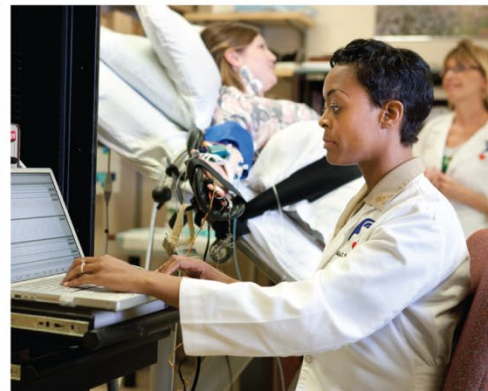
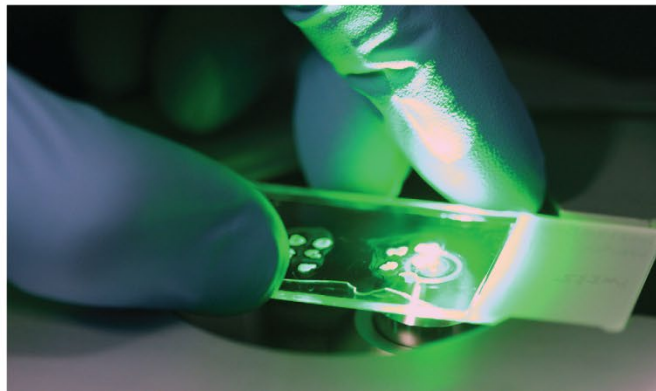
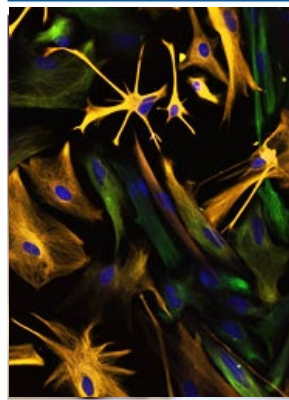
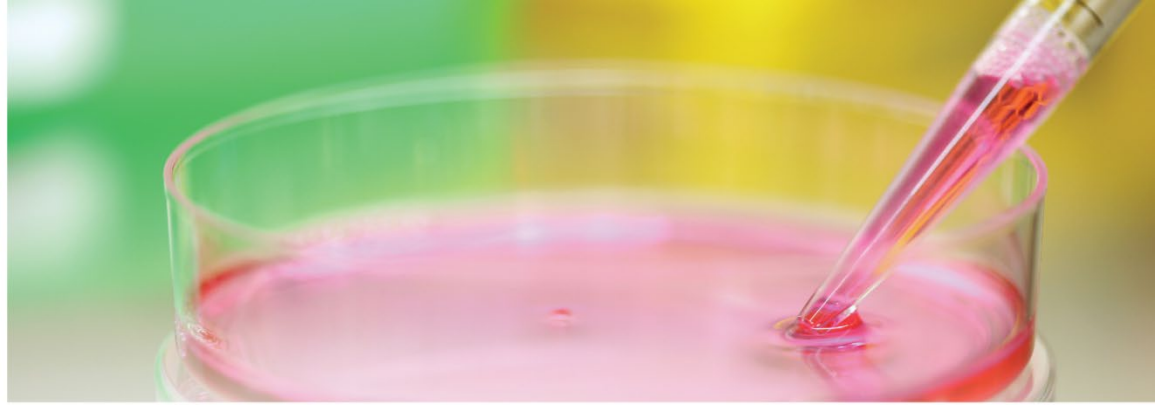


Mechanisms of Fatigue in Health and Disease

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

Aging

Neuroendocrine

Hypothyroidism
Hypothalamic Pituitary Adrenal Axis

Metabolic

Renal failure
Heart Failure
Anemia

Drug AEs

Inflammatory/Rheumatic Diseases

Environmental

Heat
Altitude sickness

Infectious and Post Infectious

Mononucleosis
Lyme
Influenza

Psychological

Depression
Post traumatic stress disorder
Anxiety Disorder

Muscle Nerve

Overtraining Syndrome
Myasthenia Gravis
Mitochondrial disorders
Chronic Guillain Barre

Cancer

Cancer and Post cancer
Radiation and Chemotherapy

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 $B \gg A$
 - - *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.

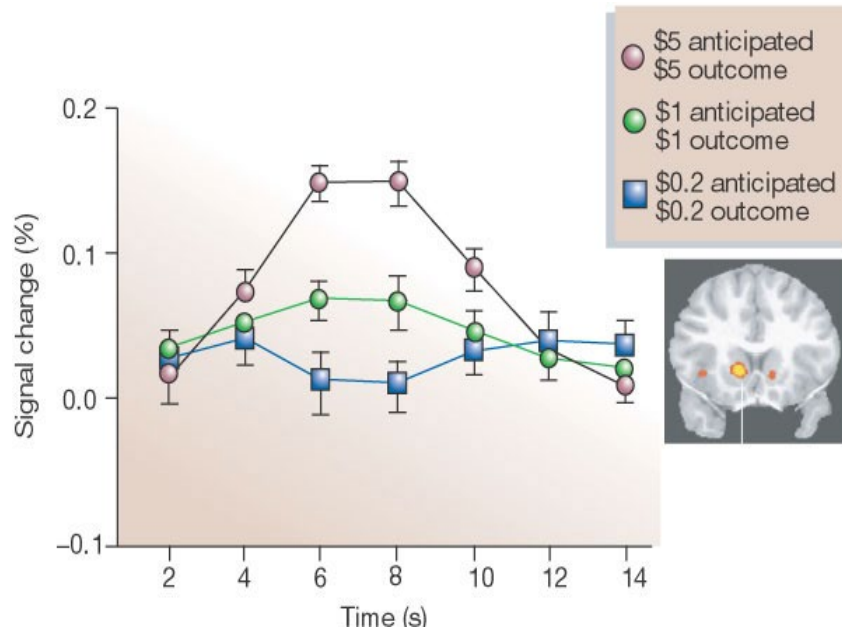


Neuroeconomics: A potential means to understand neural mechanisms of fatigue.

Nature **431**, 760-767 (14 October 2004)

Computational roles for dopamine in behavioural control

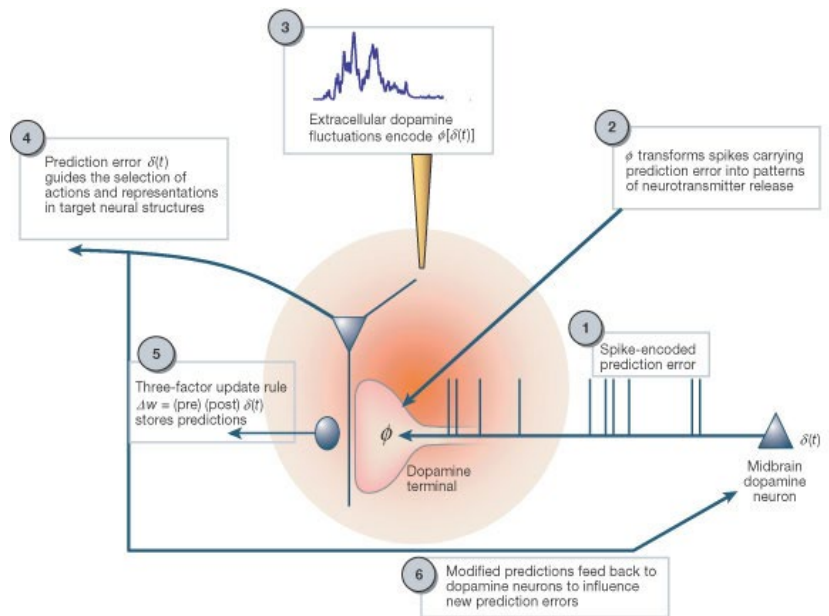
P. Read Montague^{1,2}, Steven E. Hyman³ & Jonathan D. Cohen^{4,5}



Subsecond dopamine fluctuations in human striatum encode superposed error signals about actual and counterfactual reward

Kenneth T. Kishida^{a,1}, Ignacio Saez^{a,2}, Terry Lohrenz^a, Mark R. Witcher^b, Adrian W. Laxton^b, Stephen B. Tatter^b, Jason P. White^a, Thomas L. Ellis^{b,3}, Paul E. M. Phillips^{c,d}, and P. Read Montague^{a,e,f,1}

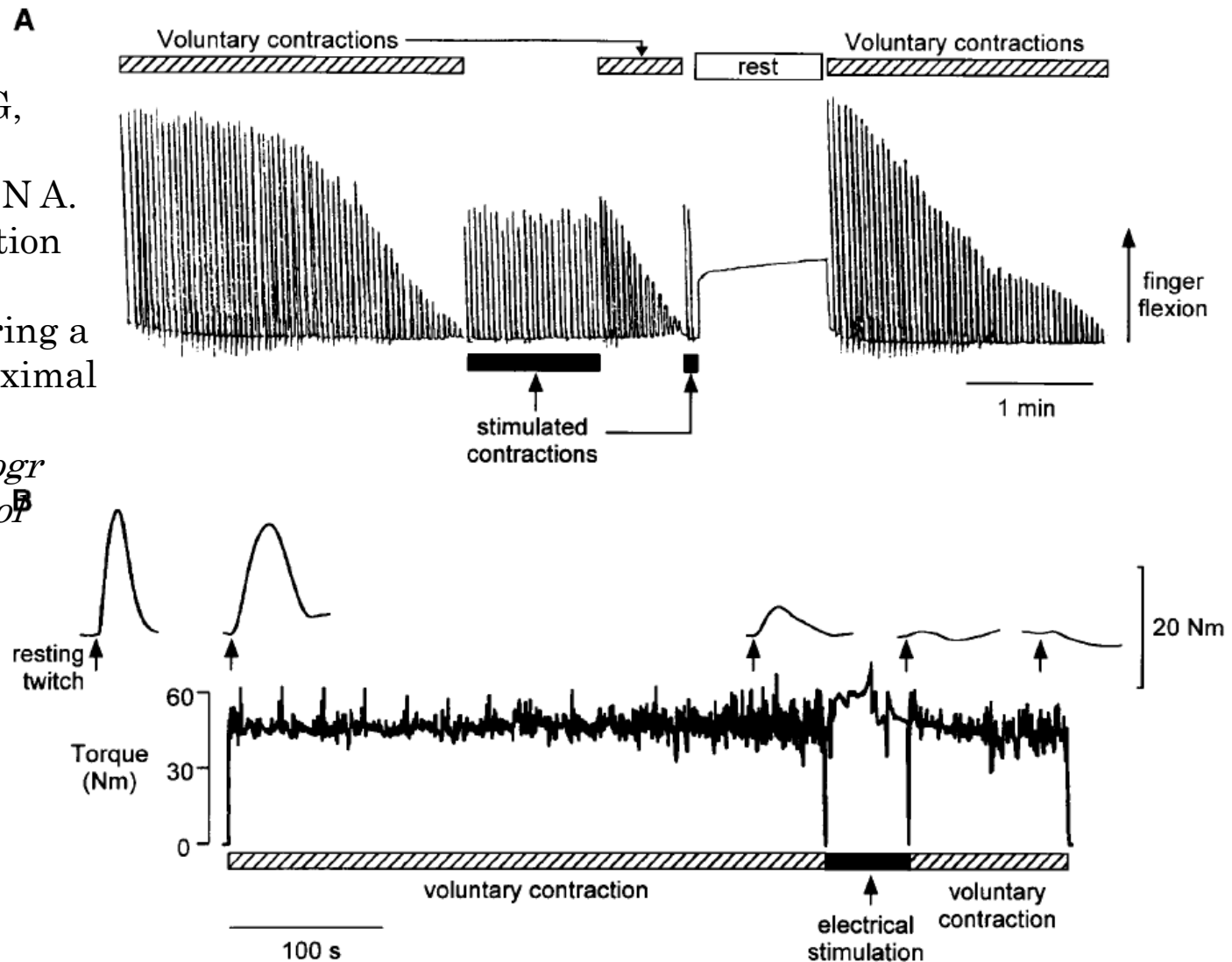
Dopamine release in human brain translates computations about actual and simulated experiences to embodied states of feeling



During muscular fatigue the force generation is submaximal: implicating a central controller

LOSCHER WN,
CRESSWELL AG,
AND
THORSTENSSON A.
Recurrent inhibition of soleus alpha-
motoneurons during a
sustained submaximal
plantar flexion.

*Electroencephalogr
Clin Neurophysiol*
101: 334–
338, 1996



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.

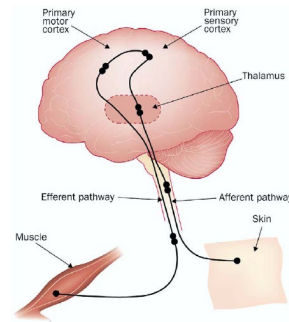


Figure 2: Integration of sensory and motor pathways for physical activities

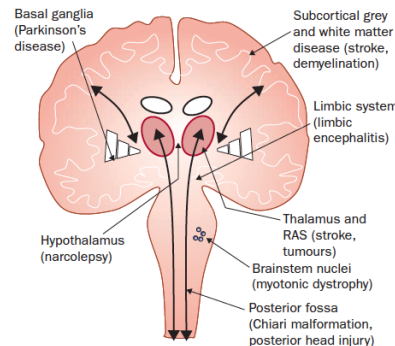
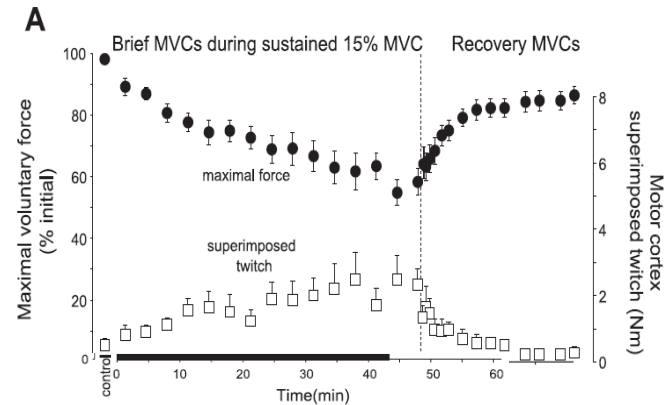


Figure 5: General sites of pathology in central fatigue
RAS=reticular activating system.

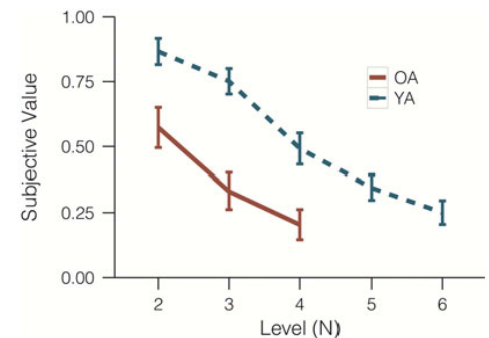


Figure 1 (Westbrook & Braver). Subjective value of a cash offer, or conversely, motivation to engage with a task, decreases with increasing working memory load for both young adults (YA) and older adults (OA).

Animal Models of Fatigue

Neurobiological studies of fatigue

Mary E. Harrington

Progress in Neurobiology, Volume 99, Issue 2, 2012, 93–105

Physical fatigue

forced swim, exercise, heat exposure, sleep deprivation

Immunologically induced

Synthetic analog of dsRNA systemically

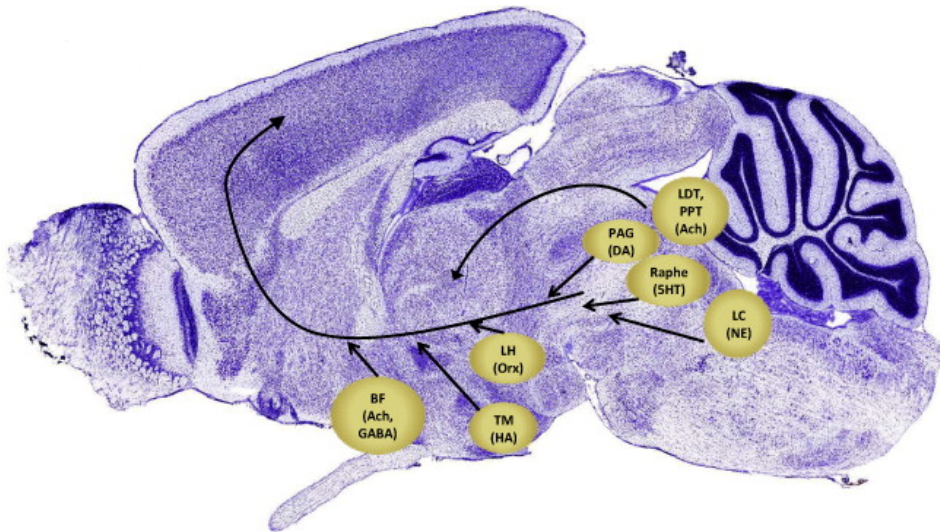
Parasitic infections

Brucella Ag

LPS

IL1Beta

Aging



Arousal system in rat

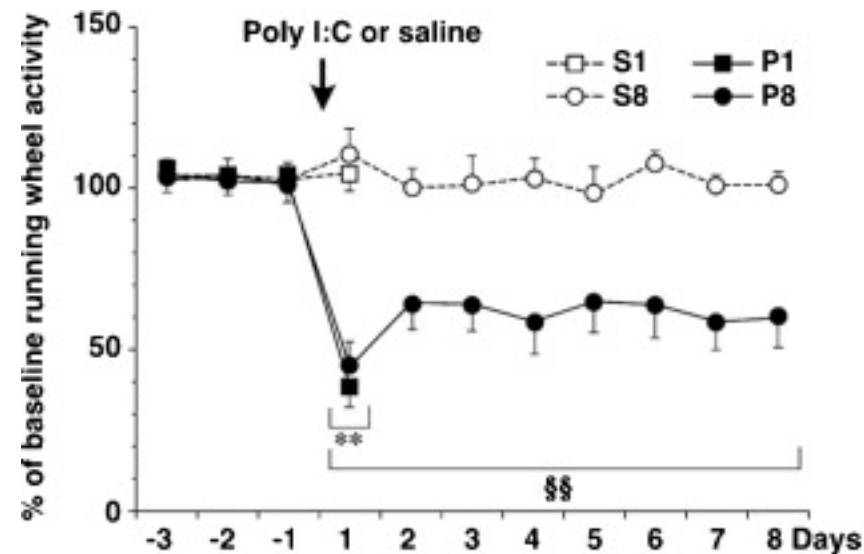


Fig. 1. Suppression of spontaneous wheel-running activity following poly I:C. Male Wistar rats were administered poly I:C (P; 3 mg/kg) or saline (S) and killed on day 1 or day 8 following injection. Total daily wheel-running activity was expressed as a percent...

New Circuit Technologies

“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

• Nature 2020 Oct;586(7827):87-94. doi: 10.1038

- 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.

Capturing and Manipulating Activated Neuronal Ensembles with CANE Delineates a Hypothalamic Social-Fear Circuit

Katsuyasu Sakurai,¹ Shengli Zhao,¹ Jun Takato,¹ Erica Rodriguez,¹ Jinghao Lu,¹ Andrew D. Leavitt,² Min Fu,¹ Bao-Xia Han,¹ and Fan Wang^{1,3,*}

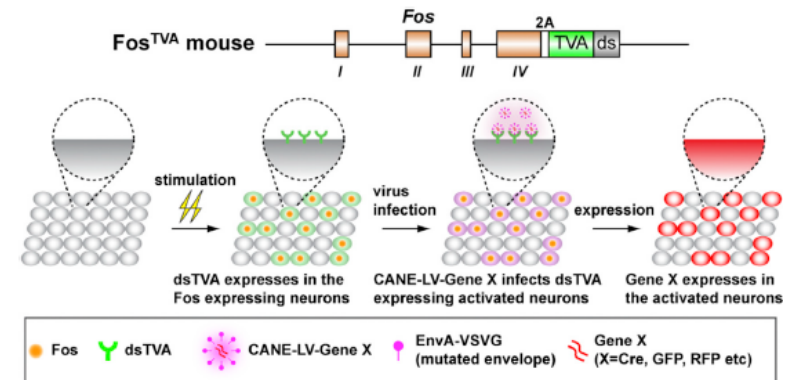
¹Department of Neurobiology, Duke University Medical Center, Durham, NC 27710, USA

²Department of Laboratory Medicine, UCSF, San Francisco, CA 94143, USA

³Lead Contact

*Correspondence: fan.wang@duke.edu

<http://dx.doi.org/10.1016/j.neuron.2016.10.015>



Labeling of active neural circuits in vivo with designed calcium integrators

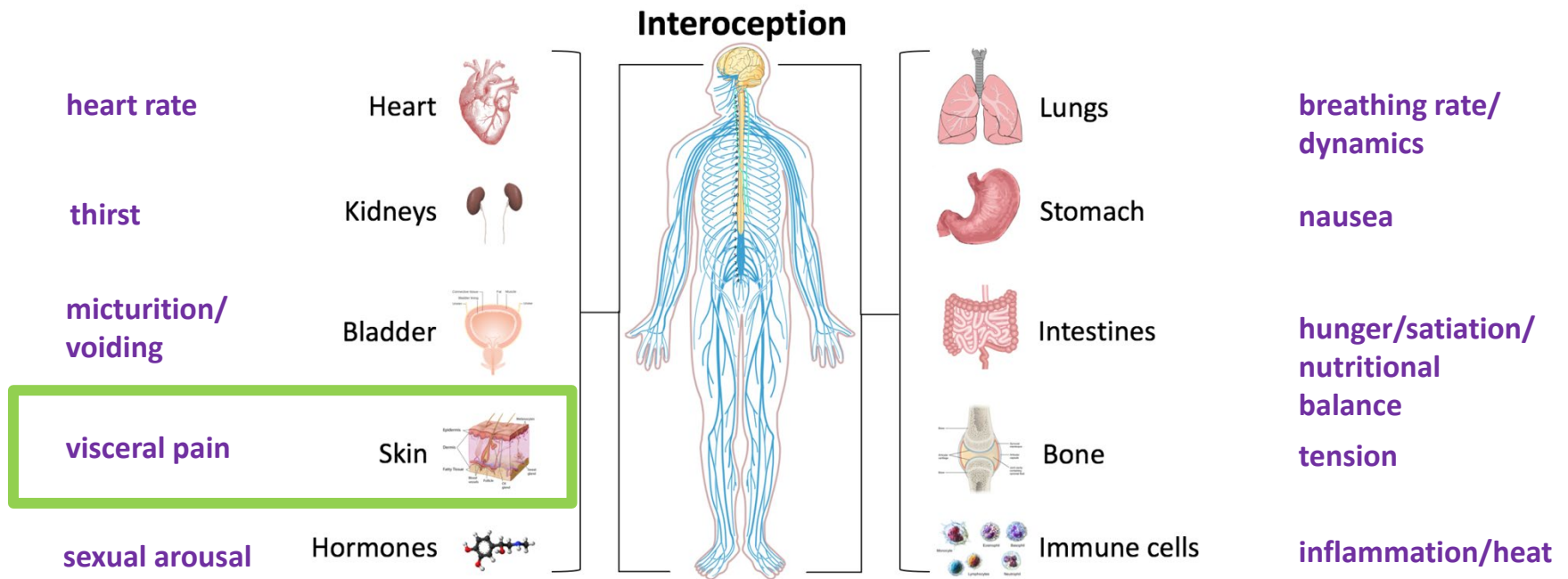
Benjamin F. Fosque,*† Yi Sun,* Hod Dana,* Chao-Tsung Yang, Tomoko Ohyama, Michael R. Tadross, Ronak Patel, Marta Zlatić, Douglas S. Kim, Misha B. Ahrens, Vivek Jayaraman, Loren L. Looger, Eric R. Schreiner†

13 FEBRUARY 2015 • VOL 347 ISSUE 6223

temporally precise “activity snapshot” of a large tissue volume.

Blueprint Interoception Program- Representation and Regulation of the Internal World

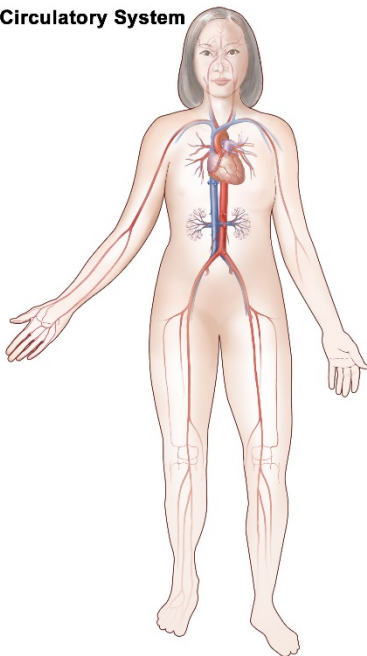
Why we feel the way we do.



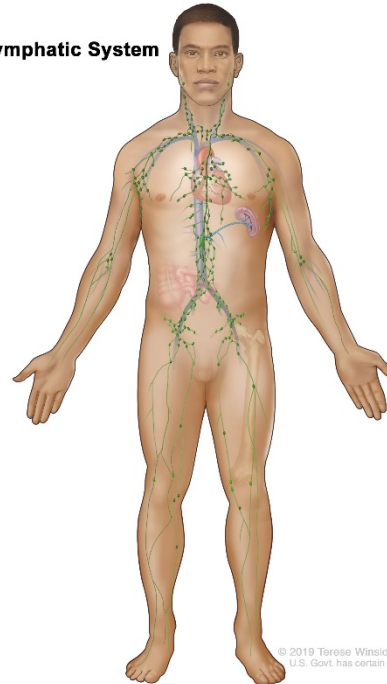
It is about the representation of the internal, not the external world.

Interoception - Representation and Regulation of the Internal World

Circulatory System

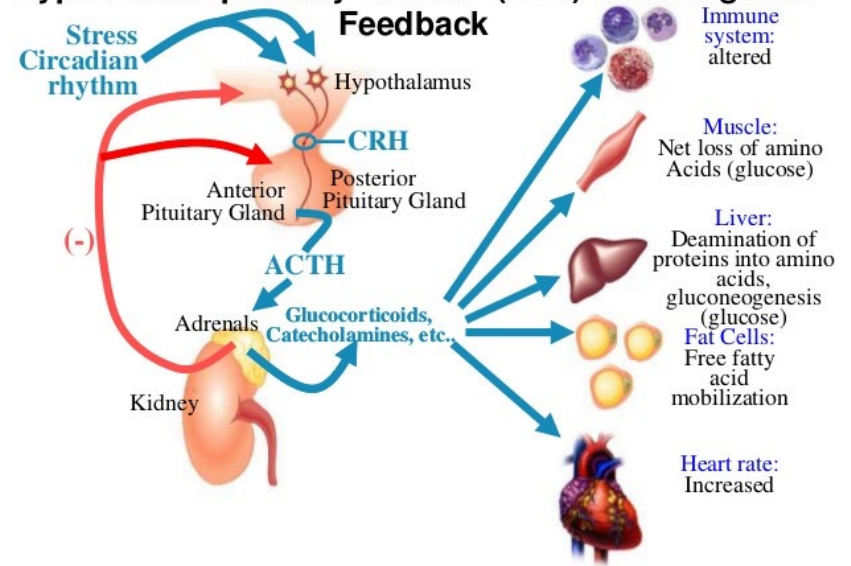


Lymphatic System



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Hypothalampituitary adrenal (HPA) axis: Negative Feedback



NIH Common Fund Program: Stimulating Peripheral Activity to Relieve Conditions (SPARC)

SPARC Primarily Focuses on Local Neural Circuits around Peripheral Organs



➤ \$200 million

- [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](#)

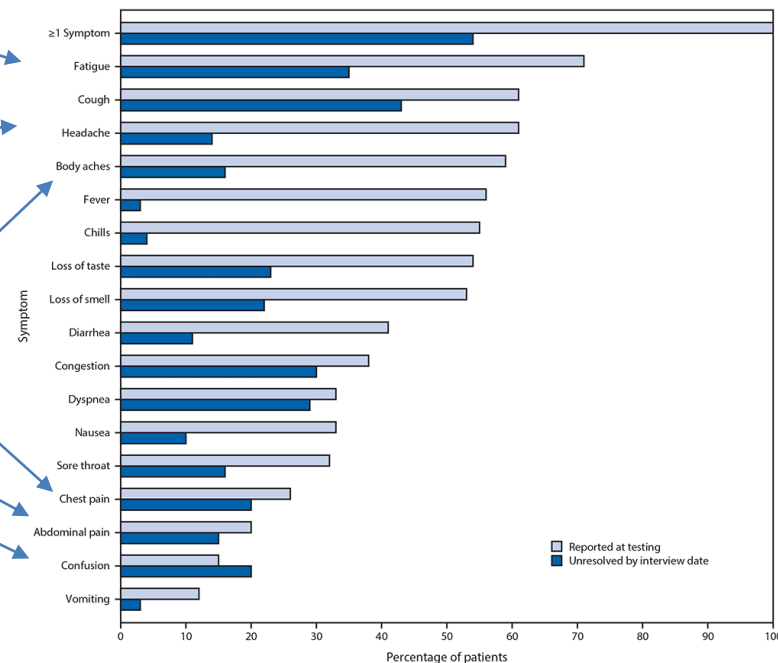
Long term COVID-19 effects on the nervous system

- 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.

CDC study of symptom-duration in outpatients



* 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



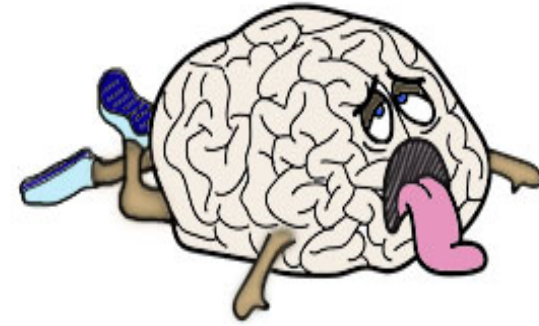
ACUTE INFECTION RECOVERY COHORT

POST-ACUTE INFECTION CASE-CONTROL COHORT

Anticipated Study Sizes

Acute & Post-Acute Infection Cohorts	EHR/Health Sys. records	Autopsy
Pediatric (N=18,500 including up to 1000 MIS-C) Adult (N=17,680 including 2,450 Pregnancy) <ul style="list-style-type: none">Acute (N=9000),Post-acute Prospective (N=3,580), Retrospective (N=5,100)	<ul style="list-style-type: none">70+M records, 3.7M+ with SARS-CoV-2 infection	<ul style="list-style-type: none">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

Restore wakefulness, promote learning and boost memory

Reverse the hormonal impact of a night of poor sleep

Enhance both physical & cognitive performance

Reduce stress and immune perturbations after a short night

Have caffeine right before you nap to improve post-nap alertness and cognitive functioning

