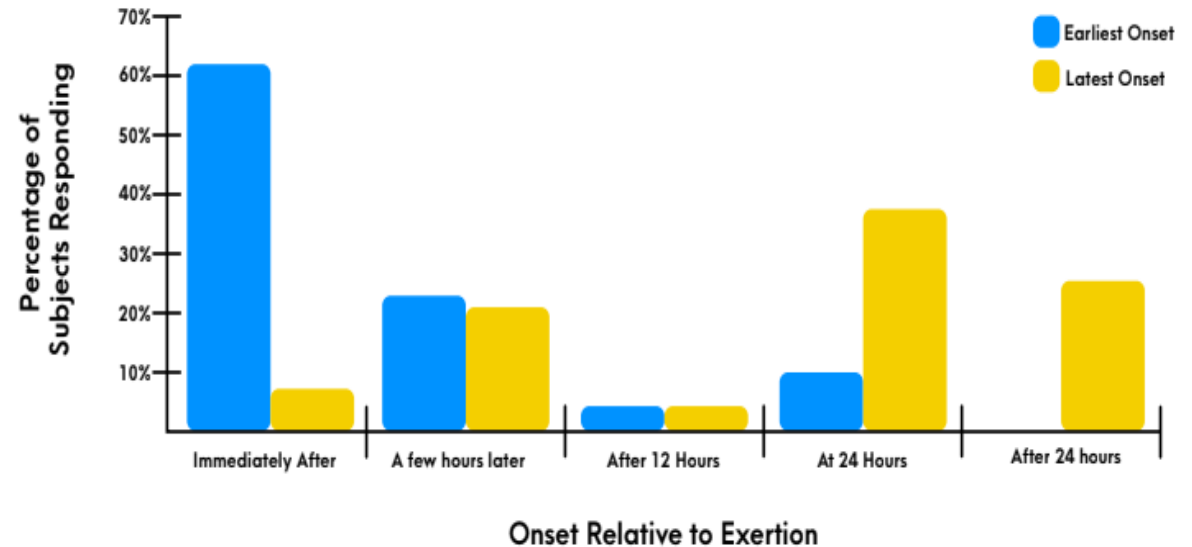


Chu L, Valencia JJ, Garvert DW, Montoya JG. Deconstructing post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: A patient-centered, cross-sectional survey. PLoS One. 2018;13(6):e0197811. Published 2018 Jun 1. doi:10.1371/journal.pone.0197811

- 2018 survey of 150 individuals with ME/CFS
- Over 90% of these individuals clearly recognized “bad days,” worse than their baseline function consistent with the definition of PEM
- Duration of PEM episodes varied widely among individuals and even among individuals themselves, depending upon the degree of “exertion” of the triggering event(s)

- Expert clinicians almost universally agree that PEM onset is often **delayed by 24-48 hours after an inciting event(s)**
- Patients, however, often believe their PEM begins immediately after inciting events
- This discrepancy in patient reporting is likely the consequence of the physiological impact of orthostatic intolerance occurring immediately after a taxing physical or cognitive task adversely affecting how patients feel and leading them to need rest
- Good clinical history is critical in identifying PEM among your patients!

Range of PEM Onset Times



Chu L, Valencia LJ, Garvert DW, Montoya JG. Deconstructing post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: A patient-centered, cross-sectional survey. PLoS One. 2018;13(6):e0197811. Published 2018 Jun 1. doi:10.1371/journal.pone.0197811

PEM = Debt?

\$1.00 per day to spend on energy exertion

- Spending spree of \$10.00 in one day!
- Spend \$1.25 on most days over the course of a time period....eventually the debt must be paid...with interest



Cardiopulmonary Exercise Testing

- **VALIDATED** tool for assessment of functional capacity among healthy people and people with debilitating and fatiguing illnesses
- Assesses the coordinated contributions of metabolic, cardiovascular, respiratory, and muscular inputs to energy generation
- **Serial 2-day CPET Testing** Reliable, reproducible, accurate measure of PEM
 - Variability from one day to the next is low among healthy individuals and those with CHF, COPD, ESRD, pulm HTN, CF and other impairing illnesses
 - ME/CFS patients are unique in that they **cannot reproduce CPET outcome measures on day 2 of testing** compared to day 1 of testing, independent of effort

Day One



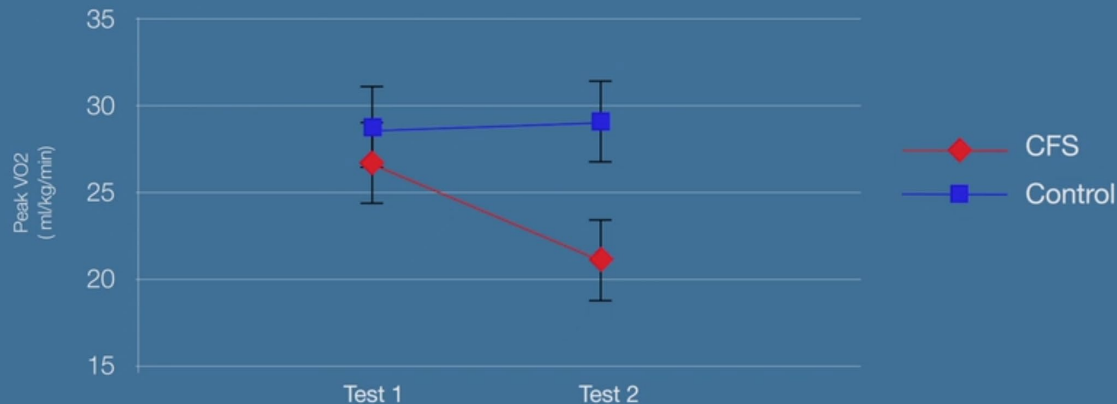
Day Two



Cardiopulmonary Exercise Testing

Oxidative Impairment in the Post-Exertional State

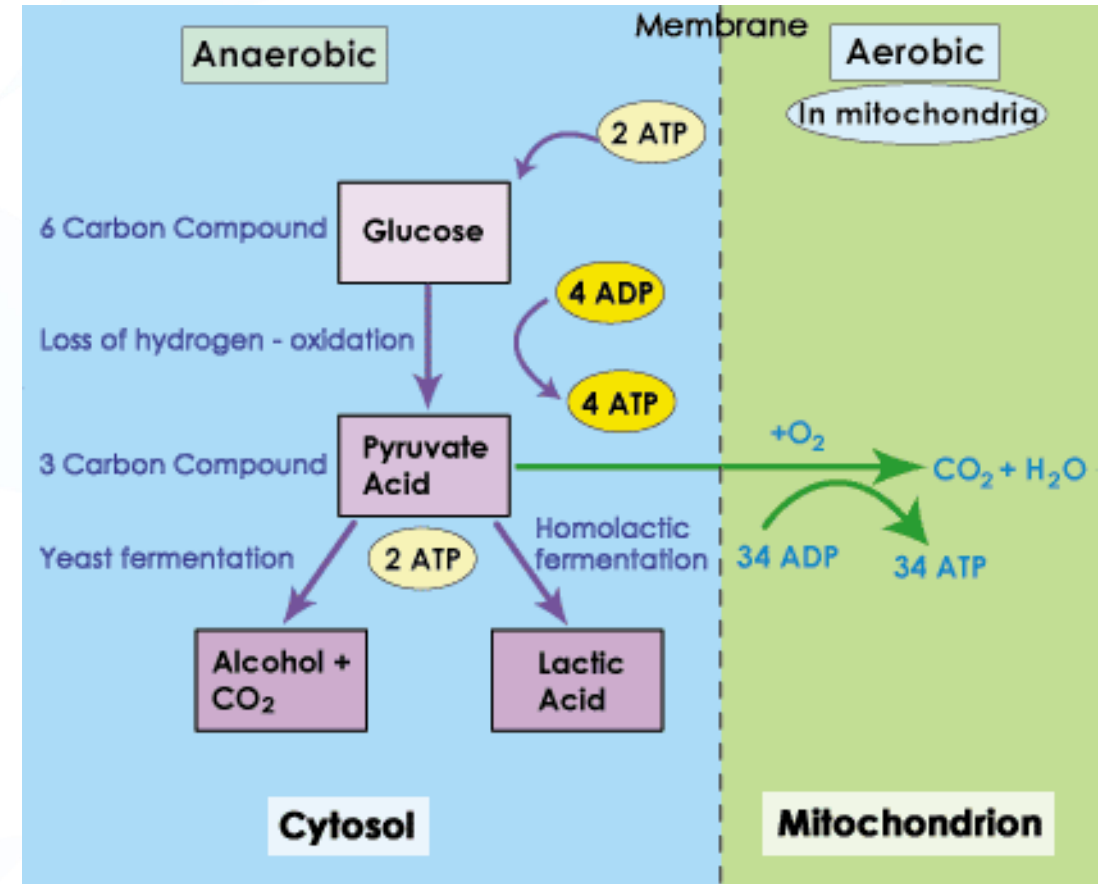
VanNess, J.M., Snell, C.R. and Stevens, S.R. (2007). Diminished Cardiopulmonary Capacity During Post-Exertional Malaise in Chronic Fatigue Syndrome. *Journal of Chronic Fatigue Syndrome*, 14(2): 77-85.



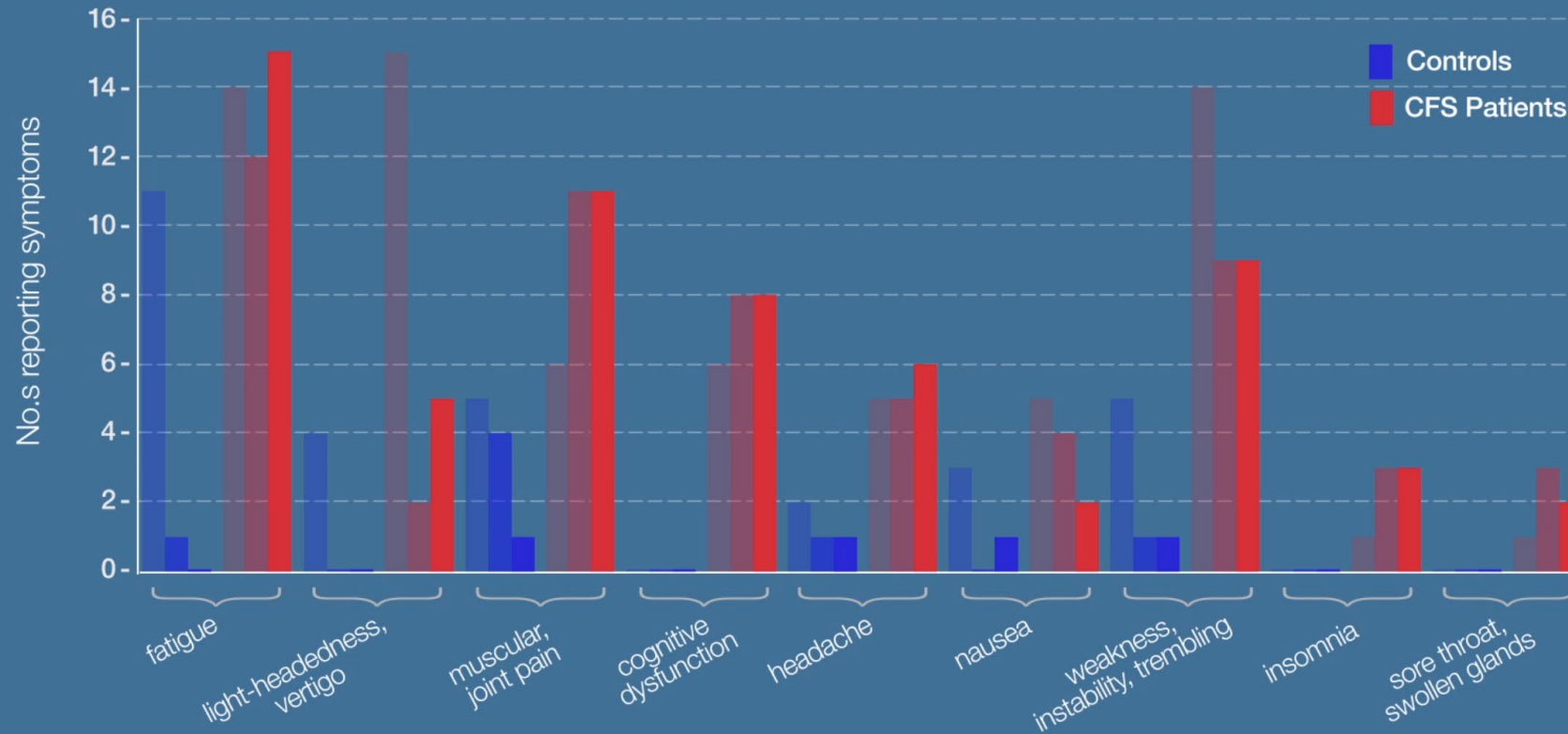
- Particularly effective for measuring “peak oxygen consumption” or “VO2 Peak,” during exercise
- VO2 Peak is a well-recognized indicator of functional capacity as a surrogate measure of the maximum energy available for work
- Deficits on Serial 2-day CPET Testing:
 - Reduced VO2 peak
 - Unable to reach ventilatory threshold
 - Unable to achieve peak workload
 - Unable to duplicate workload at ventilatory threshold compared to day 1

Cardiopulmonary Exercise Testing

- CPET also effective for measuring Ventilatory Anaerobic Threshold (VAT) as a function of increases in muscle and blood pH, as well as lactate and CO₂ concentrations
- VAT is considered a reliable marker for detecting a patient's anaerobic threshold upon physiological exertion
- CPET testing has demonstrated notable VAT reductions, suggesting a reduced capacity to maintain aerobic metabolism before engaging a compensatory and less efficient anaerobic method of ATP generation



Symptoms reported two or more days after exercise test



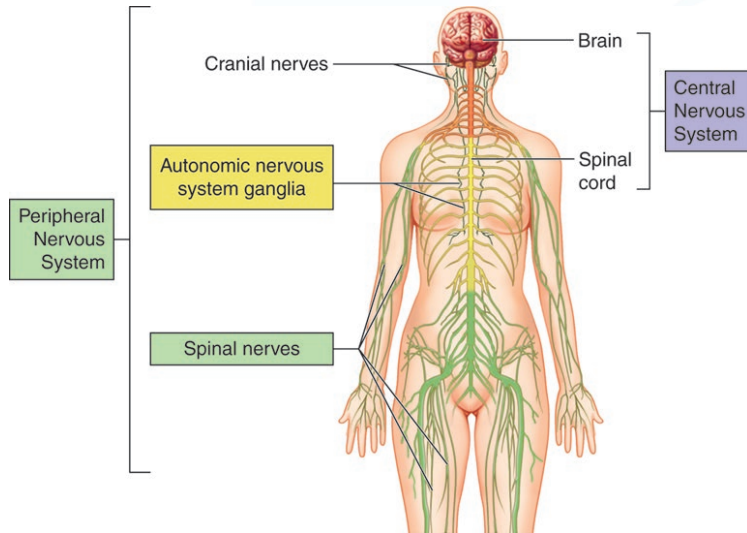
Post-Exertional Malaise in Women with Chronic Fatigue Syndrome (2010)

M. VanNess, S. Stevens, L. Bateman, T. Stiles, & C. Snell (2010). Journal of Women's Health

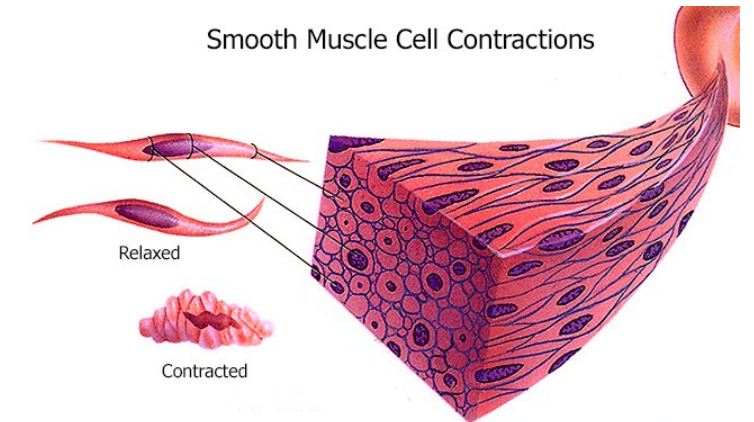
Altered Cellular Metabolism in PEM

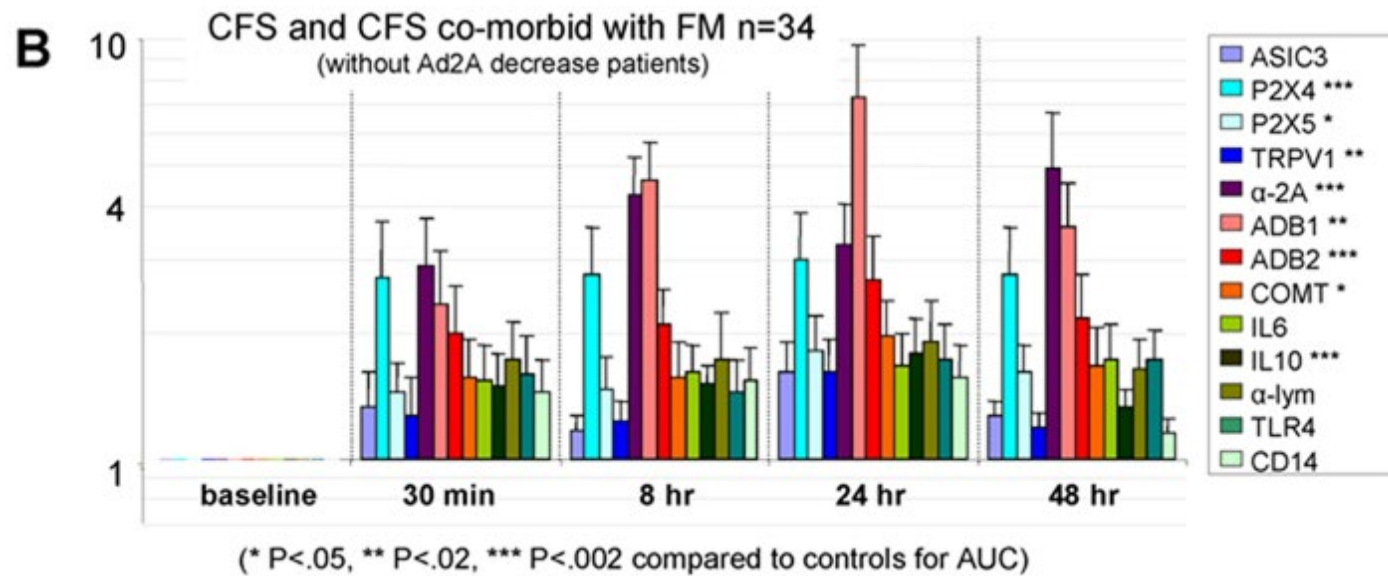
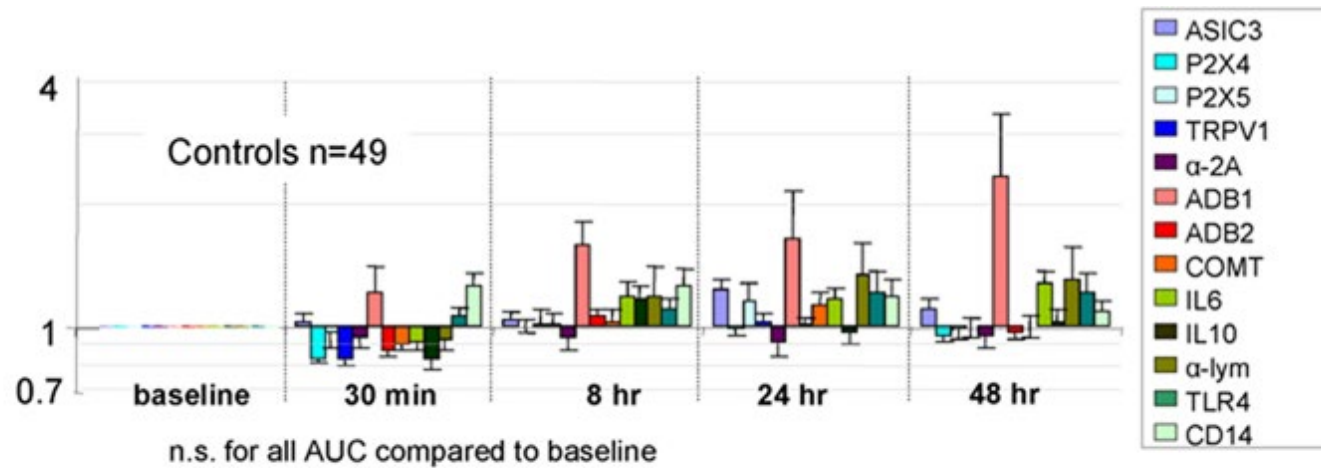
Fuel
Sources

Glucose
Fatty Acids
Amino Acids



- If one considers the impact of impaired cellular metabolism and reduced ATP production or utilization upon skeletal, cardiac, vascular, and GI smooth muscle, as well as upon grey and white matter of both the central and peripheral nervous system, the varied and diverse symptoms of PEM become less foreign....

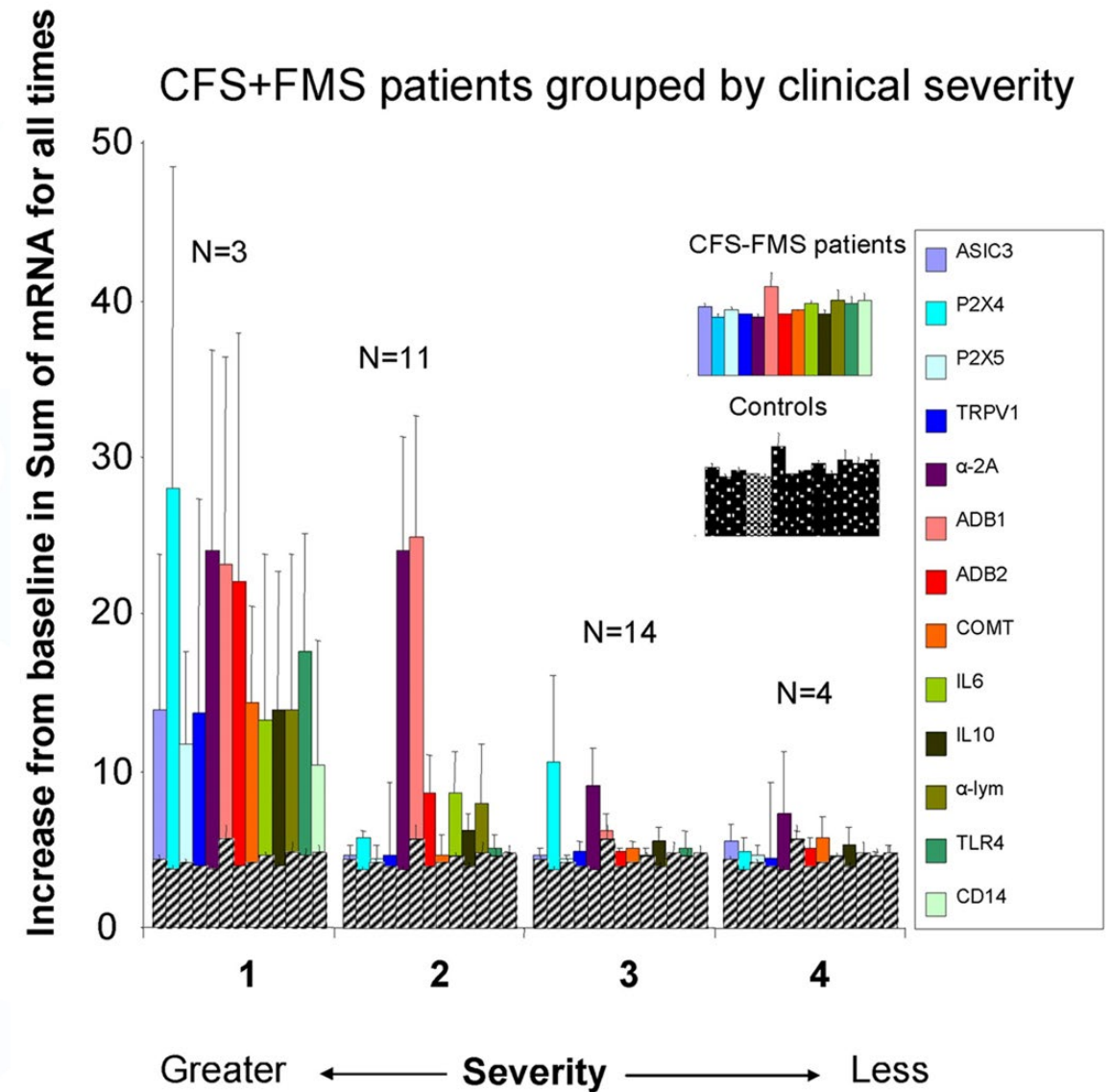




- Gene expression (as a function of measured levels of mRNA) has also been evaluated after exercise challenge
- Gene expression remained mostly similar across controls and a comparator group with multiple sclerosis
- Those with ME/CFS demonstrated elevated mRNA expression for alpha-2 and beta-2 adrenergic receptors, interleukin-10, and purinergic 2X4 receptors in the post-exercise period



- A similarly structured study suggested that the magnitude of increases in gene expression in response to exercise challenge tracked directly with the severity of symptoms reported by those with ME/CFS in the post-exercise interval



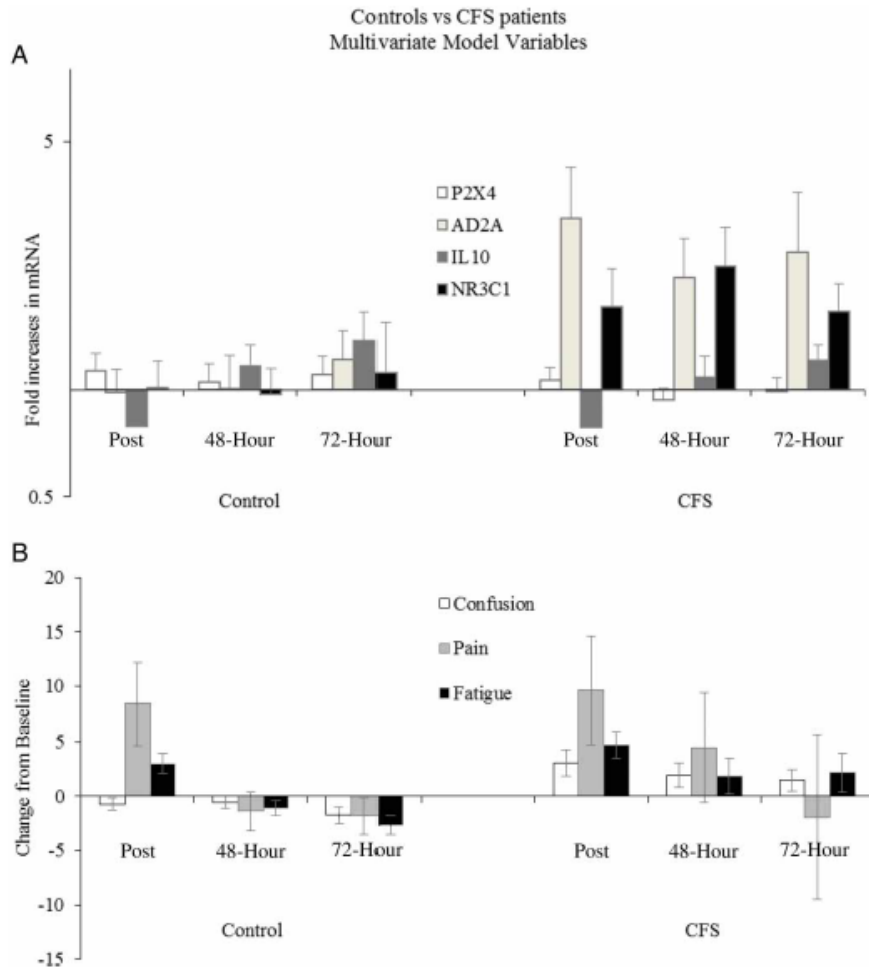
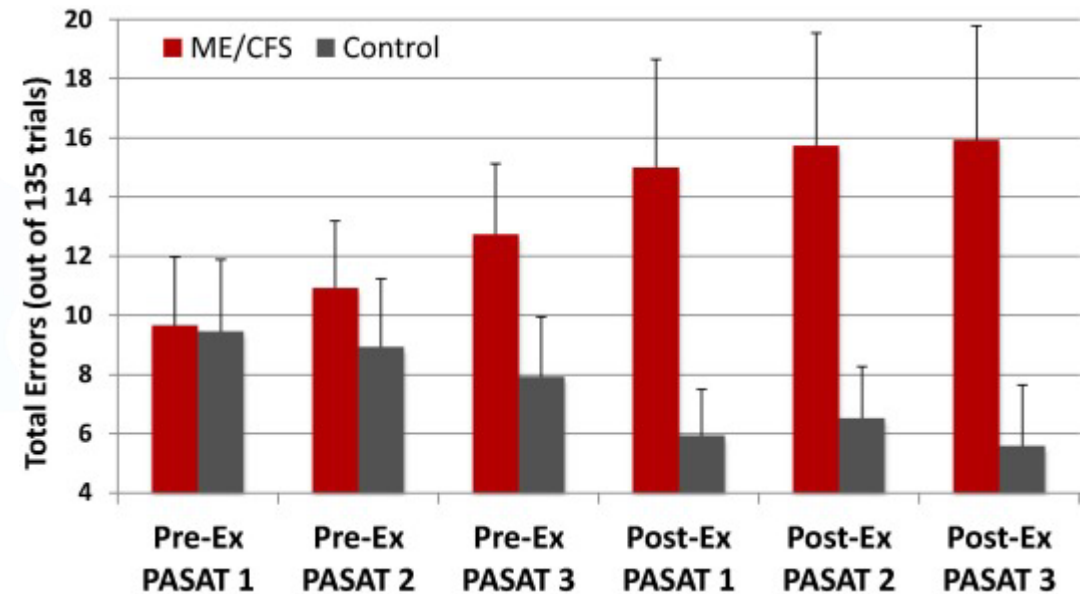


Figure 1. Psychobiological response to exercise in chronic fatigue syndrome patients and healthy controls. (A) Changes in transcription compared to baseline of genetic variables included in the multivariate model. (B) Changes in symptoms compared to baseline of symptom variables included in the multivariate model. There was a main effect of group for the overall model and for AD2A, NR3C1, fatigue, and confusion. Abbreviations: P2X4, purinergic type 2X4 receptor; AD2A, adrenergic type α -2A receptor; IL10, interleukin 10 receptor; NR3C1, glucocorticoid receptor; CFS, chronic fatigue syndrome.

- Another follow-up study tracked the most statistically significant post-exercise gene expression receptors against patient-reported symptoms of pain, fatigue, mood, and confusion to attempt to correlate gene expression with symptoms
- Largest increases in post-exercise transcription of receptor mRNA were found in alpha-2 adrenergic receptors and glucocorticoid NR3C1 receptors
- Also detected a correlation between expression of NR3C1 glucocorticoid receptors and overall severity of symptom exacerbation during PEM
- Has been hypothesized that this receptor's upregulation during PEM could alter cortisol sensitivity during this time period

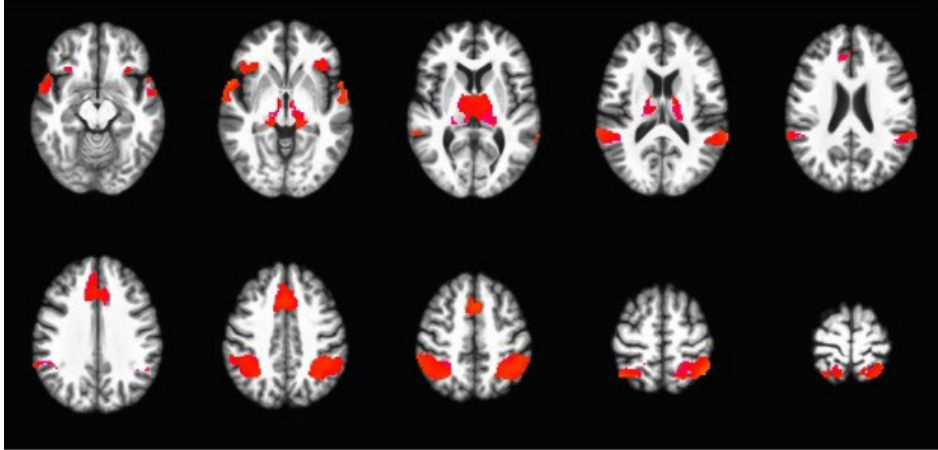
Neurobiological Changes in PEM

- Patients with ME/CFS, and controls with similar and matched physiological responses to exercise, were asked to perform pre-exercise and post-exercise paced auditory serial task addition (PASAT) cognitive tasks
- Healthy controls showed improvements in the cognitive tasks with less mistakes after exercise, suggestive of learned task improvement
- Those with ME/CFS made MORE errors and experienced a decrement in performance after exercise

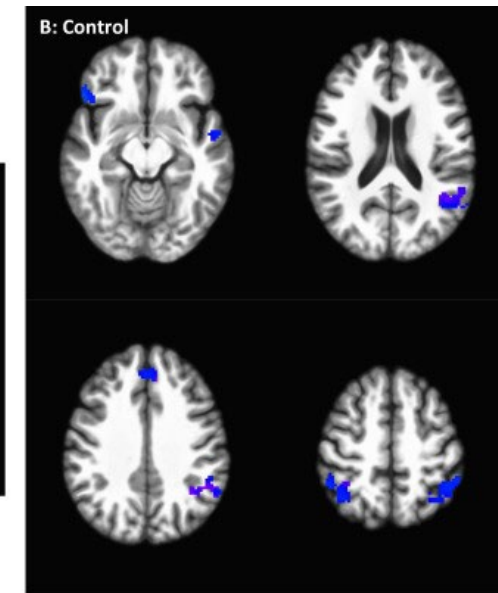
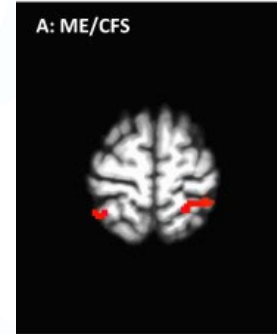
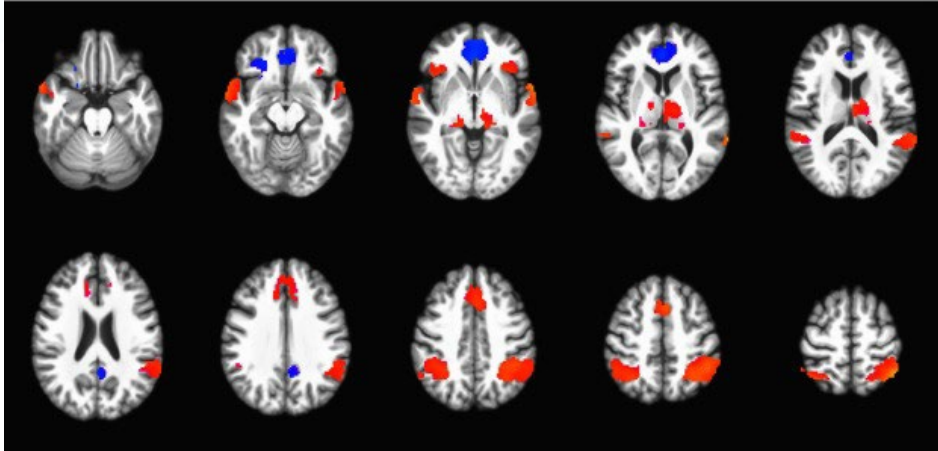


Neurobiological Changes in PEM

ME/CFS:



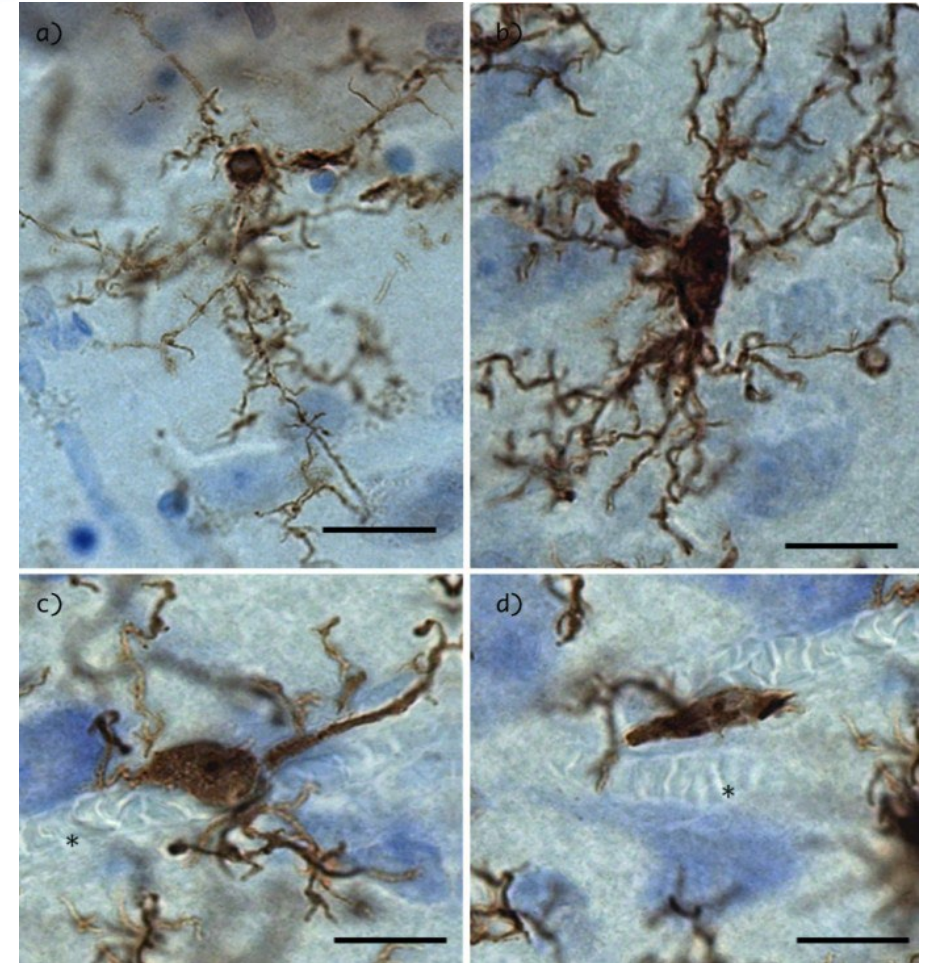
Control:



- The decline in PASAT performance was accompanied by significant increases in post-exercise brain activity, most notably in the inferior and superior parietal and cingulate cortices
- The magnitude of changes in brain activity in the post-exercise state were directly correlated with the number and magnitude of patient-reported PEM symptoms in the following days

Could these detrimental neurophysiological consequences be the result of “neuroinflammation?”

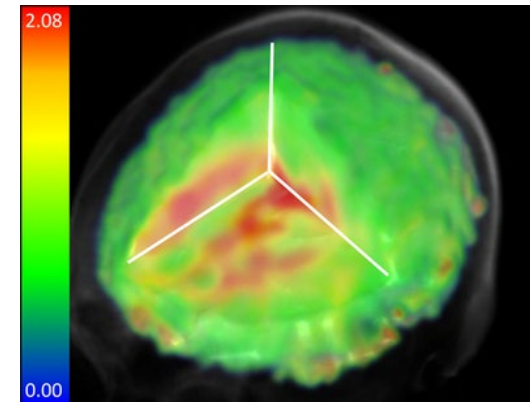
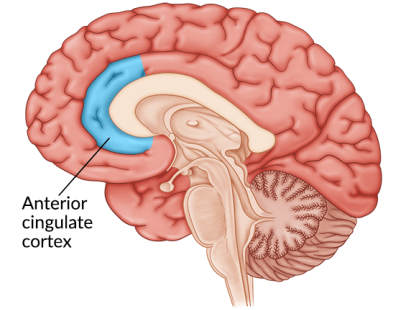
- Defined by microglial cells moving from a resting state to a proinflammatory state with associated structural changes and functional adaptations including the release of proinflammatory cytokines (IL-6, TNF-alpha, IL-1-beta...)
- Presence of these cytokines in specific regions of the brain can lead to “sickness response” with associated symptoms of heavy fatigue, brain fog, confusion, malaise, and low motivation
- In healthy individuals, these microglial changes occur transiently, such as with active infection, but rapidly recover to their resting state
- In ME/CFS, there is evidence suggesting microglial cells are more easily, and abnormally, activated and either appear stuck in this activated position or flip back and forth between activated and inactivated very quickly



Metabolic Activity Associated with Neuroinflammation

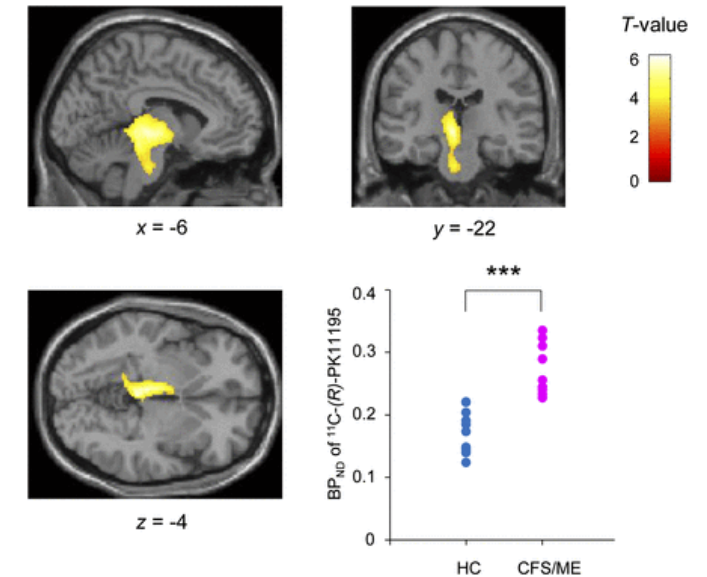
MR-spectroscopy can quantify metabolites of neuroinflammation within the brains of those with ME/CFS

- Lactate is found at levels 4x greater than in controls in the ventricles, corpus callosum, occipital cortex, and most notably, within the **anterior cingulate cortex**, a region intimately tied to the “sickness response, feelings of malaise, and depressed mood”
- Brain lactate rarely becomes elevated and only does so when neurons run out of glucose and astrocytes begin to produce lactate as an alternative energy source (usually associated with malignancy or significant vascular pathology)
- Choline (marker for high neuronal cell turnover) elevated in the left anterior cingulate cortex of those with ME/CFS
- “Brain Thermometry,” a technique used to assess areas of the brain under excessive metabolic demand, shows that the very same locations where choline and lactate are elevated also run about 1 degree Fahrenheit hotter than surrounding brain areas in those with ME/CFS



Metabolic Activity Associated with Neuroinflammation

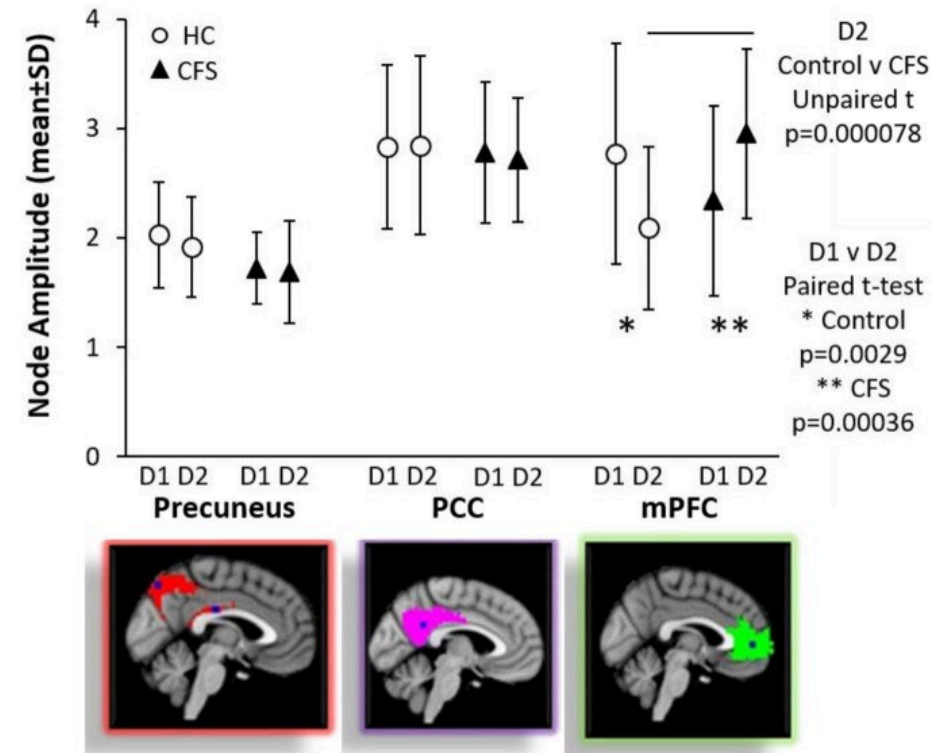
- Positron Emission Tomography is also being used to measure a radiolabeled isotope ligand to the translocator (or TSPO) protein
- TSPO is a microglial cell receptor protein whose expression is magnified when microglia enter their activated and cytokine-releasing state
- Elevated TSPO levels have been observed in the thalamus, cingulate, and hippocampus of those with ME/CFS
- These areas have all been implicated in other MR-spectroscopy metabolic studies as well



Active studies are underway to determine if there are major discrepancies in these same metabolic markers within the same patient to compare their baseline functional impairment with PEM

Neurobiological Activity Unique to PEM

- Blood oxygenation level dependent scans (BOLD scans) were performed at rest and after exercise challenge in ME/CFS patients to evaluate clustered neuronal networks that activate together and appear to be part of the same processing units
- Strikingly elevated activity detected in the medial prefrontal cortex, which is an anterior node of the Default Mode Network (DMN), compared to the pre-exercise day, though this region showed decreased activation in controls
- All regions of the DMN, except this anterior node of the medial prefrontal cortex (mPFC), were found to have a lower resting state in ME/CFS compared to controls both before and after exercise
- Controls had higher BOLD signals suggesting reduced global cerebral blood flow in ME/CFS



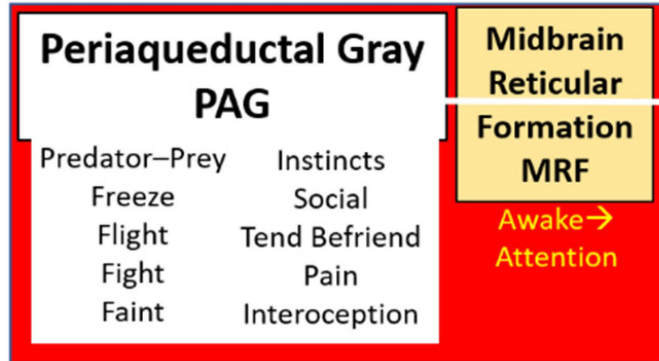
Neurobiological Activity Unique to PEM

- DMN is a collection of brain regions with correlated activation during rest when there is no external task to perform
- DMN regions become deactivated when switching from rest to task performance while other brain regions become activated in coordinated specific task networks
- The DMN is involved in self-referential thought, mind-wandering, social awareness, affective processing, and goal-directed behavior
- The relative activation of the medial prefrontal cortex (mPFC) of the DMN caused by exercise in those with ME/CFS may represent a decoupling from the posterior nodes of the DMN and a loss of regulatory input
- As such, exercise induced uncoupling may be a pathological consequence and even serve as a biomarker for the presence of post-exertional malaise

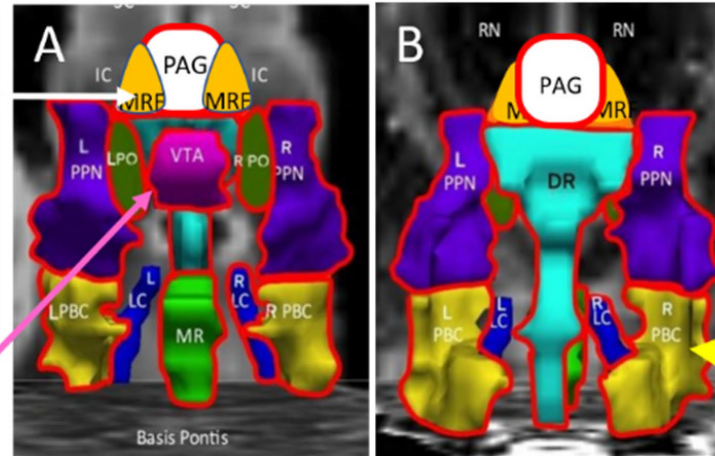
Post-Exercise Neurobiological Activity in the Dorsal Midbrain

- Submaximal exercise has also been observed to create changes in activation in the dorsal midbrain during post-exercise high cognitive load working memory tasks, whereas controls show no activation here
- It is interesting to consider that the nuclei of the ascending arousal network including the midbrain and the isthmus participate in:
 - Threat assessment
 - Awareness
 - Attention
 - Mood
 - Cognition
 - Pain
 - Tenderness
 - Sleep
 - Thermoregulation
 - Light and sound sensitivity
 - Autonomic functions

IMMINENT THREAT ASSESSMENT!!! Arousal!!! Survival!!!



Serene Balance



Superior Colliculus
Visual

Inferior Colliculus
Auditory
Startle

Metabolic Vulnerability
Blood flow
O₂
Toxins
Pyruvate
EtOH

Ventral Tegmental Area VTA
Dopamine
Reward

Consciousness
Posterior DMN
Precuneus
Posterior Cingulate Cortex

Motivation
Depression
Anhedonia
Orgasm

Dorsal Raphe
Limbic
Anxiety
Affective
Hippocampus
memory

Serotonin
"Chill"

Median Raphe
Inhibit fight flight
Tolerance & coping of adversity

Parabrachial Complex PBC
Malaise
Sickness behaviours
Thermoregulation
Defensive behaviours
Visceral Interoception

Tenderness
Systemic Hyperalgesia
Glutamate ↑ GABA ↓
Pain

Locus Coeruleus
Norepinephrine
Attention
Battle Stations!!!
Sympathetic

Cerebrum
Arousal

Pedunculotegmental Nucleus PTN
Acetylcholine
Wakefulness Update Working Memory

Pontis Oralis
Sleep
REM

Protective Adaptation → **Maladaptation**

Clinical Implications of PEM



- PEM is perhaps the most **DEBILITATING** and miserable aspect of ME/CFS and PASC as an illness
- It has been long-recognized by clinical providers who treat ME/CFS that continued and repeated episodes of PEM within any one individual appear to be associated with a worsened long-term functional prognosis
- When patients choose to or are spurred to “push through” their symptoms to the point of repeated inducing PEM, they may eventually experience a particularly severe or prolonged episode of PEM followed by a resetting of their already reduced “baseline function” where their “bad days” now represent “good days” and they experience even more functionally limited “bad days”

Clinical Implications of PEM

- It has been postulated that the neurophysiological responses taking place during PEM may accrue over time, leaving a permanently altered function or injury upon exceeding some threshold or frequency and intensity of these biological processes



Stubbed Toe Analogy

How to Clinically Manage PEM

PACING

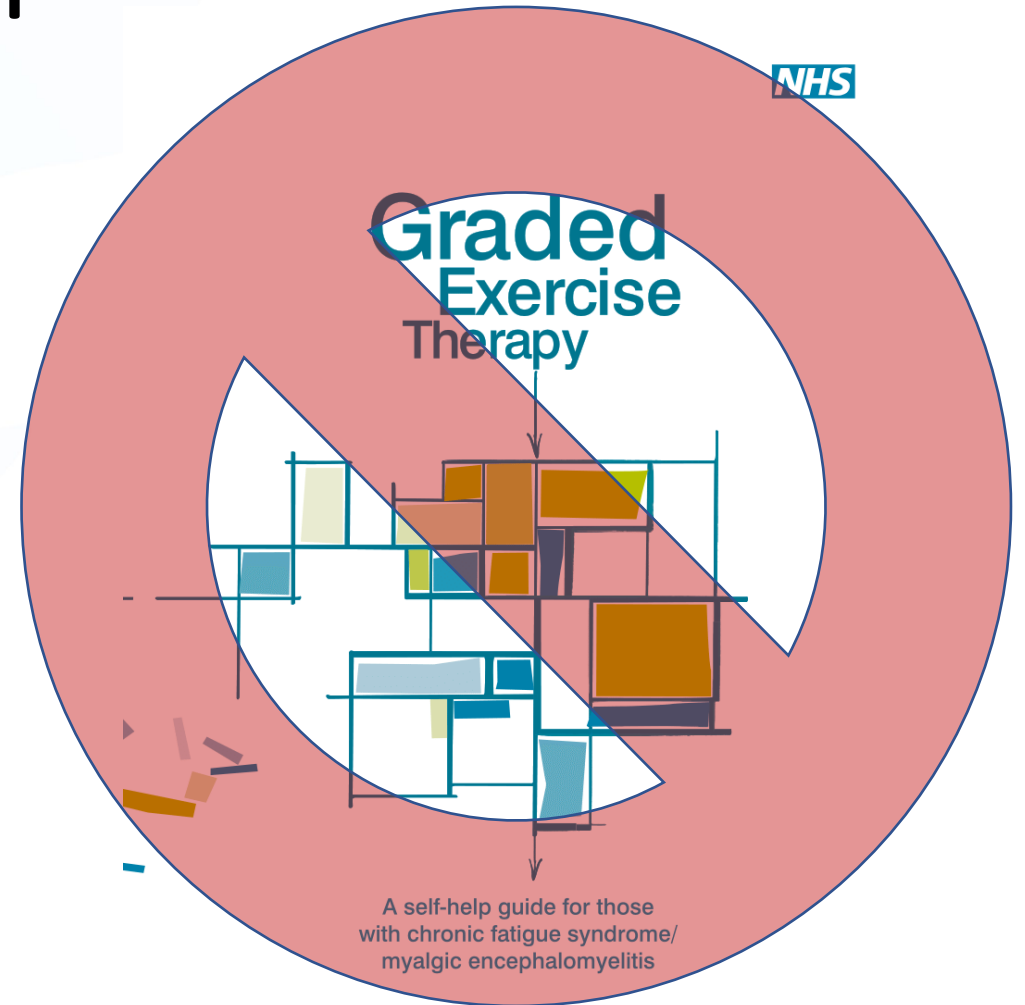
PACING



PACING

How to Clinically Manage PEM

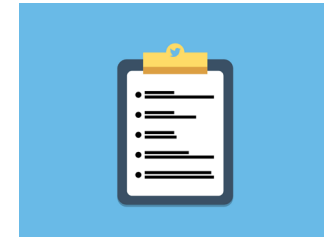
- There is nothing that definitively speeds up recovery from PEM other than not making it worse by continuing to “fight” or “push through” the limitations of this physiologically altered state
- Forcing continued, repeated, and exertional exercise to combat an underlying decompensated state, while seemingly logical, only appears to promote worsened long-term outcomes (Graded Exercise Therapy)
- A patient does not manage ME/CFS or PASC on the whole by fighting harder, but by being smarter and employing discipline and calculated intelligence so as to minimize the intensity and duration of PEM or avoid PEM altogether



How to Clinically Manage PEM

Patients should:

- Remember that cognitive exertion (even subconscious processing of sensory inputs) and emotional exertion are as damaging as physical exertion
- Remain within their “energy envelope” or “battery”
- Take frequent, restorative breaks
- Set timers during activities
- Modify activities to provide less physiological stress (laying down, reclining, legs elevated, sitting)
- Plan a day’s activities carefully and not overfill any particular day
- Choose what is important use of their time
- Set voice reminders and lists on their phone
- Consider grocery delivery services, home cleaning services, etc. as able
- Learn to ask for **HELP** from others



Off-Label Pharmacotherapy in/surrounding PEM

- Low dose naltrexone (4.5 mg or less) – modulates microglial cells through TLR4 to suppress activation of these microglial cells
- Dextromethorphan (standard doses) – downregulates the cough reflex through sigma opioid receptors and can act as an NMDA antagonist; might it also downregulate other dorsal midbrain or pons-related disordered autonomic reflexes
 - Its use before or directly after an exertional event seems to prevent PEM or mitigate the intensity and duration of PEM in patient-reported cases



How to Clinically Manage PEM

SETBACKS TO WATCH FOR:

- Remember that if there is a successful clinical intervention for another aspect of ME/CFS or PASC that improves their overall feeling of wellness, they might be inclined to “make up for lost time” when they feel well and accidentally induce PEM
- In this instance, did the clinical intervention *help* or *hurt* them...perhaps a little of both



How to Clinically Manage PEM

- Over time, continued limitation of PEM or complete avoidance does seem to lead to clinical symptom stability and gradual improvements in the limits of patient's energy envelopes so that they can ultimately gain back additional function without triggering PEM



Other resources

BHC YouTube site education videos: <https://www.youtube.com/user/OFFERUtah>

BHC website → provider resources: <https://batemanhornecenter.org/>

ME/CFS: [https://www.mayoclinicproceedings.org/article/S0025-6196\(21\)00513-9/fulltext](https://www.mayoclinicproceedings.org/article/S0025-6196(21)00513-9/fulltext)