Mechanisms of Fatigue in Health and Disease

NIH Blueprint for Neuroscience
Fatigue Prominent in Many Disorders

Central Nervous System
- Multiple Sclerosis
- Post Stroke
- Post TBI
- Post Polio Syndrome
- Post posterior fossa surgery/path

Muscle Nerve
- Overtraining Syndrome
- Myasthenia Gravis
- Mitochondrial disorders
- Chronic Guillain Barre

Neuroendocrine
- Hypothyroidism
- Hypothalamic Pituitary Adrenal Axis

Metabolic
- Renal failure
- Heart Failure
- Anemia

Inflammatory/Rheumatic Diseases
- Environmental
  - Heat
  - Altitude sickness

Infectious and Post Infectious
- Mononucleosis
- Lyme
- Influenza

Drug AEs
- Aging

Cancer
- Cancer and Post cancer
- Radiation and Chemotherapy

Psychological
- Depression
- Post traumatic stress disorder
- Anxiety Disorder

Environmental
- Heat
- Altitude sickness
Definition of Fatigue

• **Fatigue:** Difficulty in sustaining voluntary mental and physical activities.
  • “To continue or stop?”

• **Simplistic Fatigue model:** “Work” output is a function of:
  • A) motivational input (*reward*) – *subject of intense study*
  • B) feedback from motor, sensory, autonomic and cognitive systems that establishes the *level of perceived exertion.* – *the biological basis of “exertion” for cognitive tasks, and how relevant feedback from the body is processed in the CNS is poorly understood.*
  • C) *sense* of fatigue occurs when value of B>>A
    • - *poorly understood how and where that calculation happens.*

• **Persistent Illness-related Fatigue:** the subjective sense of persistent “tiredness” or “loss of energy” that interferes with the performance of daily life activities and is not relieved by rest.
Neuroeconomics: A potential means to understand neural mechanisms of fatigue.

Nature 431, 760-767 (14 October 2004)
Computational roles for dopamine in behavioural control
P. Read Montague1,2, Steven E. Hyman3 & Jonathan D. Cohen4,5

Subsecond dopamine fluctuations in human striatum encode superposed error signals about actual and counterfactual reward
Kenneth T. Kishida1, Ignacio Saiz2, Terry Lohrenz3, Mark R. Witcher4, Adrian W. Laxton5, Stephen B. Tatter5, Jason P. White6, Thomas L. Ellis4,5, Paul E. M. Phillips4,5, and P. Read Montague1,2,6,7

Dopamine release in human brain translates computations about actual and simulated experiences to embodied states of feeling
During muscular fatigue the force generation is submaximal: implicating a central controller

Two major categories of fatigue.

**Physical fatigue** is an exercise-induced reduction in maximal voluntary muscle force.

- the central nervous system fails to drive the motoneurons maximally. Due to inhibitory process upstream of motor cortex.
- How the brain interprets signals from muscle to produce sense of fatigue is not clear.

- **Mental fatigue** is associated with affective, behavioral, and cognitive impairments especially in attention, planning, increased distractability.
  - N.B. It is **not** related to ATP.
Animal Models of Fatigue

Neurobiological studies of fatigue
Mary E. Harrington

**Physical fatigue**
forced swim, exercise, heat exposure, sleep deprivation

**Immunologically induced**
Synthetic analog of dsRNA systemically
Parasitic infections
Brucella Ag
LPS
IL1Beta

**Aging**

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Fig. 1. Suppression of spontaneous wheel-running activity following poly I:C. Male Wistar rats were administered poly I:C (P; 3 mg/kg) or saline (S) and killed on day 1 or day 8 following injection. Total daily wheel-running activity was expressed as a percent...
“Advanced imaging methods now allow cell-type-specific recording of neural activity across the mammalian brain, potentially enabling the exploration of how brain-wide dynamical patterns give rise to complex behavioural states.”

Deep posteromedial cortical rhythm underlying dissociation. Vesuna, Kauvar, Richman, Gore, Oskotsky, Sava-Segal, Luo, Malenka, Henderson, Nuyujukian, Parvizi & Karl Deisseroth

- Ketamine found to induce 1-3Hz rhythm in layer 5 retrosplenial neurons
- Optogenetic activation of these cells recapitulated dissociative behavior
- Recordings in an epilepsy pt show same localized rhythm as part of a dissociative experience as part of aura.
Blueprint Interoception Program - Representation and Regulation of the Internal World

Why we feel the way we do.

Heart rate
Thirst
Micturition/voiding
Visceral pain
Sexual arousal
Heart
Kidneys
Bladder
Hormones

Interoception

Heart
Kidneys
Bladder
Hormones

Lungs
Stomach
Intestines
Bone
Immune cells

It is about the representation of the internal, not the external world.
Interoception Pathways: between Internal Body Signals and Brain through circulatory and lymphatic systems

Interoception - Representation and Regulation of the Internal World

Numerous brain-peripheral organ axis remain to be identified and characterized at molecular and functional levels.
NIH Common Fund Program: 
Stimulating Peripheral Activity to Relieve Conditions (SPARC)

SPARC Primarily Focuses on Local Neural Circuits around Peripheral Organs

- Technologies to Understand the Control of Organ Function by the Peripheral Nervous System (OT2) RFA-RM-17-010

- Foundational Peripheral Neuroanatomy and Functional Neurobiology in Under-Studied Organs (U01) RFA-RM-17-003

- Comprehensive Functional Mapping of Neuroanatomy and Neurobiology of Organs (OT2) RFA-RM-15-018

- Pre-clinical Development of Existing Market-approved Devices to Support New Market Indications (U18) RFA-RM-16-009
Long term COVID-19 effects on the nervous system

- The perception of “Fatigue” is the most common:
  - 57% of hospitalized patients in Italian & 39% in British study (12 wks), 97% of the 35% with persistent symptoms in CDC outpt study (2-3 wks)
- Headache in 61% of the symptomatic persons in CDC study of outpatients (2-3 weeks post + test), 2% in British study 12 wks post admission
- Insomnia in 26% in British post hospital study
- Loss of smell and taste
- Pain syndromes- chest, abdomen, muscles in CDC and British studies.
- Difficulty with concentration, labeled in media “brain fog” is exceedingly common and usually associated with fatigue.

Not reported in this study, but others report significant Anxiety Disorders (PTSD) & Depression.

In contrast 90% of outpatients with influenza recover within 2 weeks of + test.

* 294 patients responded to 14–21-day interview, did not report a previous positive SARS-CoV-2 test before the reference test, and answered questions about symptoms; 276 (94%) of these reported one or more symptoms at the time of SARS-CoV-2 RT-PCR testing; those who were interviewed at 7 days were excluded, with 274 included here.
† Patients were randomly sampled from 14 academic health care systems in 13 states.
RECOVER Initiative: Researching Covid to Enhance Recovery

Setting the Strategic Direction for RECOVER

**Goal**
Rapidly improve our understanding of and ability to predict, treat and prevent PASC

**Key Scientific Aims**
1. Understand clinical spectrum/biology underlying recovery over time
2. Define risk factors, incidence/prevalence, and distinct sub-phenotypes of PASC
3. Study pathogenesis over time and possible relation to other organ dysfunction/disorders
4. Identify interventions to treat and prevent PASC

**Guiding Principles**
- Patient-centered, participants as partners
- Inclusive, diverse participation & community engagement
- Multi-disciplinary, trans-NIH collaborative teams and network
- Adaptive approaches based on emerging science

RECOVER, a research initiative from the National Institutes of Health (NIH), seeks to understand, prevent, and treat Post Acute Sequelae of COVID-19 infection, including Long COVID.
RECOVER Meta-Cohort: A Comprehensive and Complementary Approach

Anticipated Study Sizes

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<th>Acute &amp; Post-Acute Infection Cohorts</th>
<th>EHR/Health Sys. records</th>
<th>Autopsy</th>
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| Pediatric (N=18,500 including up to 1000 MIS-C) Adult (N=17,680 including 2,450 Pregnancy)  
  - Acute (N=9000),  
  - Post-acute Prospective (N=3,580), Retros. (N=5,100) | 70+M records, 3.7M+ with SARS-CoV-2 infection | 700 cases |
Til’ we better understand the mechanisms of fatigue we suggest:

**POWER NAP**

- **15-20 minutes**
  - Restore alertness
  - Easy way to get some relaxation and to reduce mental fatigue
  - Have caffeine right before you nap to improve post-nap alertness and cognitive functioning

- Enhance both physical & cognitive performance
- Reduce stress and immune perturbations after a short night
- Restore wakefulness, promote learning and boost memory
- Reverse the hormonal impact of a night of poor sleep