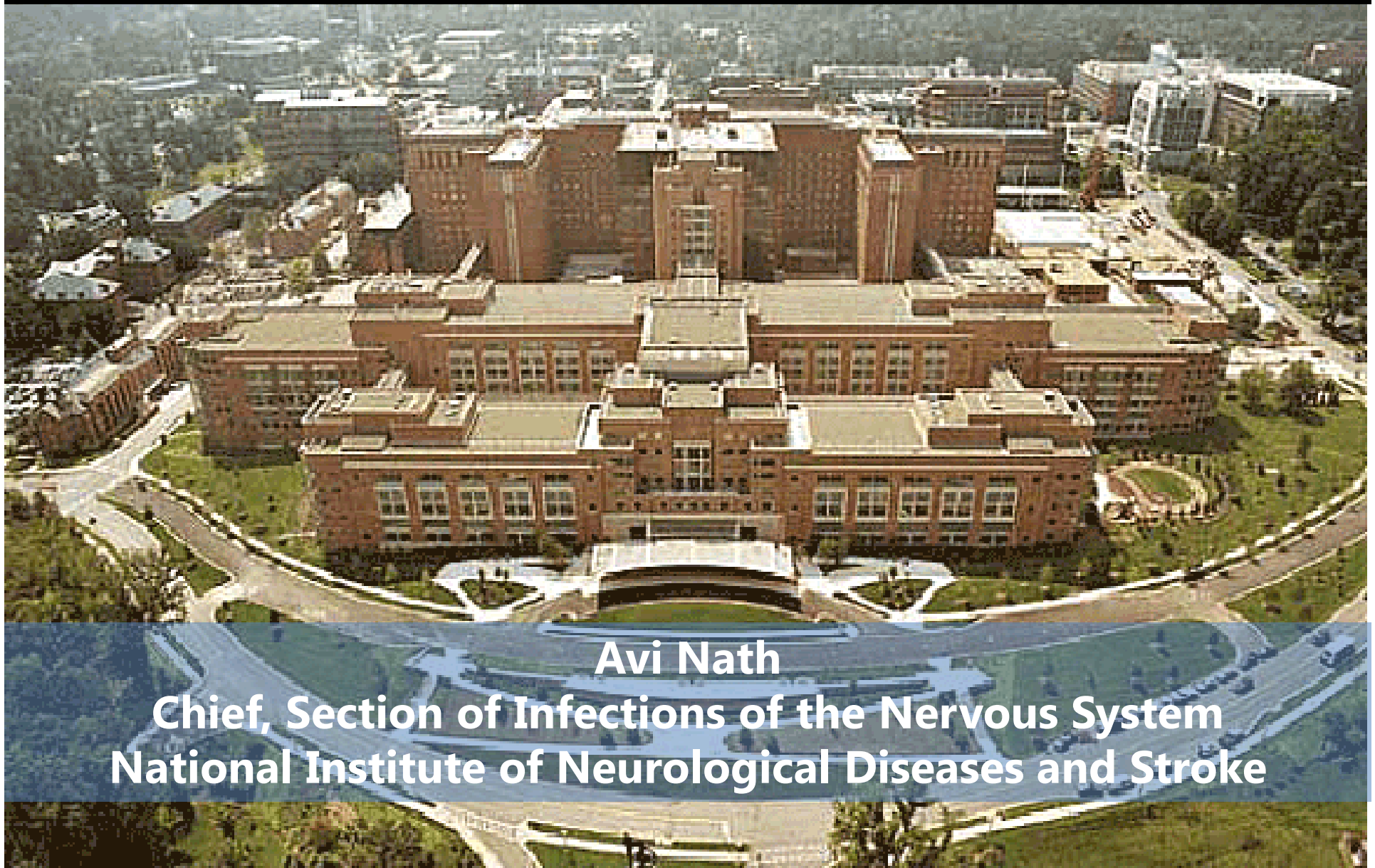
Post-Infectious Myalgic Encephalomyelopathy/Chronic Fatigue Syndrome



Avi Nath
Chief, Section of Infections of the Nervous System
National Institute of Neurological Diseases and Stroke

Dear Dr. Collins: I'm Disabled. Can the N.I.H. Spare a Few Dimes?

By: Brian Vastag | July 14, 2015

Three years ago, a sudden fever struck veteran science writer Brian Vastag on a blue-sky Wisconsin morning. He's been sick ever since. Now cognitively and physically disabled, he lives on the island of Kauai. On Brian's third "illiversary," he presents an opportunity to National Institutes of Health Director Francis Collins.

Congress of the United States
House of Representatives
Washington, D.C. 20515

Anna G. Eshoo
Eighteenth District
California

June 22, 2015

Francis Collins, M.D., Ph.D., Director
National Institutes of Health
1 Center Drive, Room B1-126
Bethesda, Maryland 20892-0001

Dear Dr. Collins,

Thank you for your continuing efforts to strengthen NIH's attention to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

The Institute of Medicine (IOM) report, "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness", published February 2015, and the ME/CFS P2P workshop, both confirm that future research is paramount. According to the IOM report, this under-funded and under-researched disease affects up to 2.5 million Americans. I'm interested in knowing what the next steps are for funding research into this disease to support the efforts of the numerous scientific experts that are now engaged and collaborating.

I respectfully request your response to the following questions:

- What is the strategic plan for tackling this disease, and what steps will NIH take to ensure progress continues quickly?
- Could a new "home" within one of the well-established and well-funded institutes speed progress in funding?
- Because this is a multi-system disease and might require collaboration and funding from multiple institutes, could this be a project which you personally oversee and shepherd through the process?
- Is it possible that a newly funded institute to research multi-system disorders is necessary to oversee this type of research going forward?

Given the research conducted thus far, the engagement of the community and Congress, and with many of the most brilliant scientific minds ready for the challenge, it appears that solving the problem of ME/CFS is possible.

You are uniquely positioned to help move this forward. The time has come to act boldly and bravely and make use of the scientific firepower, Congressional willpower, and renewed support from the patient community.

POSITION PAPER

Annals of Internal Medicine

National Institutes of Health Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Carmen R. Green, MD; Penney Cowan; Ronit Elk, PhD; Kathleen M. O'Neil, MD; and Angela L. Rasmussen, PhD

The National Institutes of Health (NIH) Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome was cosponsored by the NIH Office of Disease Prevention and the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research Working Group. A multidisciplinary working group developed the agenda, and an Evidence-based Practice Center prepared an evidence report through a contract with the Agency for Healthcare Research and Quality to facilitate the discussion. During the 1.5-day workshop, invited experts discussed the body of evidence and attendees had the opportunity to comment during open discussions. After weighing evidence from the evidence report, expert presentations, and public comments, an unbiased, independent panel prepared a draft report that identified research gaps and future research priorities. The report was posted on the NIH Office of Disease Prevention Web site for 4 weeks for public comment.

Ann Intern Med. 2015;162:860-865. doi:10.7326/M15-0338 **www.annals.org**
For author affiliations, see end of text.

To gain confidence of the ME/CFS community

- Monthly webinars/conference calls/Media relations
- Seminar series
- FOIA responses
- Meetings with advocates
- Engagement of health care providers
- Responsive to comments from community, changes to protocol
- Understand the fears of the community
  - Illness not taken seriously
  - Branded as being psychological
  - Inability to get disability
  - Govt conspiracy

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

- Persistent and clinically impactful fatigue for greater than six months
- Post-Exertional Malaise (PEM):
  - Fatigue, pain, cognitive difficulties, sore throat, and/or swollen lymph nodes after previously tolerated physical or mental activity
- No alternate explanation for symptoms
- Onset after significant infections estimated to be 10-12%.[1-2]

1: Hickie I, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ. 2006 Sep 16;333(7568):575.
2: Hotopf M, et al. Chronic fatigue and minor psychiatric morbidity after viral meningitis: a controlled study. J Neurol Neurosurg Psychiatry. 1996 May;60(5):504-9.

Post-Infectious –Myalgic Encephalomyelopathy/Chronic Fatigue Syndrome (PI-ME/CFS)

Overall Hypothesis: **PI-ME/CFS is triggered by a viral illness that results in immune mediated brain dysfunction**

Phase I

To conduct a cross sectional study for deep phenotyping of PI-ME/CFS to define its pathophysiology

Phase II

To validate select biomarkers from Phase I in a longitudinal study and establish objective end points for an intervention study

Phase III

To conduct an early phase intervention study with an immunomodulatory agent that targets biomarkers validated in Phase II

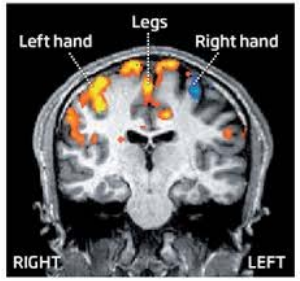
Phase I of PI-ME/CFS Study

- **Aim 1: To define the clinical phenotype**
  - History and physical exam and systemic assessment
  - Neurological assessment
  - Neurocognitive testing
  - Psychiatric evaluation
  - Pain/ headache evaluation
  - Infectious disease and rheumatologic evaluation by specialists
  - Neuro-endocrine evaluation
  - Exercise capacity for fatigue/post exertional malaise

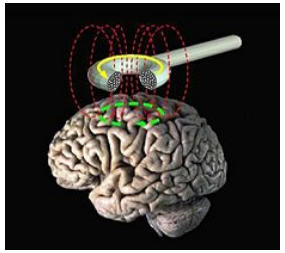
PI-ME/CFS: Post-infectious Myalgic Encephalomyelopathy/Chronic Fatigue Syndrome

Phase I of PI-ME/CFS Study

- **Aim 2: To determine the underlying physiology of fatigue/malaise (pre and post-exercise)**
  - Functional MRI



  - Metabolic studies
  - Transcranial magnetic stimulation



  - Autonomic function

PI-ME/CFS: Post-infectious myalgic encephalomyelopathy/Chronic Fatigue Syndrome

Phase I of PI-ME/CFS Study

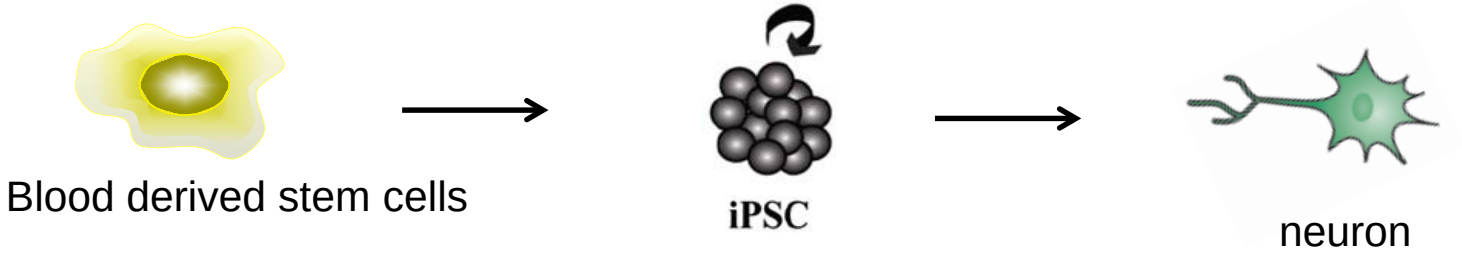
- **Aim 3: To determine if there are abnormal immune and microbiome profiles**
  - Cytokine and chemokine profile in cerebrospinal fluid and blood; after T cell stimulation in culture
  - Flow cytometry
  - B and T cell cloning and T-cell antigen receptor sequencing
  - Immunoglobulin profile
  - Autoantibodies directed against brain antigens
  - Cerebrospinal fluid proteomics and metabolomics
  - Gut and oral microbiome
  - Serum tryptase
  - Viral discovery, antibodies to herpes viruses

PI-ME/CFS: Post-infectious –Myalgic Encephalomyelopathy/Chronic Fatigue Syndrome

Phase I of PI-ME/CFS Study

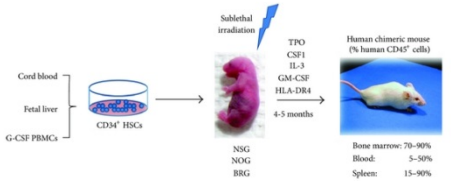
Aim 4: To determine if features can be reproduced in ex-vivo studies

- To determine if there are functional or mitochondrial abnormalities and electrophysiological properties in induced pluripotent stem cell (iPS) derived neurons from patients with PI-ME/CFS



- Effect of serum and Cerebrospinal fluid on iPS cells and derived neurons

- To determine if cerebrospinal fluid or antibodies injected in brain of rodents or humanized mice generated with cells from PI-ME/CFS patients can lead to fatigue or behavioral abnormalities



Biancotti JC, Town T. Biomed Res Int. 2013;2013:740892.

PI-ME/CFS: Post-infectious Myalgic Encephalomyelopathy/Chronic Fatigue Syndrome

Protocol T-N-3495

Selection criteria for PI-ME/CFS

- Received a lot of feedback from community. Challenges in identifying right population
- Documentation of acute onset infectious process
- Post-exertional Fatigue/Malaise more than 6 months but less than 5 years
- Meet 1994 Case Definition and Canadian Consensus Criteria

Study populations

- PI-ME/CFS (n=40)
- Healthy controls (n=20)
- Post-Lyme disease without fatigue (n=20)

Fukuda K, Straus SE, Hickie I, et al. Ann Intern Med. 1994 Dec 15: 121(12) 953-9.
Carruthers BM, van de Sande MI, De Meirleir KL, , et al. J Intern Med. 2011: 270(4) 327-338.
PI-ME/CFS: Post-infectious Myalgic Encephalomyelopathy/Chronic Fatigue Syndrome

Phenotyping Visit

Day 1		Day 2		Day 3		Day 4	
7am		7am	Avi Assessment (1 hour)	7am		7am	
8am	Enrollment Block (3 hours)	8am	Neurologic and Psychological Assessment (4 hours)	8am	Lymphocytapheresis (3 hours) ?Blood volume measurement	8am	Day 4: Ad hoc Procedures and Recovery
9am	Informed Consent Vascular Assessment/IV placement	9am	Neurological Assessment	9am		9am	Day 3 Procedures (if not done) Post-Visit Planning
10am	Blood/Urine Collection Saliva Sample	10am	Psychological Assessment (Steve) Neuropsychological Testing (Snow)	10am		10am	Tapering Schedule
11am	Clinical Assessments (5 hours + 1 hour lunch)	11am		11am	Ad hoc Time	11am	
12pm	Lunch	12pm	Lunch	12pm	Lunch	12pm	Lunch
1pm	Narrative - Walitt Medical - Gill/Friedman	1pm	PT/OT Evaluation (4 hours)	1pm	Lumbar Puncture (60 minutes)	1pm	Ad hoc Time
2pm	Symptom Profile - NP Medication Review - NP	2pm	Muscle Strength Testing Activity Monitor and Fatigue Diary Instructions	2pm	Ad hoc Time	2pm	
3pm	Symptom Assessment Forms (Pack 1)	3pm	OT Qualitative Interview OT Card Sort	3pm		3pm	
4pm		4pm	Symptom Assessment Forms (Pack 2)	4pm		4pm	
5pm	Dinner	5pm	Dinner	5pm	Dinner	5pm	Dinner
6pm	Clinical MRI (90 minutes)	6pm	Autonomic Testing (90 minutes)	6pm	Ad hoc time	6pm	Ad hoc time
7pm		7pm		7pm		7pm	
8pm	Ad hoc Time	8pm	Ad Hoc Time	8pm		8pm	

Clinical Assessment

- Narrative Collection: History of the participant's life experiences
- Symptom Profile: Current symptoms that are used in various ME/CFS case definitions
- Internal Medicine Evaluation
- Neurological Evaluation
- Psychological Evaluation: Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5)
- Medication Review: A detailed evaluation of all current therapeutic modalities
- Symptom Assessment Forms: A detailed battery of questionnaires:

Clinical Laboratory Assessment

- a. Acute care panel
- b. Mineral panel
- c. Hepatic panel
- d. CBC with differential
- e. PT, PTT, INR
- f. Thyroid function tests
- g. Iron, ferritin, transferrin saturation
- h. Lipid panel
- i. Hemoglobin A1c
- j. ANA, Rheumatoid factor, anti-cyclic citrullinated antibody (anti-CCP), anti-Smith antibody, anti-RNP, ssA, and ssB
- k. Vitamin B12, folate

l. Creatine Kinase
m. CRP, ESR and d-dimer
n. Quantitative immunoglobulins
o. Flow cytometry for lymphocyte subsets
p. HIV by ELISA
q. PCR for EBV and HHV-6
r. Antibodies to C6 peptide
s. Hepatitis panel
t. Rapid plasma reagin (RPR)
u. Serum tryptase level
v. Heavy metal screening
w. Serum pregnancy testing (for women of childbearing potential).
x. Additional blood testing if needed to investigate underlying systemic illnesses or other causes of fatigue.

Research Sample Collection

- Saliva
- Buccal Swab and Stool Sample
  - Microbiome
- Blood
  - Immune and metabolic markers (SOMAlogic), gene expression (PAXgene), markers of genetic damage, and catecholamines
- Cerebrospinal Fluid
  - Cell count, total protein, glucose, PCR for pathogens, cytokine assays, lipid profile, flow cytometry for phenotyping of immune cells, cytokine/chemokine profile, growth factors, proteome and metabolome, autoantibodies to brain antigens and neurotransmitters.
- Cytapheresis
  - iPSCs for neuronal disease and mouse disease models
  - Mitochondrial function via XP cell culture microplate (Seahorse)

Clinical MRI

- Clinical anatomic images
- MPRAGE
- DWI, SWI, and high resolution FLAIR sequences optimized for detecting inflammatory lesions and leptomeningeal enhancement
- Intravenous gadolinium contrast to determine cortical enhancement or meningeal inflammation will be given if there are no contraindications.

Polysymptom Assessment

- Patient Reported Outcome Measures:
  - Administered Multiple Times:
    - CFS Symptom Inventory: Visual Analogue Scale - 5 items related to physical fatigue, mental fatigue or mental fog, muscle aches, join aches and lightheadedness. Brief Pain Inventory (BPI): Visual Analogue Scale: Pain severity and pain interference.
  - Administered Once:
    - Multidimensional Fatigue Inventory, PROMIS, NIH-Brief Fatigue Inventory, McGill Pain Questionnaire, Neuropathic Pain Scale, Polysymptomatic Distress Scale, Patient Health Questionnaire 15, Pittsburgh Sleep Quality Index, Fatigue Catastrophizing Scale, Multiple Ability Self-Report Questionnaire, SF-36, Belief about Emotions scale, Beck Depression Inventory, Beck Anxiety Inventory, CESD-R.

Neuropsychological Assessment

- Psychological Inventories:
  - Composite International Diagnostic Interview Trauma Section (CIDI-Trauma)
  - Post-traumatic Stress Diagnostic Scale (PDS)
  - Childhood Trauma Questionnaire Short Form (CTQ-SF)
  - Patient Health Questionnaire-15 (PHQ-15)
  - Patient Reported Outcomes Measurement Information System (PROMIS):
    - Fatigue, Pain Behavior, Pain Interference, Pain Intensity, Global Health, Emotional Distress – Anxiety, Emotional Distress- Depression, Sleep Disturbance, and Sleep Impairment
  - Beck Depression Inventory –II (BDI-II)
  - Beck Anxiety Inventory (BAI): a 21-question validated self-report inventory for measuring the severity of anxiety
  - Center for Epidemiologic Studies Depression Scale – Revised (CESD-R)

Neuropsychological Assessment

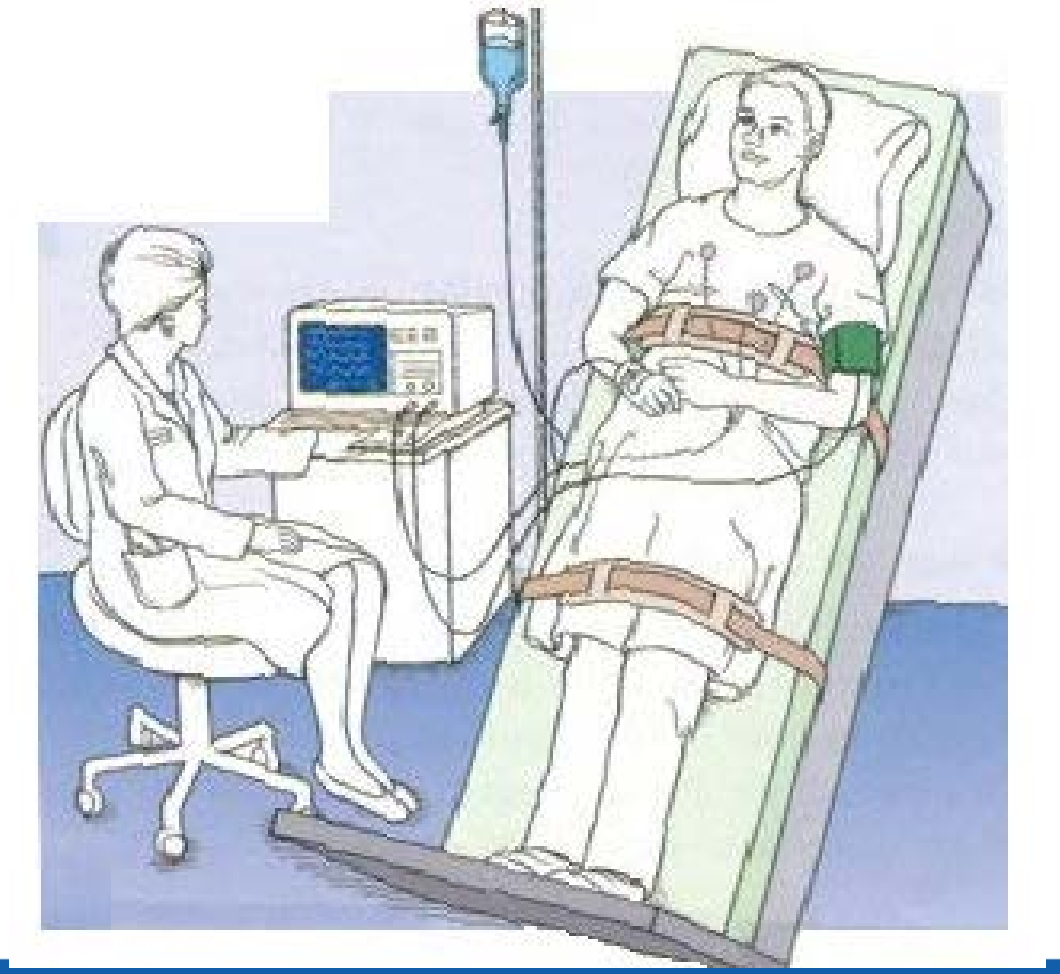
- Wechsler Test of Adult Reading (WTAR)
- Wechsler Adult Intelligence Scale – Third Edition (WAIS-III)
- Test of Variables of Attention
- Hopkins Verbal Learning Test-Revised (HVLT-R)
- Brief Visual Memory Test-Revised (BVMT-R)
- Wisconsin Card Sort Test (WCST-64)
- Controlled Oral Word Association Test (COWAT; FAS and Animals)
- Paced Auditory Serial Addition Test (PASAT)
- Minnesota Multiphasic Personality Inventory-2 Restructured Form (MMPI-2-RF)

Rehabilitation Medicine

- Muscle strength testing
  - Grip strength task
- Activity Monitoring
    - At home prior at least one week prior to Post Exertional Malaise visit
- Fatigue Diary
  - At home prior at least one week prior to Post Exertional Malaise visit
- Qualitative Interview
  - Impact of symptoms; medical uncertainty
- Functional Evaluation
  - Card sorting task

Autonomic Testing

- Deep-breathing effect on heart rate
- Valsalva maneuver
- Provocative Tilt Table Test
  - 70^0 angle
  - Blood and urine sampling for catecholamines and other neurochemicals



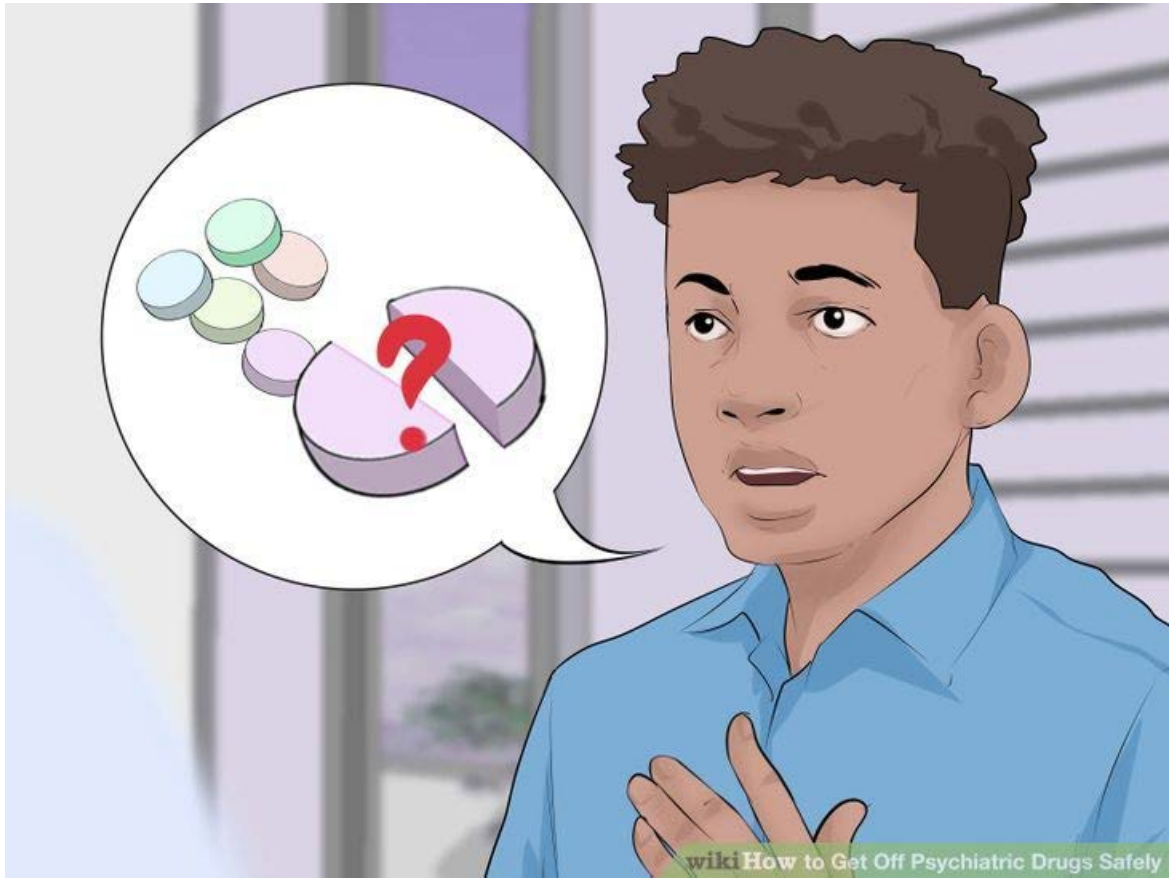
Case Adjudication

- After completion of phenotyping visit, a de-identified case packet will be created
  - Chair: Avindra Nath
  - 5 experts
- Teleconference to review patient data and deliberate
- Unanimous agreement necessary to be considered a PI-ME/CFS case

Exercise Stress Visit

- 5-10 day long inpatient admission
- Administer provocative exercise stress task to induce post exertional malaise (PEM)
- Serially measure the subjective experience, objective physiologic function, and biologic specimens over 48-96 hours

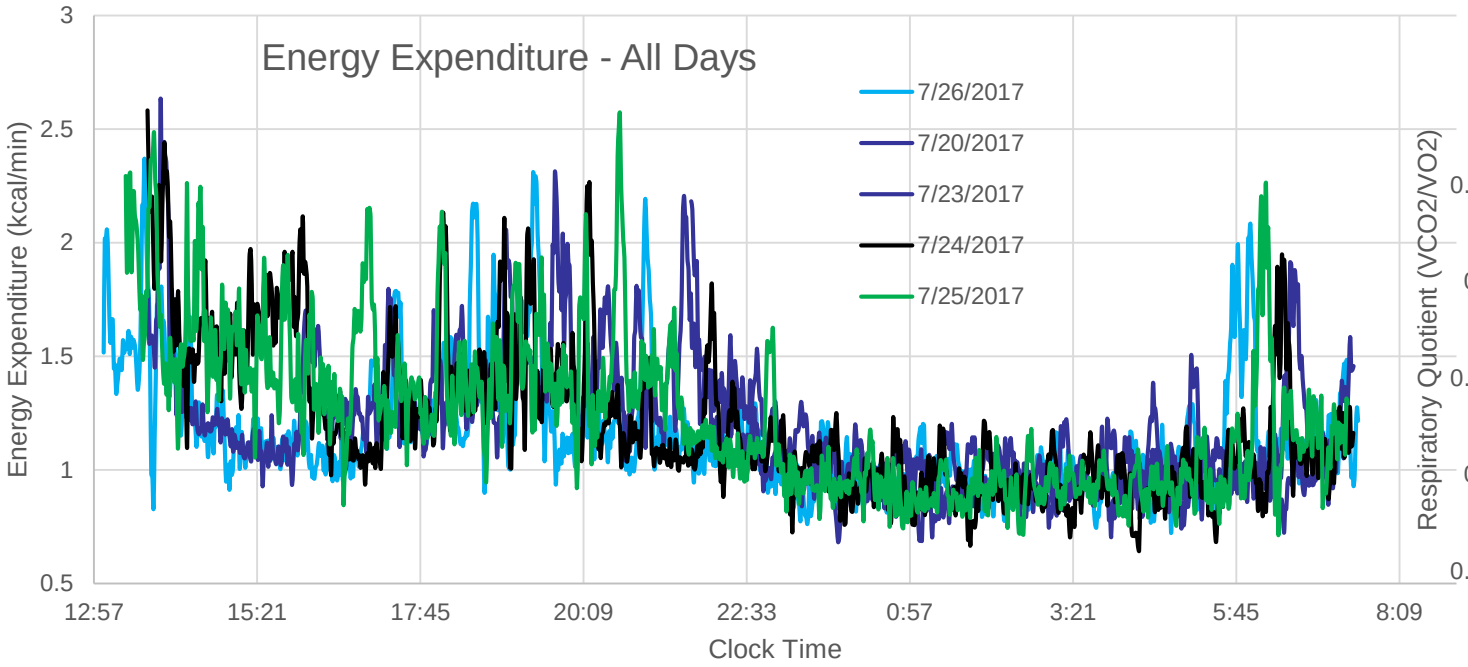
Medication Wash-out

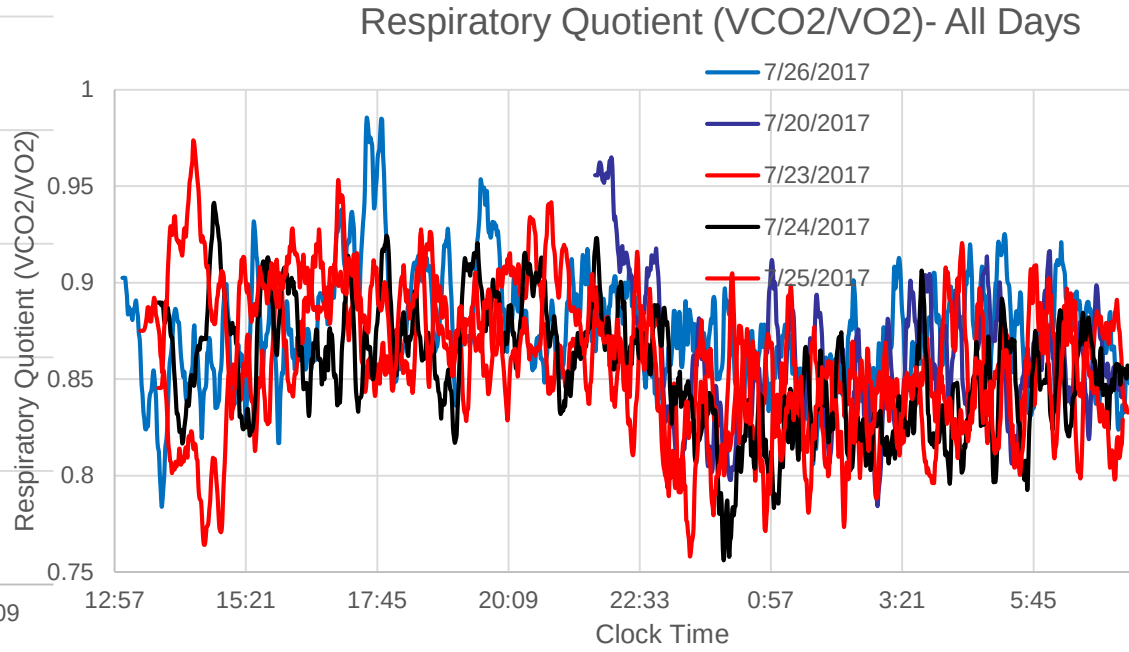


- Medication that is not medically necessary in the opinion of study investigators and the participant's physician care providers.
- Participants taking stable doses of medications for medical diseases or psychiatric diagnoses will not be withdrawn from their medications.
- Participants taking medications that cannot be withdrawn will be excluded from study participation.

Metabolic Assessment

- The “hospital bed” for the entire inpatient stay will be in the metabolic chamber
- Activity monitoring
- DEXA body composition
- Holter monitoring
- Metabolic chamber measurements



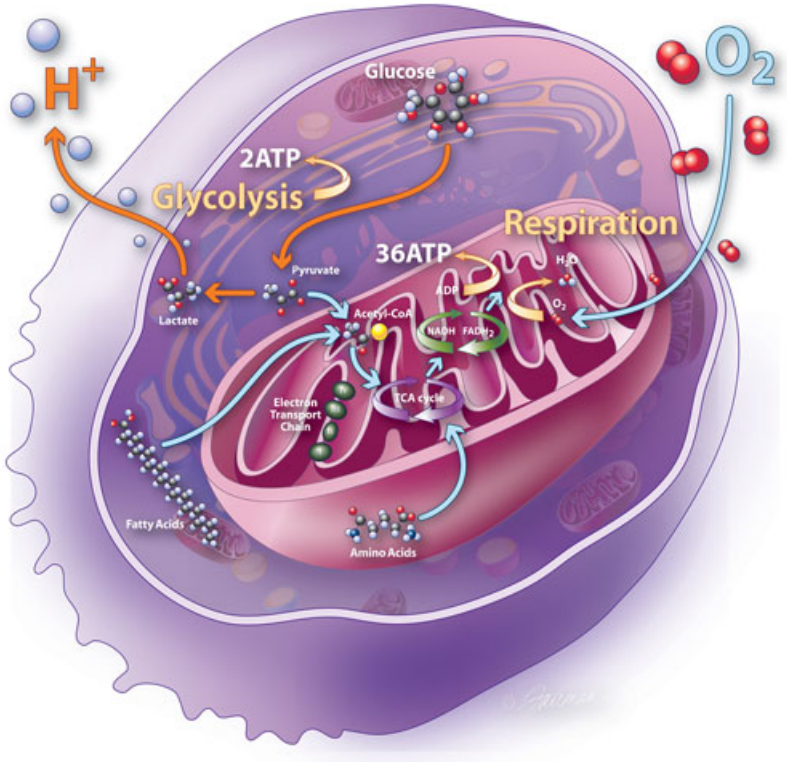


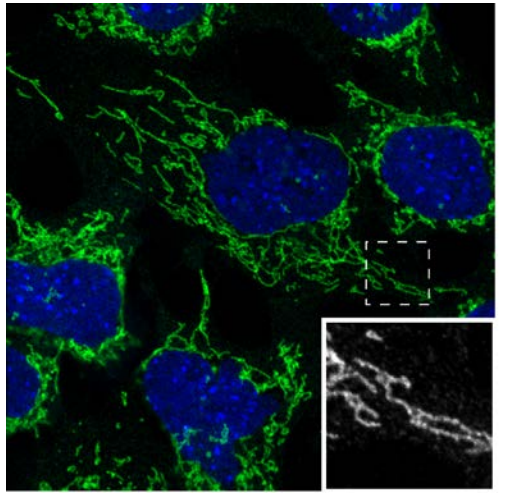
1.0=carbohydrates
0.8=protein
0.7=lipids

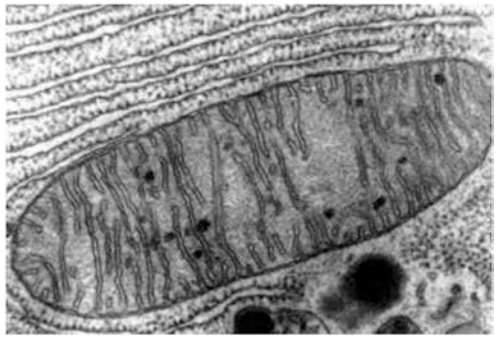
Peak Exercise Testing

- Cardiopulmonary Exercise Test:
  - Cycle ergometer protocol that slowly increases work rate until participant reaches volitional fatigue.
  - Bioimpedence plethysmography (Qt)
  - Near infrared spectrometry (muscle O2) with thigh occlusion

Mitochondria in sickness and in health



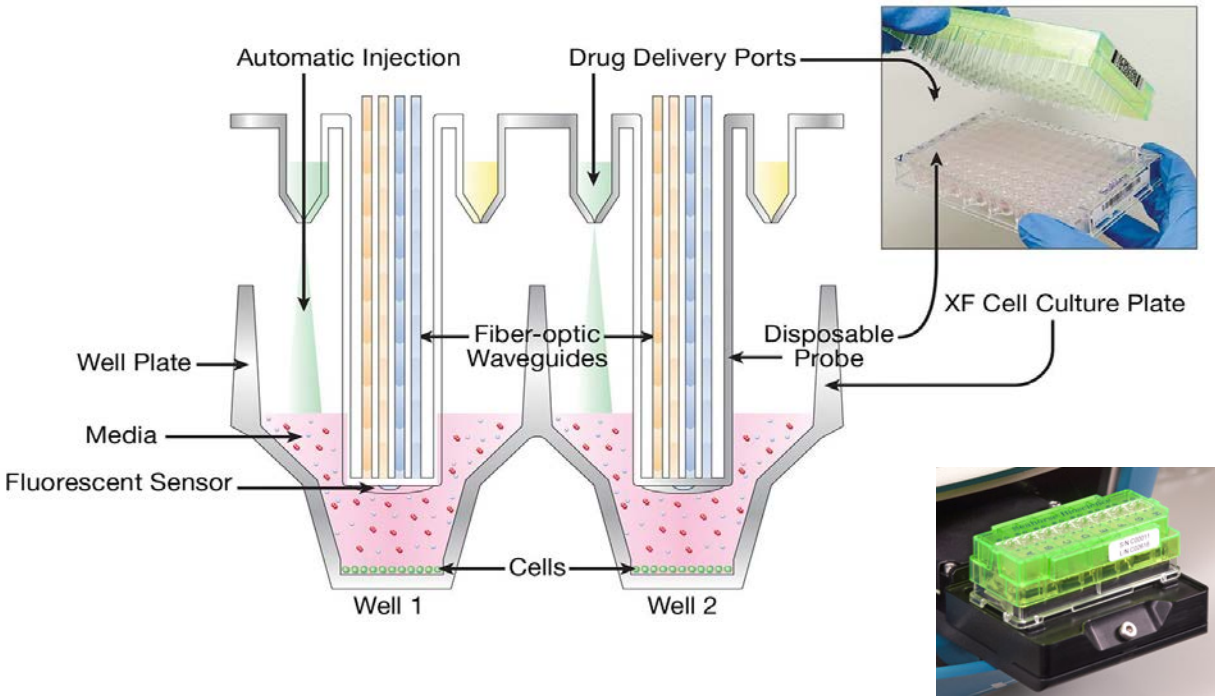


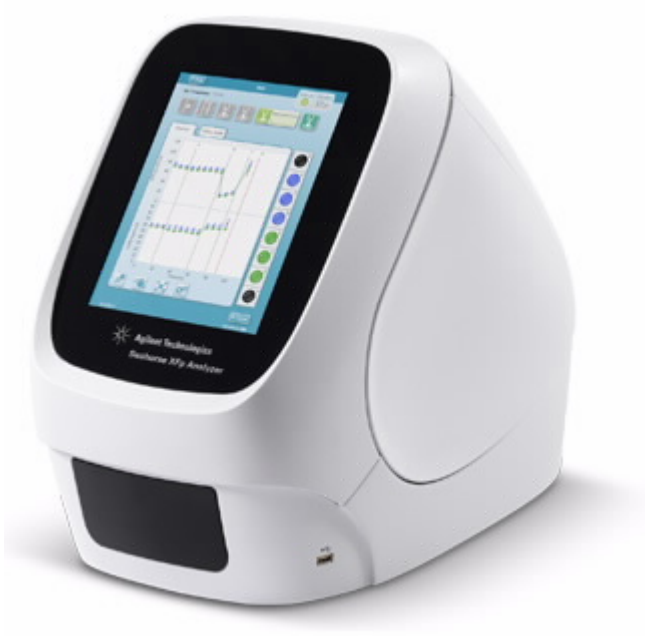


- ATP production
- Ca2+ regulation
- Cell signaling
- redox regulation
- apoptosis

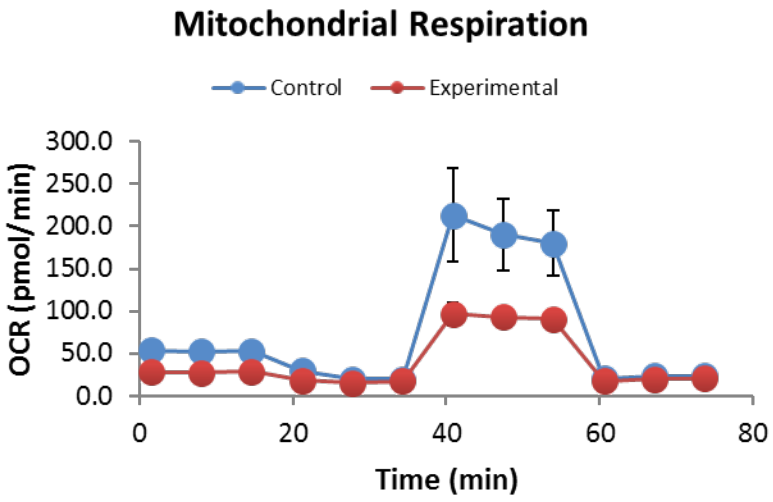
U Toronto

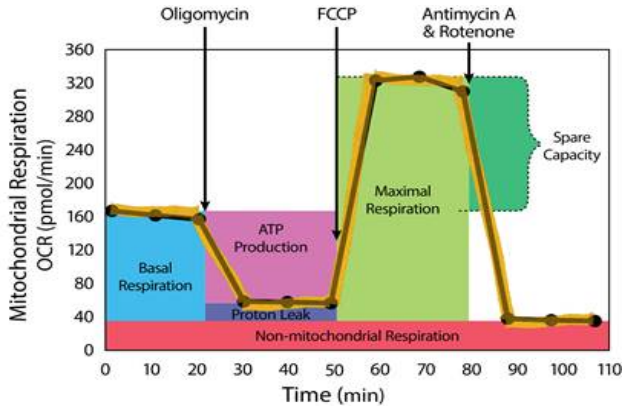
Seahorse XFp Analyzer

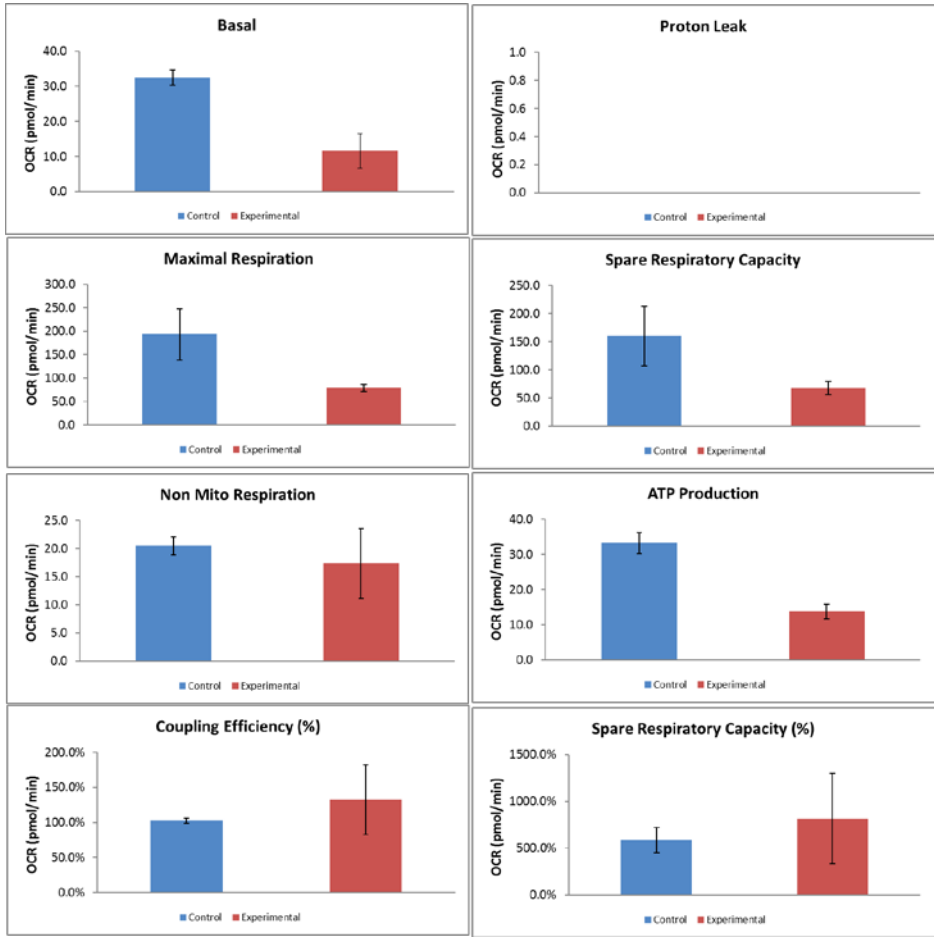




So far the data look promising



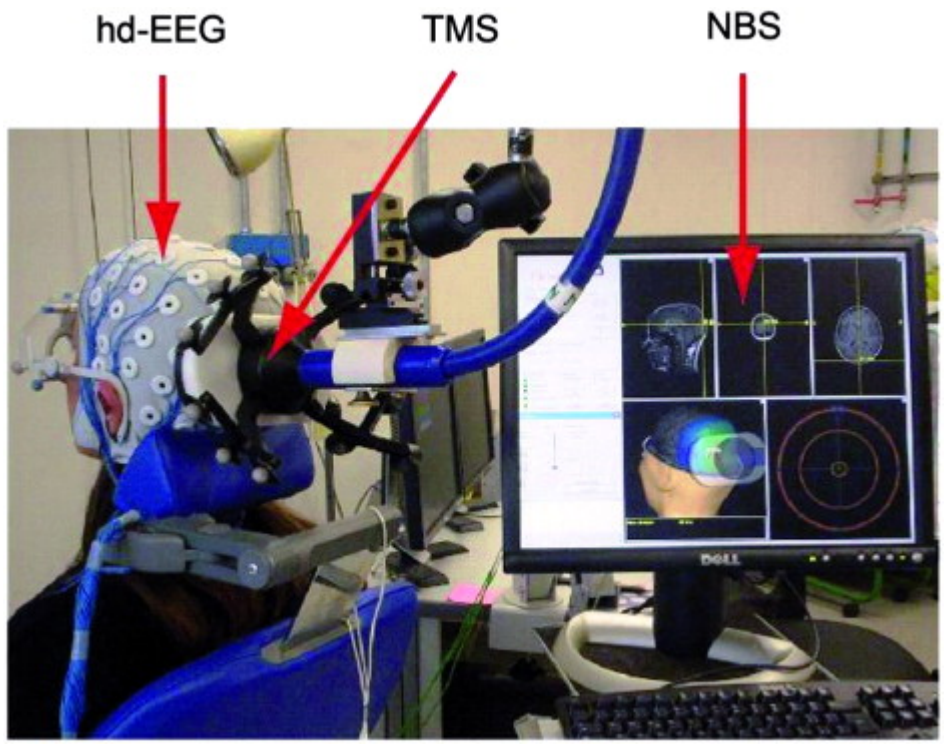




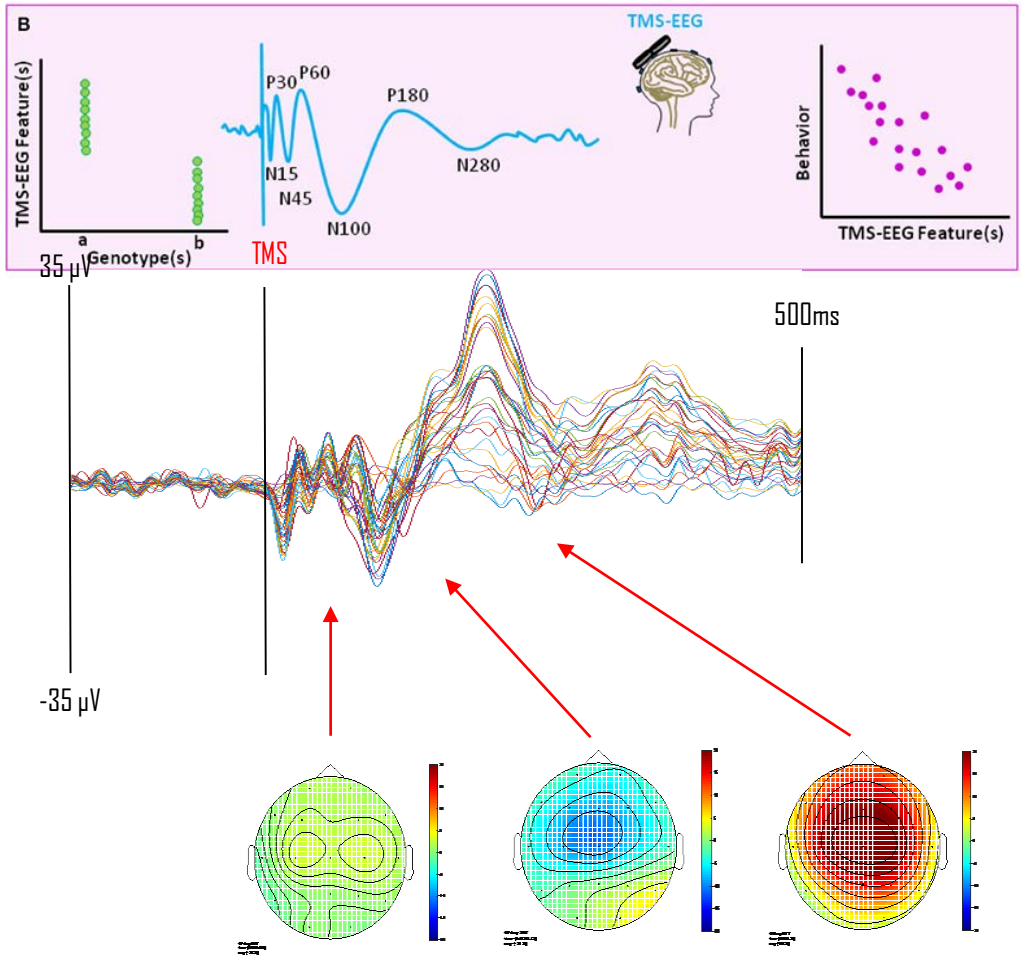
Before and After CPET measurements

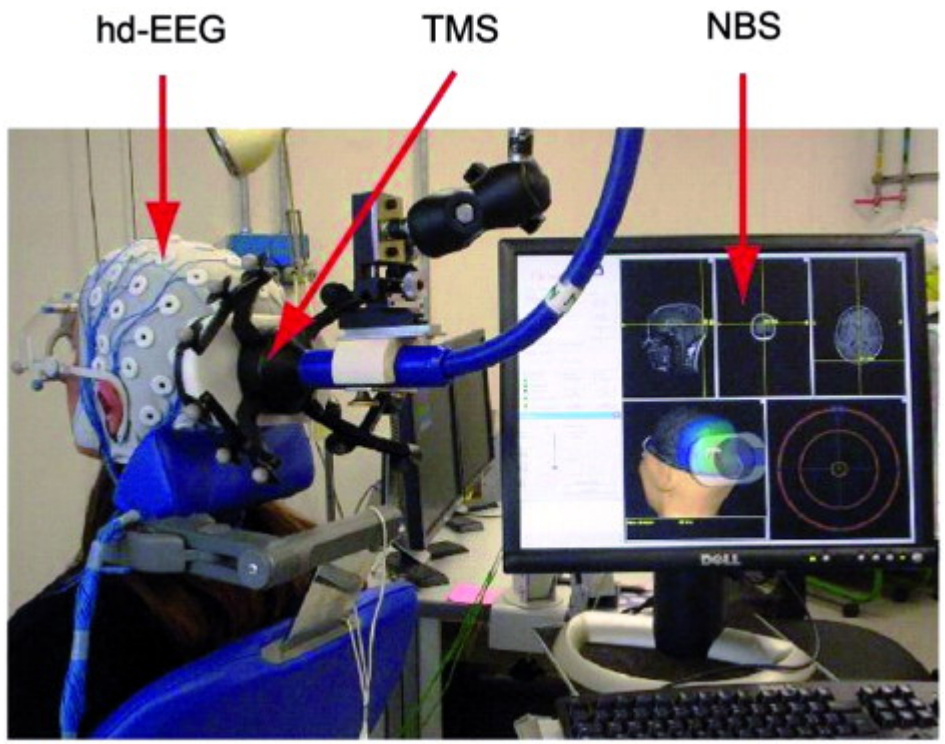
- Salivary cortisol
- Transcranial Magnetic Stimulation
  - Evoke motor potentials for extensor carpi radialis and record motor excitatory potential (MEP) amplitudes
  - EEG
- Functional Magnetic Resonance Imaging:
  - Muscle fatigue task of maximum voluntary contraction of the extensor carpi radialis (muscle function, subjective fatigue, BOLD activity)
  - Cognitive fatigue task of serial math problems (cognitive accuracy/speed, subjective fatigue, BOLD activity)
  - Voxel-Based Morphometry, Default Mode Network, Diffuse Tensor Imaging

Transcranial Magnetic Stimulation (TMS)



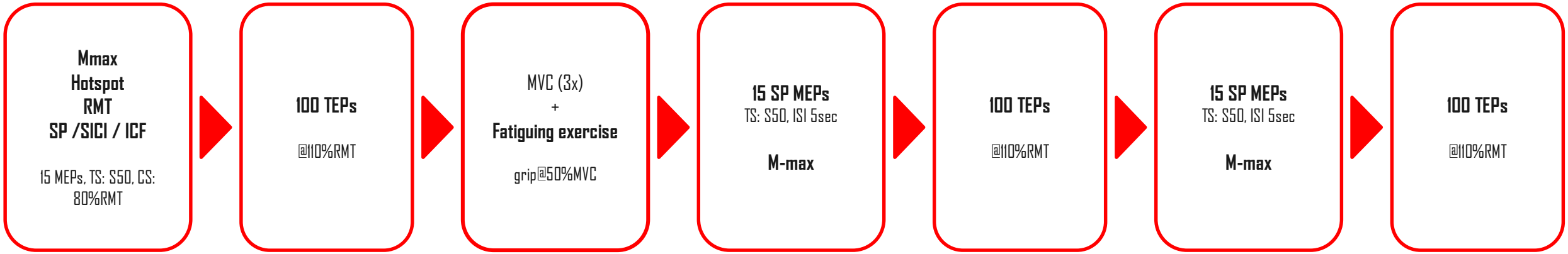
Transcranial Magnetic Stimulation (TMS)





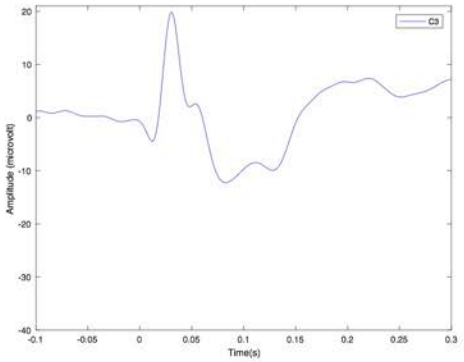
Traian Popa, Silvna Horovitz, Mark Hallett

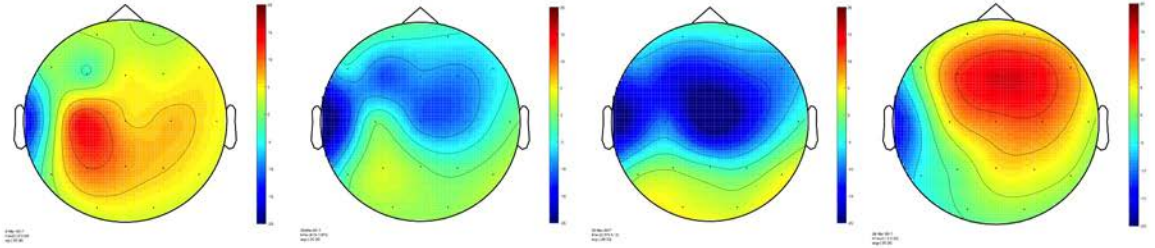
TMS study design

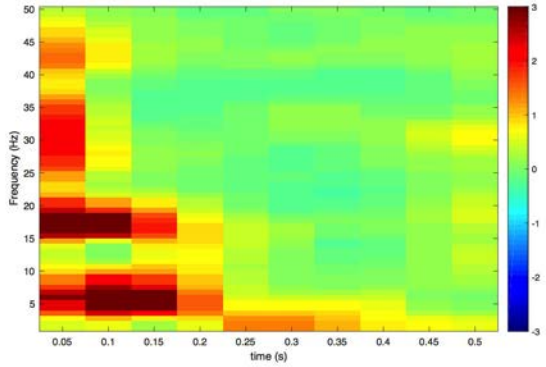


Example of TMS-EEG findings in Healthy Volunteers

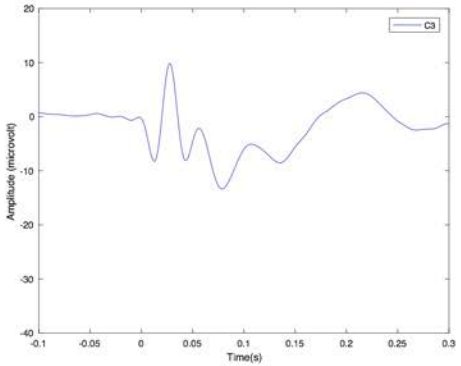
Baseline

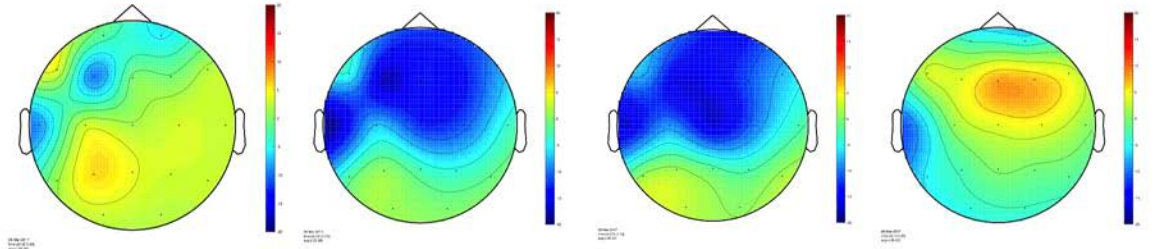


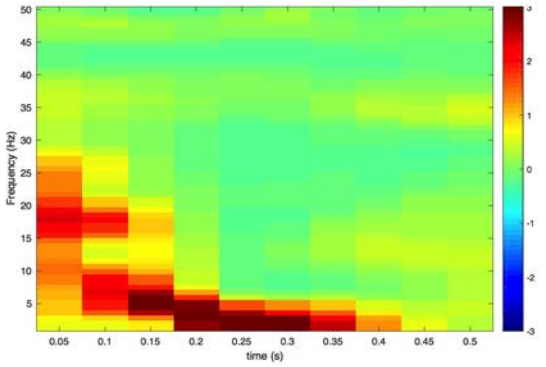




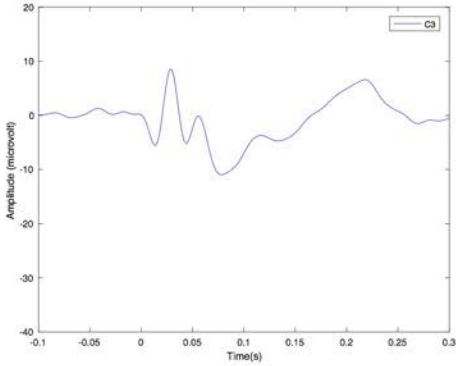
Post 1

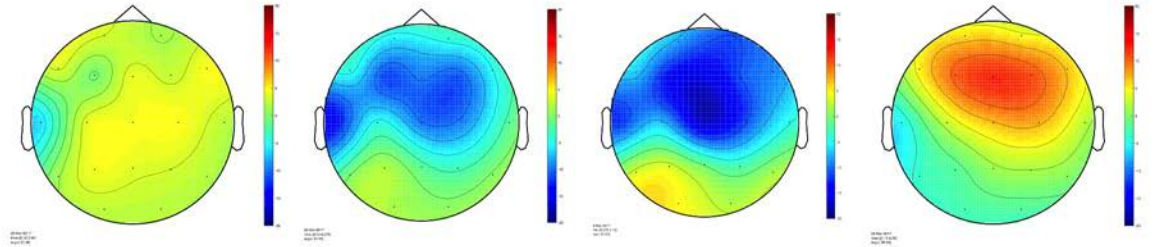


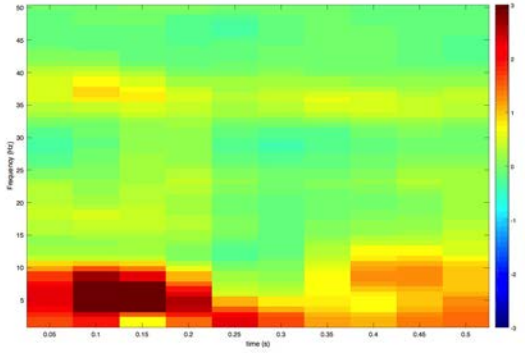




Post 2







0.02-0.04 sec | 0.04-0.075 sec | 0.075-0.12 sec | 0.15-0.25 sec

What is new in the TMS study

- Explore for the 1st time the TMS-evoked EEG potentials in CFS
- Separate intense muscle exertion from sustained effort
- Can correlate MRI-EEG with TMS-EEG outcomes
- Can explore the functional ***and*** anatomical differences between HV and patients
- Can correlate neuroimaging outcomes with

  clinical, immunologic, metabolic, genomic, and psychological evaluations

PEM Research Measurements

- Measures will be collected at:
  - Baseline (one hour before CPET)
  - One hour after CPET
  - 24 and 48 hours in all participants
  - 72 and 96 hours in PI-ME/CFS participants
- Measures include:
  - Qualitative interview of PEM experience
  - Questionnaires: CFS Symptom Inventory, Brief Pain Inventory
  - Neurocognitive testing: Grooved PegBoard, Word Memory, B test, Dot Counting Test
  - Blood
    - Immune and metabolic markers
    - Gene expression (PAXgene)
    - Markers of genetic damage
  - Cerebrospinal fluid after 48 hours

“Team Tired”

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