Title

Beyond the symptom: the biology of fatigue.

Journal

SLEEP, 46(9)

Authors

Raizen, David
Mullington, Janet
Anaclet, Christelle
et al.

Publication Date

2023-09-08

DOI

10.1093/sleep/zsad069

Peer reviewed

SLEEP, 2023, 46, 1–13
https://doi.org/10.1093/sleep/zsad069
Advance access publication 24 May 2023
Review

Review

Beyond the symptom: the biology of fatigue

David M. Raizen[1], Janet Mullington[2], Christelle Anaclet[3], Gerard Clarke[4], Hugo Critchley[5], Robert Dantzer[6], Ronald Davis[7], Kelly L. Drew[8], Josh Fessel[9], Patrick M. Fuller[10], Erin M. Gibson[11], Mary Harrington[12], W. Ian Lipkin[13], Elizabeth B. Klerman[14,16], Nancy Klimas[15], Anthony L. Komaroff[16], Walter Koroshetz[17], Lauren Krupp[18], Anna Kuppuswamy[19], Julie Lasselin[20], Laura D. Lewis[21], Pierre J. Magistretti[22], Heidi Y. Matos[17], Christine Miaskowski[23], Andrew H. Miller[24], Avindra Nath[17], Maiken Nedergaard[25], Mark R. Opp[26], Marylyn D. Ritchie[27], Dragana Rogulja[28], Asya Rolls[29], John D. Salamone[30], Clifford Saper[31], Vicky Whittemore[17,*], Glenn Wylie[32], Jarred Younger[33], Phyllis C. Zee[34] and H. Craig Heller[35]

[1]Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA,
[2]Department of Neurology, Harvard Medical School, Boston, MA, USA,
[3]Department of Neurological Surgery, University of California, Davis School of Medicine, Sacramento, CA, USA,
[4]Department of Psychiatry and Neurobehavioural Science, and APC Microbiome Ireland, University College Cork, Cork, Ireland,
[5]Brighton and Sussex Medical School Department of Neuroscience, University of Sussex, Brighton, UK,
[6]Department of Symptom Research, Division of Internal Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA,
[7]Department of Biochemistry and Genetics, Stanford University, Palo Alto, CA, USA,
[8]Department of Chemistry and Biochemistry, Institute of Arctic Biology, Center for Transformative Research in Metabolism, University of Alaska Fairbanks, Fairbanks, AK, USA,
[9]Division of Clinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD, USA,
[10]Department of Neurological Surgery, University of California, Davis School of Medicine, Sacramento, CA, USA,
[11]Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, USA,
[12]Department of Psychology, Neuroscience Program, Smith College, Northampton, MA, USA,
[13]Center for Infection and Immunity, and Departments of Neurology and Pathology, Columbia University, New York City, NY, USA,
[14]Division of Sleep Medicine, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA,
[15]Department of Clinical Immunology, College of Osteopathic Medicine, Nova Southeastern University, Ft. Lauderdale, FL, USA,
[16]Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA,
[17]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA,
[18]Department of Neurology, NYU Grossman School of Medicine, NYC, NY, USA,
[19]University College London, Queen Square Institute of Neurology, London, England,
[20]Department of Psychology, Stockholm University, Stockholm, Sweden,
[21]Center for Systems Neuroscience, Department of Biomedical Engineering, Boston University, Boston, MA, USA,
[22]Biological and Environmental Science and Engineering Division, King Abdullah University of Science and Technology, Thuwal, Kingdom of Saudi Arabia,
[23]Department of Physiological Nursing, School of Nursing, University of California, San Francisco, CA, USA,
[24]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA,
[25]Departments of Neurology and Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA,
[26]Department of Integrative Physiology, University of Colorado Boulder, Boulder, CO, USA,
[27]Department of Genetics, Institute for Biomedical Informatics, Penn Center for Precision Medicine, University of Pennsylvania, Philadelphia, PA, USA,
[28]Department of Neurobiology, Harvard University, Boston, MA, USA,
[29]Rappaport Institute for Medical Research, Technion, Israel Institute of Technology, Haifa, Israel,
[30]Department of Psychological Sciences, University of Connecticut, Storrs, CT, USA,
[31]Department of Neurology, Harvard Medical School, Boston, MA, USA,
[32]Rocco Ortenzio Neuroimaging Center at Kessler Foundation, East Hanover, NJ, USA,
[33]Department of Psychology, University of Alabama, Birmingham, Birmingham, AL, USA,
[34]Center for Circadian and Sleep Medicine, Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA and
[35]Department of Biology, Stanford University and Sleep Research Society, Stanford, CA, USA

*Corresponding author. Vicky Whittemore, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 6001 Executive Blvd., Neuroscience Center, Rockville, MD 20892. Email: Vicky.whittemore@nih.gov.

Abstract

A workshop titled "Beyond the Symptom: The Biology of Fatigue" was held virtually September 27–28, 2021. It was jointly organized by the Sleep Research Society and the Neurobiology of Fatigue Working Group of the NIH Blueprint Neuroscience Research Program. For access to the presentations and video recordings, see: https://neuroscienceblueprint.nih.gov/about/event/beyond-symptom-biology-fatigue. The goals of this workshop were to bring together clinicians and scientists who use a variety of research approaches to understand fatigue in multiple conditions and to identify key gaps in our understanding of the biology of fatigue. This workshop summary distills key issues discussed in this workshop and provides a list of promising directions for future research on this topic. We do not attempt to provide a comprehensive review of the state of our understanding of fatigue, nor to provide a comprehensive reprise of the many excellent presentations. Rather, our goal is to highlight key advances and to focus on questions and future approaches to answering them.

Submitted for publication: February 15, 2023; **Revised:** May 24, 2023

Statement of Significance

This workshop brought together investigators who study fatigue across many different model systems and human diseases to discuss common and divergent approaches to the study of the biology of fatigue. The workshop was significant because it attempted to move beyond discussing fatigue as a symptom but rather to discuss the underlying mechanisms of fatigue. The workshop summary provides a summary of the presentations and important discussions that were held during the 2-day workshop.

Introduction

A workshop titled "Beyond the Symptom: The Biology of Fatigue" was held virtually September 27–28, 2021. The goals of the workshop were to bring together clinicians and scientists who use a variety of research approaches to understand fatigue in multiple conditions and to identify key gaps in our understanding of the biology of fatigue. It was jointly organized by the Sleep Research Society and the Neurobiology of Fatigue Working Group of the NIH Blueprint Neuroscience Research Program. For access to the presentations and video recordings, see: https://neuroscienceblueprint.nih.gov/about/event/beyond-symptom-biology-fatigue.

The presentations and discussions at the workshop attempted to move beyond discussing fatigue as a symptom of disease, but rather to explore the biological underpinnings of fatigue across different human diseases and model systems. The well-attended virtual workshop provided a platform for discussion across human diseases areas and disciplines to provide overall recommendations for future research priorities to further our understanding of the biology of fatigue.

Fatigue in Sickness and in Health

What is fatigue?

The Italian physiologist, Angelo Mosso, stated more than a century ago that the word "fatigue" refers to at least two phenomena, "The first is the diminution of muscular force. The second is fatigue as a sensation". In other words, there is a physical fact that can be measured, and a psychic fact that eludes measurement [1]. Over the past century, measurements of the "sensation" of fatigue were limited to subjective self-reporting. Numerous metrics were developed to measure the severity or intensity of fatigue based on these measures [2].

Scholars have tried to define more precisely different attributes of the sensation that is called fatigue. It is generally agreed that the sensation of fatigue (1) can involve difficulty in *initiating* activity and/or in *sustaining* activity; (2) can occur with physical activity, mental activity, and/or emotional activity; (3) is a diminished ability to perform an activity despite the of motivation to do so; and (4) can involve the perception that the effort required to perform an activity is more than is required. The phenomenon of *fatigue* should be distinguished from *fatigability* (see Box). Fatigue is an internal state that is self-reported. Fatigability refers to decrements in motor or cognitive performance over time. Fatigability may reflect the balance between utilization and restoration of energy resources, that may not correspond to the self-reported sensation of fatigue [3].

To more objectively define the phenotype of fatigue, Marylyn Ritchie (University of Pennsylvania) suggested two approaches related to how the term is used in electronic medical records (EMR). One approach is to formulate a definition using diagnosis and symptom codes (structured EMR variables) along with provider notes (unstructured EMR information) which can be analyzed, for example, using natural language processing [4, 5].

Another approach is to use crowd sourcing in which a group of fatigue experts would be asked to define a fatigue phenotype based on reading medical records. Ronald Tompkins (Harvard), suggested the use of omics (e.g. transcriptomics, proteomics, metabolomics) to describe correlates of fatigue self-reports from patients recovering from critical illness.

Fatigue may have different biological causes and/or mechanisms in healthy people; people experiencing an acute illness; people experiencing chronic organ dysfunction; and people with chronic symptoms *not* clearly linked to organ dysfunction. While underlying biological causes and/or mechanisms may differ, healthy volunteers and those with chronic conditions describe the symptoms of fatigue in similar terms [2]. Factors that worsen fatigue include disrupted sleep, pain, depression, and anxiety. Whether non-refreshing sleep is a cause or consequence of fatigue remains to be elucidated (see below) but it is often intertwined with the symptom of fatigue.

Some characteristics of fatigue vary across disease states [6]. Two examples are: (1) fatigue often worsens with increased ambient temperature in people with multiple sclerosis (MS) but does not increase in systemic lupus erythematosus (SLE), another immunologically-mediated disease. (2) Exercise often worsens fatigue in people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), whereas exercise can be beneficial in individuals with MS-associated fatigue [7, 8].

Psychological contributors to fatigue need to be considered. Fatigue can be reflected in motivational affective states such as anhedonia, loss of appetite, avoidance of social interactions, and reluctance rather than inability to engage in physical activity—in other words low "positive affect". These characteristics can be linked to negative life events as well as with disease. Among individuals with disease-related fatigue, such as those with MS, the sense of "being out of control" is linked to increased fatigue [9].

The mechanisms underlying the *sensation of fatigue* involve both central and peripheral components. Neuroimaging studies found an association between the sensation of fatigue and neuroinflammation in individuals with MS [10], fibromyalgia [11], and ME/CFS [12]. However, given that fatigue is a key component of many conditions that do not affect the structure of the brain, it is reasonable to evaluate for functional networks shared across conditions. This approach could include an evaluation of central and peripheral changes in neural activity, changes in cytokine or other immune factors, changes in metabolites, or changes in brain and/or body temperature as well as energy metabolism.

Exercise-induced physiological fatigue

In the context of physical performance, fatigability is associated with the inability to continue an endurance activity or the inability to produce or sustain maximal muscle contraction. Fatigue and fatigability resulting from high levels of physical performance are adaptive responses that protects the body from consequences of over-exertion such as muscle cell injury, or deterioration of vital homeostatic functions (e.g. maintenance of cardiac output, blood

oxygenation, temperature). Both spinal and supraspinal mechanisms combine to decrease neural stimulation of spinal motor neurons during fatiguing exercise including focal changes in cortical excitation and inhibition in the motor cortex [13]. During fatigue, a variety of intramuscular receptors alter the activity of proprioceptors that project to the spinal cord and brain. Some evidence suggests that motor neurons become less excitable after repetitive contraction of their muscles [14]. In addition, evidence exists of reduced output from the motor cortex [13, 15].

One consequence of muscular overactivity is hyperthermia. Mammals have the capacity to produce heat to dangerous levels. For defense against hyperthermia, that occurs in both endurance and anaerobic activities, the body sweats to increase heat loss. Heat loss is enhanced by increases in blood flow through arterio-venous anastomoses and *rete venosa*—vascular features of the glabrous (non-hairy) skin. Extracting heat from these surfaces can greatly reduce fatigue and fatigability extending endurance in aerobic activities [16], and work volume in anaerobic activities [17, 18].

How does heat cause fatigue? Craig Heller (Stanford) cited evidence that pyruvate kinase (PK), a critical enzyme in energy production, is inactivated by high temperatures [19]. By inactivating PK, rising muscle temperature limits ATP production and decreases the ability of the muscle to exert force, avoiding hyperthermia by producing physical fatigability. This adaptive perspective on fatigability—the reduction in ability to produce ATP as a means of preventing damage may share common underlying physiological mechanisms with maladaptive fatigue that is associated with disorders such as ME/CFS.

Role of sleep and circadian rhythms in fatigue

Endogenous circadian rhythms, that are entrained primarily by environmental light stimuli, involve a hierarchy of biological clocks, including the molecular transcriptional/translational negative feedback loop that exists in virtually every cell of the body. Phyllis Zee (Northwestern) and Elizabeth Klerman (Harvard Medical School) explained that these rhythms are key regulators of overall health due to their role in modulation of sleep/wake cycles, body temperature, cell division, neuroendocrine function, inflammation, oxidative stress, and energy metabolism. The timing and duration of sleep and wake are regulated by the interaction among circadian rhythms and sleep homeostasis [20]. Circadian misalignment (discussed by Klerman), where the positioning of the sleep-wake cycle occurs at inappropriate circadian times (e.g. being awake when the circadian system is promoting sleep), reduces sleep efficiency and daytime alertness, can lead to fatigue, for example, in shift workers.

Sleep disruption, whether due to sleep curtailment or to disorders of sleep and wakefulness, is commonly associated with symptoms of fatigue and daytime sleepiness. The close relationship among sleep, circadian disruption, and fatigue is supported by the finding that interventions such as light therapy and exercise, that can affect both circadian rhythmicity and sleep quality, increase the sense of well-being in healthy individuals and mitigate fatigue symptoms of some disease [21–23].

Although sleepiness and fatigue are closely interrelated, they are different. Sleepiness is the drive to sleep. Athletes after extreme exertion can be physically fatigued, but not sleepy. Changes in resting pupillary stability is used as a measure of sleepiness. Recent work (discussed by Dr. Zee) indicates that pupillometry can detect alteration in the response to light in some patients with fatigue [24, 25]. Objective differentiation between sleepiness and fatigue is vital to establishing management approaches for both disorders of sleep and other conditions in which fatigue is prominent. Complicating the assessment is the fact that most research on sleep disturbances and fatigue are in the context of other medical, neurological, and psychiatric disorders in which both symptoms are common.

Sleepiness and fatigue can be independent consequences of sleep disorders, for example, in patients with insomnia disorder. Despite disruption of their sleep, these patients report mainly fatigue and not sleepiness, thereby distinguishing them from other sleep disorders such as narcolepsy and sleep apnea [26–28], in which sleepiness is a major component. Dr. Zee discussed that while sleep, alertness, and sleepiness can be measured objectively using polysomnography, the psychomotor vigilance task, and the multiple sleep latency test (MSLT), objective measures of fatigue are lacking.

Janet Mullington (Harvard Medical School) explained that cortical electrical signals measured using electroencephalography (EEG) and generated during wakefulness and sleep can be analyzed using Fast Fourier Transform and other quantified signal analytical methods. The nocturnal sleep of healthy sleepers leads to reduced levels of EEG power in the beta (13–30 Hz) and gamma (31–50 Hz) spectral bands measured during wakefulness in the morning compared with evening pre-sleep levels in age-matched patients with insomnia disorder [29]. The lack of reduction in the beta and gamma power brought about by sleep suggests that this change may be a marker of the impairment of the restorative function of sleep in insomnia disorder.

EEG slow-wave activity (delta, 0–4 Hz) power decreases through a night of sleep. Delta power is considered to reflect homeostatic sleep drive since its magnitude is correlated with the duration of prior wakefulness. Delta power at sleep-onset in insomnia disorder patients is lower than in age-matched healthy controls [30], suggesting that the build-up of sleep pressure during the day is reduced in insomnia [31]. In a meta-analysis [32], the investigators summarized EEG studies that show elevated fast activity and reduced delta activity in the EEG during NREM sleep, in insomnia disorder patients. Thus, novel methods of EEG analysis show promise for discovering a biomarker of non-restorative sleep, that is a cardinal feature of insomnia disorder and which characterizes the sleep of ME/CFS patients. Interestingly, in a study of monozygotic twins discordant for ME/CFS, the homeostatic slow-wave response to sleep deprivation was impaired, and patients showed reduced NREM delta power decay across the night, providing further evidence of a deficit in recovery sleep processes associated with symptoms of non-refreshing sleep [33].

One approach to investigate the role of sleep in sleepiness and fatigue is to manipulate sleep experimentally. Individuals are exposed to acute total sleep deprivation and prolonged sleep restriction, to study accrual of neurobehavioral deficits [34]. Several studies investigated subjective wellbeing-and sleepiness indices, as well as hypothalamic-pituitary-adrenal axis, autonomic, and inflammatory system consequences of prolonged sleep restriction and recovery [35–39]. The build-up and recovery of different neurobehavioral [40] and physiological systems are not uniform. For instance, inflammatory system activation due to sleep loss takes multiple days to recover after normal sleep resumes [36]. In addition, fatigue takes multiple days to recover from chronic sleep restriction, particularly in women, whereas sleepiness reverts to baseline levels more quickly [41].

Cancer-related fatigue

Fatigue is one of the most common symptoms of cancer and its treatments [42]. As discussed by Christine Miaskowski (UCSF),

cancer-related fatigue (CRF) is be defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Compared with fatigue experienced by healthy individuals, CRF is more severe, more distressing, and less likely to be relieved by rest" [42].

A large number of cancer-specific instruments exist to measure single and multiple dimensions of the experience of CRF. The majority of the single dimension measures (e.g. Brief Fatigue Inventory) evaluate symptom severity. Multidimensional measures evaluate the physical, mental, and/or cognitive dimensions of CRF. However, no consensus exists on which measure should be used across studies. This lack of uniformity impedes progress in understanding the biology of CRF.

Cross-sectional and longitudinal studies document that young female oncology patients with decreased functional status and higher level of comorbidity report higher levels of CRF [43, 44]. Oncology patients with greater degree of CRF report higher levels of global, disease-specific, and cumulative life stress [45], as well as the co-occurrence of sleep disturbance, depression, cognitive dysfunction, and pain [46–48].

While most studies of CRF report mean severity scores or dichotomize patients into low versus high severity fatigue groups, an emerging literature emphasizes inter-individual variability. Moreover, CRF shows diurnal variation: there are subgroups of patients exist with distinct morning and evening fatigue profiles [44, 47, 48]. Additional studies are needed to determine common and distinct risk factors associated with morning and evening fatigue severity that may tie back to the known circadian and sleep factors associated with fatigue.

The severity of CRF is not clearly associated with disease or treatment characteristics. Separating out the effects of cancer itself from the sequelae of cancer treatments on fatigue requires further investigation.

No objective test is available to evaluate CRF. Most of the research on the mechanisms that underlie CRF has evaluated differences in serum markers of inflammation. CRF may involve impairments in immune, neuroendocrine, mitochondrial, and metabolic function [43, 49]. Exercise is the only effective evidence-based intervention for CRF [50].

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CSF): mechanisms of post-exertional malaise

People with ME/CFS experience a sensation of fatigue that is not alleviated by rest and is accompanied by a reduction in ability to engage in normal levels of daily activities. The fatigue is accompanied by other core symptoms: cognitive impairment, orthostatic intolerance, unrefreshing sleep, and post-exertional malaise (PEM). PEM may be the most specific symptom of ME/CFS in comparison to other fatiguing diseases such as cancer or MS. In PEM, physical, mental, and/or emotional exertion is followed 8–48 h later by a flare of all of these core symptoms, particularly fatigue and cognitive dysfunction [51].

A variety of abnormalities are identified in ME/CFS including immune activation, autoantibodies of undetermined function, redox imbalance, defective energy metabolism, and dysbiosis of the gut microbiome; (see two recent review articles [52, 53]).

Attempts to explain the mechanisms of PEM have focused primarily on PEM triggered by physical exertion, using the cardiopulmonary exercise test (CPET) protocol. CPET assesses the ability of the heart, lungs, and muscles to deliver and use oxygen to produce energy for work. CPET provides an objective and reliable measure of energy production ability. A 2-day CPET protocol provides more information about the underlying mechanisms of PEM than a single CPET session. The first CPET (CPET-1) measures baseline functional capacity (energy producing capacity), the CPET-2, typically completed 24 h after test 1, assesses the effects on functional capacity of PEM that was provoked by CPET-1 [54]. This finding was confirmed by a recent meta-analysis of five studies [55]. In patients with ME/CFS, results from the CPET-2 protocol typically include a marked decline in functional capacity in comparison to CPET-1 or normative values from healthy individuals. CPET data demonstrate abnormal hemodynamic and ventilatory responses to exercise and/or abnormally low energy producing capacity in patients with ME/CFS compared to normative values for healthy people of similar age and gender—particularly a decline in work rate at ventilatory threshold [56]. In case-control studies of ME/CFS, physical exertion was found to produce intense and durable fatigue [57], as well as cognitive impairment [58]. Other measures of the effects of exercise on ME/CFS patients are elevated in comparison to controls. These measures include oxidative stress [59], nitrosative stress [60], muscle acidosis [61], lactate elevation [62], and central sensitization [63].

Summary of fatigue in sickness and in health

Both normal and pathology-associated fatigue involves disruptions in homeostatic processes—from temperature regulation, energy metabolism, and sleep and circadian rhythms to immune functions. Fatigue may be a biological protector of physiological homeostasis that can be altered in pathological states. Given evidence that fatigue can be an adaptive response to normal challenges such as hyperthermia, anoxia, and caloric restriction, pathological fatigue associated with an underlying disease may arise from exaggerated and maladaptive expression of the same physiological modifiers of homeostatic processes.

For example, fatigue during physical performance is an adaptive response to protect the muscle or the body from damage due to hyperthermia. Other inducers of fatigue—such as hypoxia, caloric restriction, or sleep loss—can also be considered as adaptive responses within a range of physiological conditions and functions across varying timescales from diurnal to annual. Outside that range, these fatigue-related changes in physiology and behavior may be maladaptive. Therefore, a question arises as to whether common mechanisms of fatigue exist that could be playing a role in a variety of medical conditions. When the organism needs to consolidate, rest, or recover, specific behaviors may be implemented to re-set the homeostatic states associated with energy metabolism. Goal-oriented types of behaviors that consume energy may understandably be suppressed.

Theoretical Mechanisms of Fatigue

There are multiple theories on the mechanisms that underly fatigue. Common potential mechanisms of fatigue onset and progression discussed in the workshop included: immune dysfunction, metabolic dysfunction, interactions between the gut and the brain, and abnormal sleep-wake physiology.

The sensory attenuation hypothesis

Anna Kuppuswamy, (University College, London) proposed a "sensory attenuation" hypothesis for the pathogenesis of fatigue. Fatigue is present when one perceives that a greater effort than expected is required to complete a task. Sensory input from a contracting muscle is a source of perceived effort in a physical task.

Self-generated muscular contractions of low force characterize most activities of daily living. Such self-generated contractions activate proprioceptive sensory signals. In most people, these signals are down-weighted ("sensory attenuation") and everyday activities feel effortless. In contrast, in patients with fatigue, a failure of attenuation occurs and everyday activities feel effortful. Both behavioral and neurophysiological experimental evidence in people with strokes support poor sensory attenuation as the basis of greater perceived effort in physical tasks [64].

Fatigue may be triggered when a person feels overwhelmed by sensory stimuli. Normally the brain can switch attention from irrelevant distractors to focus attention on a desired task. In this case, it is visual, auditory, and other sensory stimuli that are down-weighted. It is plausible that the sensation of being overwhelmed by sensory stimuli arises from a defect in attenuation [65]. Resting state studies in stroke, MS, Parkinson's disease, and traumatic brain injury reveal abnormalities in salience network activity that indicate reduction in the down-weighting of distractor signals that interfere with the ability to attend to the task at hand.

The immune system and fatigue

Several presenters provided insights into the potential roles of immune dysfunction including cytokine production and impairment of energy production through mitochondrial dysfunction in fatigue. Ian Lipkin (Columbia University), reported that patients with ME/CFS have higher circulating cytokine levels in the first three years of illness [66], and impairments in their ability to generate energy through the mitochondrial tricarboxylic acid (TCA) cycle [67–69]. Similarities in clinical features of patients with ME/CFS and other illnesses associated with fatigue, including sequelae of COVID-19 infection, suggest that similarities exist in pathophysiology [52]. Exploiting opportunities for synergistic research efforts across syndromes may lead to important insights.

Maureen Hanson (Cornell University) highlighted evidence of altered immune cell function and immune signaling in ME/CFS, both from an examination of immunometabolism and signaling proteins present in plasma and in extracellular vesicles [70, 71]. Several speakers emphasized that infectious agents that trigger immune responses lead to fatigue acutely and that the immune response promotes the progression to chronic fatigue. Dr. Lipkin noted that fatigue syndromes were reported following infection with Herpes viruses, Corona viruses, Ebola viruses, West Nile virus, the virus that causes Dengue fever, Enteroviruses, *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, *Giardia lamblia*, *Coxiella*, and *Candida* species. Among the theories about fatigue syndromes that follow infection is that the fatigue results from an abnormal host responses to the infection. Another possibility is that a cryptic chronic infection may generate fatigue and other symptoms.

Mark Davis (Stanford University) discussed immune dysfunction as it relates to T-cells. He suggested that one cause of fatigue may be an infectious disease that gives rise to autoreactive lymphocytes that degrade energy metabolism to produce common symptoms of fatigue. The existence of this T cell circuitry suggests that modulating the activity of the regulatory cells may have a therapeutic effect.

Asya Rolls (Technion-Israel Institute of Technology), presented a novel approach to bridge the gap between the evidence that immune activity in peripheral tissues affects fatigue, yet, the feeling of fatigue, is generated by the brain. How does the brain detect and represent the state of the immune system? She discussed how body awareness, also known as interoception, enables the organism to detect sensory inputs representing the condition of the body (such as hunger, pain, hypoxia, and potentially fatigue) and to execute corrective responses to maintain homeostasis. The brain, and specifically the insular cortex, a site of interoception [72–74], receives multiple layers of information from the body (e.g. tissue damage, metabolism, temperature,.), that it can integrate with other sensory (e.g. hunger, thirst, hedonia) and cognitive inputs (e.g. potential threats in the environment, past experiences) to trigger a corrective response. Changes in insula activity were associated with fatigue in patients with autoimmune disease$_{74}$ and immune reactions are registered by the insula in mice as well as in humans. The insula neurons project to autonomic nervous system control sites (dorsal motor nucleus of the vagus, rostral ventrolateral medulla). Remarkably, activation of these insular neurons can modulate peripheral immune responses. In addition, inhibition of the insular cortex alleviates inflammation in a murine inflammatory colitis model [75], suggesting a psycho-somatic interaction. Given the associations between fatigue and inflammatory conditions, it is plausible that "immunoception" may contribute to the generation of fatigue.

Gut-brain axis in fatigue

Dragana Rogulja (Harvard Medical School) discussed how gut oxidation is a major consequence of sleep loss. Experimental manipulations in *Drosophila* can eliminate the homeostatic response to sleep deprivation [76], but not the consequences of sleep loss observed in the gut [77].

Gerard Clarke, (University College, Cork) noted that the microbiota-gut-brain axis regulates behaviors and physiology relevant to fatigue and that this effect is possible via microbial regulation of the brain circuits involved in reward and motivation [78, 79]. Plausible biological pathways underpinning these observations relate to the interface between neuroinflammation and tryptophan metabolism [80]. The elaboration of mechanisms, translational research efforts, and the establishment of causality holds potential for the incorporation of microbial-based interventions into the management of fatigue. Both Drs. Lipkin and Hanson found that ME/CFS patients had a decrease in butyrate-producing bacteria in their gut [81, 82]. Dr. Hanson pointed out that the loss of these bacteria is common to a number of chronic illnesses.

The metabolic trap hypothesis

Ron Davis (Stanford University) described a "metabolic trap" hypothesis that could explain the energy deficiency in ME/CFS and perhaps other chronic fatigue conditions. This hypothesis focuses on the enzyme IDO1 that catalyzes the conversion of tryptophan to kynurenine. Kynurenine is an important contributor to the production of NAD, that is critically involved in production of ATP. IDO1 has the unusual property of being inhibited by high levels of its reactant, tryptophan. Normally, an enzyme is facilitated by high levels of its reactant, therefore, in this unusual metabolic trap situation, high levels of tryptophan shut down the enzyme and the production of kyurenine. Shutting down kyurenine production, due to its effects on NAD levels, may compromise energy metabolism.

Brain energy metabolism

Pierre J. Magistretti (King Abdullah University of Science and Technology) noted that neuronal metabolism depends on a unique energy source—lactate—supplied to the neurons from astrocytes [83]. Therefore, mental fatigue may result from insufficient lactate produced by astrocytic aerobic glycolysis to feed the neuronal mitochondria activity. In addition, lactate functions both as an energy substrate and as a signaling molecule

for long-term memory consolidation and its cellular substrates [84], and is involved in depression [85], and sleep regulation and possibly in ME/CFS.

Summary of theories for mechanisms of fatigue

A discussion occurred on whether targeting individual cytokines would be useful. While it was recognized that anti-TNF and anti-alpha interferon treatments can affect sleep patterns and may improve fatigue in some conditions (Andrew Miller, Emory University), many human conditions are complex with multiple pathways being activated. Therefore, targeting single cytokines may not have the desired effect as was observed with sepsis (Mark Opp, University of Colorado, Boulder).

The issue of autoreactive T and B cells was discussed. It was suggested that single cell sequencing may allow identification of the specific T and B cell receptors and help to identify the reactive antigen. Repeated infections may lead to the development of autoreactive immune cells in some individuals (Mark Davis, Stanford University). The duration of the illness may dictate the immune response, which may differ in the early versus the late phase of the illness. This phenomenon can be studied in the post-acute sequel of SARS-CoV-2 infection patients (Nancy Klimas, Nova Southeastern University). Prolonged duration of an immune disorder may lead to epitope spreading and energy failure among other things (Mark Davis). It is possible that the pathophysiology of fatigue in autoimmune conditions and cancer, in which a much stronger association exists between immune abnormalities with fatigue, are different from those in ME/CFS, where the link is weaker.

Fatigue as a Component of Sickness Behavior

An approach to study fatigue circuits in the brain, and the molecules that activate them, starts with the observation that fatigue is observed across a wide spectrum of diseases that involve some degree of immune system activation. Examples of immune system activation-associated conditions include infection, multiple sclerosis, cancer, depression, ME/CFS, and rheumatoid arthritis. Currently, how (and where) in the brain peripheral immune activation is sensed involves animal models and some human studies. Although fatigue, as a subjective symptom, cannot be directly studied in animals, it is possible to study sickness behavior, that is correlated with fatigue. Sickness behavior can be induced by injecting bacterial cell wall components or by studying mice bearing tumors [86], or ones with infectious disease [87]. Sickness behaviors in humans and other animals is a constellation of behaviors including reduced movement, reduced feeding/eating, anhedonia, and social withdrawal [88]. The translatability of sickness behavior provides a unique way to study fatigue in humans and animals.

Julie Lasselin (Stockholm University) and Andrew Miller (Emory University) set the stage for the human work by discussing the effects of immune cell activation on fatigue in humans. Lasselin uses the bacterial cell wall component lipopolysaccharide (LPS) to activate an acute immune response and induce sickness behavior in otherwise healthy human volunteers. Advantages of this LPS model include its defined time course of sickness and its inherent translatability to animal models of fatigue [89]. A cognitive task that appears affected in fatigued individual is the "Effort Expenditure for Reward" task. In this task participants are offered a choice between engagement in a low effort/low monetary reward task and in a high effort/high monetary reward task. Fatigued individuals due to LPS injection showed an increased willingness to expend more effort to receive more reward [90], while a decrease in incentive motivation was found in another study using the same model but a different task [91]. This highlights the role of contextual factors in adaptive, physiological fatigue induced by inflammation. Andrew Miller (Emory University) reviewed studies demonstrating an association between the inflammatory cytokine interferon alpha (IFN-α) and fatigue [92], LPS and fatigue [93], and typhoid fever vaccine and fatigue [94]. Neuroimaging studies of participants performing a hedonic gambling task showed reduced ventral striatum activation following IFN-α injections and the induction of fatigue. IFN-α treatment was associated with reduced striatal dopamine release in non-human primates. In addition, functional MRI evidence suggests that connectivity of motivational circuitry was decreased in the setting of systemic inflammation. He speculated that inflammation in the brain affects neural circuits that mediate the willingness to expend effort for reward. Increased metabolic demands of an activated immune system may be communicated to subcortical brain structures such as the striatum, resulting in reduced exploratory behavior.

Robert Dantzer (MD Anderson) suggested studying fatigue behavior in animals by assessing two aspects of fatigue; First, reduced physical activity aspect of fatigue can be operationalized as a reduced willingness to participate in effortful activity. In practice, this effect can be assessed by measuring rodent voluntary wheel running activity (VWRA). Second, the motivational aspect to fatigue may reflect the reduced effort for perceived reward. In rodents, motivational change can be captured by measuring the degree that a rodent is willing to work to earn reward using a progressive ratio schedule of effort for food reward. Dantzer showed that the effects of systemic inflammation caused both reduced VWRA and reduced motivation for reward, therefore, the effects of an implanted tumor only reduced VWRA and not motivation for reward [86].

John Salamone (University of Connecticut) discussed another behavioral assay in which the rodent makes a choice between low effort/low reward and high effort/high reward. He summarized data suggesting that dopaminergic neurotransmission is required for the high effort/high reward choice. Tetrabenazine, a drug that depletes dopamine by blocking vesicular storage induces fatigue in humans and can be studied for behavioral effects in rodents. Dr. Salamone summarized data suggesting that tetrabenazine specifically affects the willingness of the animals to work for food and does not affect hedonic aspects of food choices [95]. The effort-related work for reinforcement assay can be used to study the pharmacology of fatigue. He presented data on the effects of cytokines, as well as drugs that affect dopaminergic and adenosinergic neurotransmission (A_{2A} receptor antagonists), on the decision by rodents to exert physical effort to get a reward [96].

Mark Opp (University of Colorado, Boulder) suggested that infection may trigger fatigue and its progression. He described features of mice infected with murine gamma herpes virus 68 (γHV68) that makes them a useful model for fatigue. The impact of γHV68 infection in mice on physiology and behavior differs between the acute, infectious period in the lung and chronic infection in the spleen. During the acute stage, VWRA is reduced and Non-REM sleep is increased. However, these changes are not characteristic of the chronic stage (latent infection). However, LPS challenge during the chronic infection stage produces a profoundly exaggerated behavioral response. These mice seem to manifest the behavioral correlates of fatigue.

Two recent publications using mice identified neurons in the hypothalamic ventral medial preoptic area (VMPO) [97], and the brain stem area postrema [98], that are activated by LPS and orchestrate some components of sickness behavior. These neurons serve as hubs to integrate immune signals and orchestrate multiple sickness symptoms in response to infection [97]. The discovery of these nuclei in mice may help to understand the linkage between inflammatory markers and fatigue.

Since sickness behavior is conserved across all animals, it is possible to study this behavior in invertebrates, which offer the ability to perform rapid genetic manipulations and use unbiased genetic discovery approaches. David Raizen (University of Pennsylvania) discussed converging research using *Drosophila melanogaster* [99], and *Caenorhabditis elegans* [100], that demonstrated key roles for anti-microbial peptides (AMPs) as signals to the brain to induce sleep behavior during sickness. The *C. elegans* research demonstrated that 17 distinct AMPs must be simultaneously eliminated before a defect in sickness behavior is detected [100]. This high degree of genetic redundancy speaks to the evolutionary importance of sickness behavior. Recent research led to the identification of central nervous system peptidergic neurons that play key roles in sickness behavior in invertebrates [101, 102].

Kelly Drew (University of Alaska) presented another animal-model based approach for understanding fatigue by studying the biology of hibernation. Hibernation is an energy-conserving adaptive behavior. She proposed that fatigue may limit physical and mental energy to serve a metabolic function in the setting of resource limitation. Although humans do not hibernate, they do sleep longer during the winter [103]. She discussed the role of adenosine signaling in the regulation of hibernation and suggested that the role of purinergic signaling and metabolic changes in general should be studied in relationship to fatigue. She mentioned that tanycytes lining the brain ventricles may play a role in fatigue since they are positioned to regulate body–brain communication. It is of interest that a "torpor nucleus" has been identified in mice [104–106].

Neuroanatomy of Fatigue

In contrast to studies in mice, our understanding of the neural circuits mediating the sensation of fatigue in humans remain poorly described. One approach to identify the brain region(s) that play a role in human fatigue involves the analysis of patients who experienced discrete brain lesions such as those who have had a stroke, MS, Parkinson's disease, and/or traumatic brain injury (TBI). The thalamus, basal ganglia, and frontal and parietal lobes, that subserve aspects of attention, are considered areas of interest and data exist to support their role in fatigue [107, 108]. The lesion-based approach for understanding fatigue circuitry has not been productive. Fatigue in neurological/neurovascular diseases is not explained by disease severity, lesion location, neuroinflammation or motor and cognitive deficits [109, 110].

A second approach to understanding the neural circuitry of fatigue is the use of functional neuroimaging approaches. The use of fMRI has revealed that brain regions implicated in fatigue include the striatum, the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), the ventro-medial prefrontal cortex (vmPFC) and the anterior insula [111]. The existence of this network of fatigue-related areas supports the importance of interoception (the insula), motivation and reward (the striatum and vmPFC), and cognitive control (DLPFC) in fatigue. Research needs to assess connectivity between these regions. In addition, the thalamus, basal ganglia, and frontal and parietal lobes sub-serving aspects of attention are considered areas of interest, with data to support a role in fatigue [107, 108].

Jarred Younger (University of Alabama at Birmingham) discussed functional neuroimaging tools used to study fatigue in healthy and in clinical populations. These tools include positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI). Arterial spin labeling (ASL) is a form of fMRI that can show abnormal hypoperfusion or hyperperfusion. Pharmacological MRI (phMRI), which involves administering intravenous drugs during fMRI imaging, can reveal CNS mechanisms of drug action.

Hugo Critchley (University of Sussex) discussed psychomotor slowing as a behavioral proxy for fatigue. Psychomotor slowing involves motor (e.g. reduced activity), speech (e.g. reduced speech production), and cognition (e.g. increased reaction time on cognitive tasks) behaviors. Neuroimaging studies implicate the anterior insula in the interoception of somatic autonomic states [112]. Following typhoid fever vaccination, which causes systemic inflammation, anterior insula activity is correlated with changes in fatigue score changes [94]. Critchley speculated that the systemic inflammation could be communicating with the brain via the vagal nerve and/or via cytokine action in circumventricular organs. In contrast, reaction time slowing, which was correlated with levels of the pro-inflammatory cytokine interleukin 6, was associated with reduced activity of the substantia nigra as assessed with fMRI.

Glenn Wylie (Kessler Foundation) discussed networks of fatigue-related areas of the brain. Using a task to induce the fatigue state in people with MS, they found fMRI evidence of activation of the anterior insula, the ventro-medial prefrontal cortex, the dorsolateral prefrontal cortex, and the ventral striatum. Activation of these same brain regions was associated with fatigue in other conditions. Fatigue also affected structural connectivity [113] and functional connectivity [114] between these areas.

Patrick Fuller (University of California, Davis) and Christelle Anaclet (University of California, Davis) focused on understanding the neural circuitry that controls sleep and wake. Virtually every aspect of an animal's physiology is regulated by the hypothalamus. Therefore, it is a plausible hypothesis that fatigue involves hypothalamic circuits. Interestingly, the posterior hypothalamus makes extensive anatomical connections with the anterior insula discussed above. Viral- or experimental-induced lesions restricted to the posterior hypothalamus/supramammillary region produce marked reductions in the level of arousal [115]. If it is possible that a reduced level of arousal contributes to fatigue or is a manifestation of fatigue; further investigation of the underlying role of this hypothalamic arousal circuitry is warranted. Studies implicate GABAergic neurons in the parafacial zone as strongly sleep-promoting. In addition, the brain stem's involvement in sleep regulation suggests that it may be involved in fatigue. When the parafacial zone is experimentally activated, the resulting slow-wave sleep can reverse certain deficits associated with aging and neurodegeneration. Whether a similar manipulation can treat fatigue and non-refreshing sleep (such as that observed in ME/CFS) remains unknown.

While most work associated with neural correlates of fatigue has centered on neuronal populations, glia are understudied in relation to fatigue. Microglia serve multiple functions: they are the resident immune cells of the CNS and play a role in sculpting and pruning synapses. Microglia are dysregulated in most

neurological and neuroimmune disorders such as MS [116, 117]. Astrocytes are vital to energy homeostasis and control of neural excitability and waste clearance throughout the brain [118, 119]. Oligodendrocytes, the cells that produce myelin, that is necessary for proper neural conduction and metabolic support of axons, are commonly dysregulated in fatigue-associated disorders like MS [120].

The brain glymphatic system may be involved in mediating fatigue. This system was shown to facilitate macromolecular toxin clearance from the sleeping brain [121, 122]. Maiken Nedergaard (University of Rochester) showed the relationship between tracer spread in the brain and the spectral power in delta EEG frequencies. Anesthetics that cause the highest delta power (e.g. ketamine/xylazine), promote the greatest tracer spread. Her group found that NREM sleep is characterized by oscillatory increases in the vasoconstrictor, norepinephrine [123], and speculated that slow vasomotion is a key driver of glymphatic waste clearance based on human neuroimaging studies [124]. These data supported the hypothesis that one reason fatigued individuals such as those with ME/CFS complain of non-refreshing sleep is both that the refreshing part of NREM sleep and glymphatic clearance is impaired. Such a hypothesis is potentially testable in pre-clinical and clinical studies by combining glymphatic manipulations with measures of cognitive functions.

Laura Lewis (Boston University) showed evidence for coupling among neural activity, brain metabolism, and CSF fluid flow during sleep [125]. She suggested that multiple mechanisms exist by which CSF dynamics and waste clearance may be impaired including disruption of neural, glial, vascular, and fluid dynamics [126] that may contribute to non-refreshing sleep.

General Discussion and Promising Future Directions

During the discussion period, several suggestions were made for future research. While post-acute sequelae of SARS-CoV-2 infection (PASC) is a devastating consequence of the SARS-CoV-2 infection, it represents an opportunity to study the pathophysiology of fatigue, because these patients experience a defined viral infection and can be followed from the acute infectious phase to the chronic post infectious phase. Host responses can be more easily discerned. This condition provides an opportunity to address the question of a persistent viral infection that may be driving host immune responses. Direct comparisons can be made between PASC patients and patients with ME/CFS, Gulf War illness, and chronic Lyme disease. Are there biological variables that predict fatigue in long COVID-19 patients?

Other discussion points included: (1) understanding mechanisms for sex differences in fatigue; (2). understanding non-refreshing sleep, that may illuminate both our understanding of fatigue as well as our understanding of sleep function; (3) the role of metabolism, and in particular immunometabolism in fatigue; and (4). the role of particular metabolites such as lactate in signaling in both muscle and in the brain warrants further study. The workshop participants identified the following areas for future research:

Instruments to measure the sensation of fatigue

It would advance research if investigators studying the self-reported sensation of fatigue could agree on the use of a small number of standardized instruments for this purpose. The instruments would distinguish the various *attributes* of the sensation of fatigue such as an inability to initiate movement, a lack of drive to act, a perception of exaggerated effort. Each of these attributes may turn out to have different biological causes and may benefit from different therapies. Having standardized instruments would enable comparison between fatigue and fatiguability in different diseases and in different studies.

Biomarkers of mechanisms for the sensation of fatigue

Further research is needed to identify biomarkers and mechanisms associated with the different attributes of the sensation of fatigue. The associations may include neuronal network changes, as well as genetic, biochemical, immunological, microbiomal, and metabolic alterations that could be detected with omic-based approaches. Work in pre-clinical animal models may facilitate the identification of these biomarkers.

Identifying common mechanisms

Studies are required to compare and contrast similarities and differences in self-reported attributes of fatigue, biomarkers, and mechanisms associated with these attributes, in healthy people and those with various disease states.

Understanding mechanism of physiological neuromuscular fatigability

Improving our understanding of normal fatigability will lead to a better understanding of pathological fatigability and pathological fatigue.

Developing animal models to study observable correlates of fatigue

Development of novel animal models and continued use of animal models currently used in biomedical research (including mice, zebrafish, fruit flies, and round worms) would be powerful for genetic manipulations and neural circuit analysis.

Determining risk factors for, and prediction models of, fatigue

Determining risk factors for fatigue and predictive indicators of fatigue will require the collection of additional data about biopsychosocial variables, past and current medical history, and other factors, along with the instruments to assess fatigue and various biomarkers linked to fatigue. Appropriate study populations should be recruited. Both longitudinal and cross-sectional protocols should be conducted.

Determining the underlying mechanisms for inter-individual variability in fatigue severity

A variety of molecular mechanisms within the peripheral and central nervous systems may contribute to inter-individual variability in the sensation of fatigue. These mechanisms warrant evaluation across chronic conditions.

Distinguishing perception from motivation

Perception and the processing of sensory signals in those regions of the brain that first receive the signals are largely ignored in the study of fatigue. This area of research is important because such first-order sensory processing influences further downstream processing, including motivation and motivated behavior—and motivated behavior is linked to fatigue. This work should be done in multiple study populations.

Distinguishing acute vs. chronic fatigue

While common mechanisms underly fatigue across conditions, it is probable that acute and chronic fatigue have different mechanisms. For example, acute fatigue is often related to high levels of inflammation and demotivated behavior. In contrast, this mechanism does not appear to be true for the chronic fatigue experienced by patients with neurological diseases.

Use of new technologies to study fatigue

New technologies such as ambulatory EEG and wearable technology to monitor autonomic function and activity should be deployed in multi-day studies of various conditions characterized by fatigue in multiple populations.

Understanding interoception

An improved understanding of how the brain represents internal states such as sleepiness, hunger, hypoxia, thirst, and others would advance our understanding of how the brain represents fatigue in adaptive and pathological states. This research should be done in different populations.

Measurements of changes in the brain that are associated with improvement in fatigue

Another way to understand the underlying mechanisms of fatigue is to identify changes in the brain that are correlated with improvement from various therapies: yoga, mindfulness, cognitive behavioral therapy, meditation, adaptation of energy conservation techniques, techniques that help individuals to develop an increased sense of control over their immediate situation, pharmaceuticals and other interventions. This should be done in different populations and in acute and chronic fatigue conditions.

Concluding Remarks

Fatigue research has not yet established itself as a distinct field of scientific inquiry. A large number of researchers are studying fatigue from different theoretical and experimental perspectives. Therefore, insights gained from this workshop should provide a foundation for continued research efforts on understanding the biology of fatigue.

BOX 1: DEFINITIONS

Fatigue: a person-reported internal state.

Physiological fatigue: an internal state that prevents over-exertion and allows re-allocation and restoration of energetic resources. Physiological fatigue is alleviated by rest and/or sleep. Examples: fatigue due to physical activity, mental effort, sleep deprivation, infection.

Pathological fatigue: Pathological fatigue that is not eliminated, though may be partially alleviated, by rest and/or sleep (non-restorative sleep). Examples: fatigue in ME/CFS, rheumatological disease, multiple sclerosis, Parkinson's disease, PASC.

Fatigability: an externally measured decline in performance (neuromuscular or mental) with time. Examples: Weight lifting, running, psychomotor vigilance task, wakefulness.

Sickness behavior: Physiological, adaptative response to sickness or injury. Responses can include social withdrawal, reduced feeding, hyperalgesia, anhedonia, and increased sleep. Example causes: trauma, chemotherapy, bacterial or viral infection.

Acknowledgments

This report was written by experts who attended and presented at the workshop. Opinions expressed by the authors, however, do not represent the policy or position of the NIH. We are grateful to the NIH Blueprint Neuroscience Research Program for their financial support of the workshop.

Funding

David M. Raizen is funded by the National Institute of Neurological Disease and Stroke (NINDS) of the National Institutes of Health (NIH) under award number: R01NS122779 and by a Department of Defense (DoD) under award number W81XWH-22-1-0069. Janet Mullington is funded by the National Heart, Lung, and Blood Institute (NHLBI) of the NIH under award number: R01HL125379. C. Anaclet has no Financial or Non-Financial Disclosures; she is funded by NINDS of the NIH under award number: R01NS073613 and by the BrightFocus Foundation. Christelle Anaclet is funded by NINDS of the NIH under award number: R01NS073613 and by the BrightFocus Foundation. Robert Dantzer is funded by the National Cancer Institute (NCI) of the NIH under award number: R01 CA193522. Ron Davis receives funding from the Open Medicine Foundation, the ARPA Foundation, donations from patients and caregivers, and is funded by the National Institute of Allergy and Infectious Diseases (NIAID) of the NIH under award number: R01AI139550. Kelly L. Drew and has received research support from Be Cool Pharmaceutics for work unrelated to this project and is funded by the National Institute of General Medical Sciences (NIGMS) of the NIH under award number: P20GM130443. Patrick M. Fuller is funded by NINDS of the NIH under award numbers: R01NS103161 and R01NS073613 and by NHLBI of the NIH under award number: P01HL149630. Erin M. Gibson is funded by NCI of the NIH under award number: R21CA267135, by NINDS of the NIH under award number: R01NS126610, and the DoD under award number: W81XWH2110846. Mary Harrington is funded by the NIGMS of the NIH under award number: R15 GM126545. W. Ian Lipkin is funded by NIAID of the NIH under award number: U54AI138370-06. Elizabeth B. Klerman is funded by NINDS of the NIH under award numbers R01-NS099055, U01-NS114001, R01-NS114526-02S1, by the National Institute of Aging (NIA) of the NIH under award number: U54-AG062322, by the National Institute of Drug Abuse of the NIH under award number R21-DA052861, by the National Institute of Child Health and Human Development (NICHD) of the NIH under award number: R01-HD107064; by the DoD under award number: W81XWH201076; and by the Leducq Trans-Atlantic Network of Excellence On Circadian Effects in Stroke. Anthony L. Komaroff is funded by NIAID of the NIH under award number: 1U54AI138370. Anna Kuppuswamy is funded by Wellcome Trust under award number: 202346/Z/16/Z. Lauren D. Lewis is funded by NIA of the NIH under award number: R01AG070135, by the National Center for Complementary and Integrative Health (NCCIH) of the NIH under award number: R01AT011429, and by NINDS of the NIH under award number R21NS123412. Maiken Nedergaard is funded by NINDS of the NIH under award numbers: RF1NS110049 and U19NS128613 and by NCCIH of the NIH under award number: R01AT011439. Mark R. Opp is funded by the NIA of the NIH under award number: R01AG064465, and by the DoD under award number: W81XXWH221084. Dragana Rogulja is funded by The New York Stem Cell Foundation. A Rolls is funded by the European Research Council (ERC) STG-NEIMO. John D. Salamone is funded by the National Institute of Mental Health (NIMH)

of the NIH under the award number: R01MH121350, and by Otsuka, and the University of Connecticut Research Foundation. Clifford Saper is funded by NINDS of the NIH under award number: R01 NS072337, by NIMH of the NIH under award number: R01 MH112714, by NHLBI under award number: P01 HL149630, and by a subcontract from the University of Tsukuba, Japan. Glenn Wylie is funded by the Department of Veterans' Affairs under award number: 5I01CX000893, by the National Multiple Sclerosis Society under award number: RG 4232A1, and by the New Jersey Commission for Brain Injury Research under award number: 10.005.BIR1. Jarred Younger is funded by NINDS of the NIH under award number: R01-NS109529, and by the DoD under award number W81XWH-19-1-0725. Phyllis C. Zee is funded by NHLBI of the NIH under award number: R01HL140580, by NIA of the NIH under award numbers: P01AG011412, R01AG059291 and R01AG068579, and by NICHD of the NIH under award number: R01HD097786. The workshop was supported by funding from the NIH Blueprint Neuroscience Research Program. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosure Statements

Financial Conflicts of Interest: The following authors have no Financial Conflicts of Interest: David M. Raizen, Janet Mullington, Christelle Anaclet, Hugo Critchley, Robert Dantzer, Ron Davis, Josh Fessel, Patrick M. Fuller, Erin M. Gibson, Mary Harrington, W. Ian Lipkin, Nancy Klimas, Anthony L. Komaroff, Walter Koroshetz, Anna Kuppuswamy, Julie Lasselin, Lauren Lewis, Pierre J Magistretti, Heidi Y. Matos, Christine Miaskowski, Avindra Nath, Maiken Nedergaard, Mark R. Opp, Marilyn D. Ritchie, Dragana Rogulja, Asya Rolls, Vicky Whittemore, Glenn Wylie, and Jarred Younger. Gerard Clarke has received honoraria from Janssen, Probi, and Apsen as an invited speaker; is in receipt of research funding from Pharmavite, Nestle, Tate and Lyle, Reckitt and Fonterra; and is a paid consultant for Yakult, Zentiva and Heel Pharmaceuticals. Robert Dantzer receives an honorarium from GoodCap. Kelly L. Drew has commercial interest in Be Cool Pharmaceutics. Elizabeth B. Klerman consults for the American Academy of Sleep Medicine Foundation, Circadian Therapeutics, National Sleep Foundation, Sleep Research Society Foundation, Yale University Press; received travel support from the European Biological Rhythms Society; and her partner owns Chronsulting. Lauren Krupp has received research or programmatic funding, or has received compensation for consulting, speaking, travel and meal allowances, or serving on dSMB committees from Biogen, Novartis, Eisai, Roche, Gerson Lehrman, Janssen, Medscape, NeuroLive, Peer View, WebMD, Bristol Myers Squibb, CME Outfitters, General Dynamics Information, At the Limits, Cambridge Medical Technologies and Medergy Marketing; she is also a non-compensated consultant and/or advisory board member with Novartis and Celgene and she receives royalties for use of the Fatigue Severity Scale by various biopharmaceutical entities. Andrew H Miller is a paid consultant for Cerevel Therapeutics and Sirtsei Pharmaceuticals, Inc. John D. Salamone receives grants and consulting fees for Shire, Prexa, Chronos, Blackthorn, Lundbeck, NOEMA, and Acadia. Clifford Saper receives royalties for published textbooks from McGraw-Hill and Oxford University Press. Phyliss C. Zee is a consultant for Eisai, Idorsia, Harmony Bioscience, Jazz, Sleep Number, CVS Caremark. H. Craig Heller is a scientific advisor to Arteria, which makes CoolMitt. **Non-Financial Conflicts of Interest**: The following authors have no non-financial conflicts of interest: David M. Raizen, Janet Mullington, Christelle Anaclet, Hugo Critchley, Robert Dantzer, Ron Davis, Josh Fessel, Patrick M. Fuller, Erin M. Gibson, Mary Harrington, W. Ian Lipkin, Nancy Klimas, Anthony L. Komaroff, Walter Koroshetz, Anna Kuppuswamy, Julie Lasselin, Pierre J. Magistretti, Heidi Y. Matos, Christine Miaskowski, Avindra Nath, Maiken Nedergaard, Mark R. Opp, Marilyn D. Ritchie, Dragana Rogulja, Asya Rolls, Vicky Whittemore, Glenn Wylie, and Jarred Younger. Lauren D. Lewis is an author on a patent application for a method for measuring CSF flow. H. Craig Heller holds patents on Palmar Cooing Technology.

References

1. Kuppuswamy A. The fatigue conundrum. *Brain*. 2017;**140**:2240–2245. doi:10.1093/brain/awx153.
2. Krupp LB, *et al*. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;**46**:1121–1123. doi:10.1001/archneur.1989.00520460115022.
3. Kluger BM, *et al*. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology*. 2013;**80**:409–416. doi:10.1212/WNL.0b013e31827f07be.
4. Latourelle JC, *et al*. Large-scale identification of clinical and genetic predictors of motor progression in patients with newly diagnosed Parkinson's disease: a longitudinal cohort study and validation. *Lancet Neurol*. 2017;**16**(11):908–916. doi:10.1016/S1474-4422(17)30328-9.
5. Kirby JC, *et al*. PheKB: a catalog and workflow for creating electronic phenotype algorithms for transportability. *J Am Med Infor Assoc*. 2016;**23**(6):1046–1052.
6. Monahan RC, *et al*. Fatigue in patients with systemic lupus erythematosus and neuropsychiatric symptoms is associated with anxiety and depression rather than inflammatory disease activity. *Lupus*. 2021;**30**:1124–1132. doi:10.1177/09612033211005014.
7. Andreasen, AK, Stenager, E, Dalgas, U. The effect of exercise therapy on fatigue in multiple sclerosis. *Mult Scler*. 2011;**17**:1041–1054.
8. Pilutti LA, *et al*. Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis. *Psychosom Med*. 2013;**75**:575–580. doi:10.1097/PSY.0b013e31829b4525.
9. Schwartz CE, *et al*. Psychosocial correlates of fatigue in multiple sclerosis. *Arch Phys Med Rehabil*. 1996;**77**:165–170. doi:10.1016/s0003-9993(96)90162-8.
10. Singhal T, *et al*. Regional microglial activation in the substantia nigra is linked with fatigue in MS. *Neurol Neuroimmunol Neuroinflamm*. 2020;**7**:e854. doi:10.1212/NXI.0000000000000854.
11. Albrecht DS, *et al*. Brain glial activation in fibromyalgia—a multi-site positron emission tomography investigation. *Brain Behav Immun*. 2019;**75**:72–83. doi:10.1016/j.bbi.2018.09.018.
12. Nakatomi Y, *et al*. Neuroinflammation in patients with chronic fatigue syndrome/myalgic encephalomyelitis: an (1)(1)C-(R)-PK11195 PET Study. *J Nucl Med*. 2014;**55**:945–950. doi:10.2967/jnumed.113.131045.
13. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev*. 2001;**81**(4):1725–1789. doi:10.1152/physrev.2001.81.4.1725.
14. McNeil CJ, *et al*. The reduction in human motoneurone responsiveness during muscle fatigue is not prevented by increased muscle spindle discharge. *J Physiol*. 2011;**589**(Pt 15):3731–3738. doi:10.1113/jphysiol.2011.210252.

15. Di Lazzaro V, *et al*. Direct demonstration of reduction of the output of the human motor cortex induced by a fatiguing muscle contraction. *Exp Brain Res*. 2003;**149**(4):535–538. doi:10.1007/s00221-003-1408-6.
16. Grahn DA, *et al*. Heat extraction through the palm of one hand improves aerobic exercise endurance in a hot environment. *J Appl Physiol*. 2005;**99**:972–978. doi:10.1152/japplphysiol.00093.2005.
17. Grahn DA, *et al*. Work volume and strength training responses to resistive exercise improve with periodic heat extraction from the palm. *J Strength Cond Res*. 2012;**26**:2558–2569.
18. Heller HC Grahn D. Enhancing thermal exchange in humans and practical applications. *Disruptive Sci Technol*. 2012;**1**:11–19.
19. Herman P Lee JC. Functional energetic landscape in the allosteric regulation of muscle pyruvate kinase. 3. Mechanism. *Biochemistry*. 2009;**48**:9466–9470.
20. Borbely AA. A two process model of sleep regulation. *Hum Neurobiol*. 1982;**1**:195–204.
21. Baron KG, *et al*. Exercise to improve sleep in insomnia: exploration of the bidirectional effects. *J Clin Sleep Med*. 2013;**9**:819–824. doi:10.5664/jcsm.2930.
22. Redd WH, *et al*. Systematic light exposure in the treatment of cancer-related fatigue: a preliminary study. *Psychooncology*. 2014;**23**:1431–1434.
23. Reid KJ, *et al*. Aerobic exercise improves self-reported sleep and quality of life in older adults with insomnia. *Sleep Med*. 2010;**11**:934–940. doi:10.1016/j.sleep.2010.04.014.
24. Bafna T, Hansen, JP. Mental fatigue measurement using eye metrics: a systematic literature review. *Psychophysiology*. 2021;**58**:e13828.
25. LeDuc PA, *et al*. Involuntary eye responses as measures of fatigue in US Army Apache aviators. *Aviat Space Environ Med*. 2005;**76**:C86–C91.
26. Endeshaw YW. Do sleep complaints predict persistent fatigue in older adults? *J Am Geriatr Soc*. 2015;**63**:716–721. doi:10.1111/jgs.13329.
27. Hossain JL, *et al*. Subjective fatigue and subjective sleepiness: two independent consequences of sleep disorders? *J Sleep Res*. 2005;**14**:245–253. doi:10.1111/j.1365-2869.2005.00466.x.
28. Martin T, *et al*. The relationship between fatigue and actigraphy-derived sleep and rest-activity patterns in cancer survivors. *Curr Oncol*. 2021;**28**:1170–1182. doi:10.3390/curroncol28020113.
29. Corsi-Cabrera M, *et al*. Waking EEG signs of non-restoring sleep in primary insomnia patients. *Clin Neurophysiol*. 2016;**127**:1813–1821. doi:10.1016/j.clinph.2015.08.023.
30. Grimaldi D, *et al*. Autonomic dysregulation and sleep homeostasis in insomnia. *Sleep*. 2021;**44**:zsaa274. doi:10.1093/sleep/zsaa274.
31. Goldstein MR, *et al*. Pain, fatigue, and altered reactivity to a repeated physiological stressor in insomnia patients: an explanatory-driven analysis. *Sleep*. 2020;**43**:A90–A90. doi:10.1093/sleep/zsaa056.231.
32. Zhao W, *et al*. EEG spectral analysis in insomnia disorder: a systematic review and meta-analysis. *Sleep Med Rev*. 2021;**59**:101457.
33. Armitage R, *et al*. The impact of a 4-hour sleep delay on slow wave activity in twins discordant for chronic fatigue syndrome. *Sleep*. 2007;**30**:657–662. doi:10.1093/sleep/30.5.657.
34. Van Dongen HP, *et al*. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep*. 2003;**26**:117–126. doi:10.1093/sleep/26.2.117.
35. Haack M, *et al*. Sustained sleep restriction reduces emotional and physical well-being. *Pain*. 2005;**119**(1–3):56–64. doi:10.1016/j.pain.2005.09.011.
36. Simpson NS, *et al*. Repeating patterns of sleep restriction and recovery: Do we get used to it? *Brain Behav Immun*. 2016;**58**:142–151. doi:10.1016/j.bbi.2016.06.001.
37. Yang H, *et al*. Repetitive exposure to shortened sleep leads to blunted sleep-associated blood pressure dipping. *J Hypertens*. 2017;**35**(6):1187–1194.
38. Yang H, *et al*. Heart rate variability rebound following exposure to persistent and repetitive sleep restriction. *Sleep*. 2019;**42**:1–9.
39. Yang H, *et al*. Macro- and microvascular reactivity during repetitive exposure to shortened sleep: sex differences. *Sleep*. 2021;**44**(5):zsaa257. doi:10.1093/sleep/zsaa257.
40. Banks S, *et al*. Neurobehavioral dynamics following chronic sleep restriction: dose-response effects of one night for recovery. *Sleep*. 2010;**33**(8):1013–1026. doi:10.1093/sleep/33.8.1013.
41. Besedovsky L, *et al*. Differential effects of an experimental model of prolonged sleep disturbance on inflammation in healthy females and males. *PNAS Nexus*. 2022;**1**(1):pgac004.
42. Berger A, *et al*. NCCM Guidelines Version 1.2020-cancer-related fatigue. *J National Comprehensive Cancer Network*. 2020;**8**(8):904–931.
43. Saligan LN, *et al*.; Multinational Association of Supportive Care in Cancer Fatigue Study Group-Biomarker Working Group. The biology of cancer-related fatigue: a review of the literature. *Support Care Cancer*. 2015;**23**:2461–2478. doi:10.1007/s00520-015-2763-0.
44. Wright F, *et al*. Predictors and trajectories of morning fatigue are distinct from evening fatigue. *J Pain Symptom Manag*. 2015;**50**:176–189.
45. Wright F, *et al*. Higher levels of stress and different coping strategies are associated with greater morning and evening fatigue severity in oncology patients receiving chemotherapy. *Support Care Cancer*. 2020;**28**:4697–4706. doi:10.1007/s00520-020-05303-5.
46. Feng LR, *et al*. Co-occurring symptoms contribute to persistent fatigue in prostate cancer. *Oncology (Huntingt)*. 2019;**96**:183–191. doi:10.1159/000494620.
47. Wright F, *et al*. Distinct evening fatigue profiles in oncology outpatients receiving chemotherapy. *Fatigue*. 2017;**5**:131–144. doi:10.1080/21641846.2017.1322233.
48. Wright F, *et al*. Morning fatigue severity profiles in oncology outpatients receiving chemotherapy. *Cancer Nurs*. 2019;**42**:355–364. doi:10.1097/NCC.0000000000000626.
49. Bower JE. The role of neuro-immune interactions in cancer-related fatigue: biobehavioral risk factors and mechanisms. *Cancer*. 2019;**125**:353–364. doi:10.1002/cncr.31790.
50. Thong MSY, *et al*. Cancer-related fatigue: causes and current treatment options. *Curr Treat Option Oncol*. 2020;**21**:17.
51. Stussman B, *et al*. Characterization of post-exertional malaise in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Front Neurol*. 2020;**11**:1025. doi:10.3389/fneur.2020.01025.
52. Komaroff AL, *et al*. Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome. *Trends Mol Med*. 2021;**27**:895–906. doi:10.1016/j.molmed.2021.06.002.
53. Paul BD, *et al*. Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome. *P Natl Acad Sci USA*. 2021;**118**(34):e2024358118.
54. Stevens S, *et al*. Cardiopulmonary exercise test methodology for assessing exertion intolerance in myalgic encephalomyelitis/chronic fatigue syndrome. *Front Pediatr*. 2018;**6**:242. doi:10.3389/fped.2018.00242.
55. Lim EJ, *et al*. Systematic review and meta-analysis of the prevalence of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). *J Transl Med*. 2020;**18**:100. doi:10.1186/s12967-020-02269-0.

56. Nelson MJ, *et al*. Diagnostic sensitivity of 2-day cardiopulmonary exercise testing in myalgic encephalomyelitis/chronic fatigue syndrome. *J Transl Med*. 2019;**1**:80.
57. Shukla SK, *et al*. Changes in gut and plasma microbiome following exercise challenge in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *PLoS One*. 2015;**10**:e0145453. doi:10.1371/journal.pone.0145453.
58. Cook DB, *et al*. Neural consequences of post-exertion malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Brain Behav Immun*. 2017;**62**:87–99. doi:10.1016/j.bbi.2017.02.009.
59. Jammes Y, *et al*. Chronic fatigue syndrome: acute infection and history of physical activity affect resting levels and response to exercise of plasma oxidant/antioxidant status and heat shock proteins. *J Intern Med*. 2012;**272**:74–84. doi:10.1111/j.1365-2796.2011.02488.x.
60. Suarez A, *et al*. Nitric oxide metabolite production during exercise in chronic fatigue syndrome: a case-control study. *J Womens Health*. 2010;**19**:1073–1077.
61. Jones DE, *et al*. Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study. *Eur J Clin Invest*. 2012;**42**:186–194. doi:10.1111/j.1365-2362.2011.02567.x.
62. Lien K, *et al*. Abnormal blood lactate accumulation during repeated exercise testing in myalgic encephalomyelitis/chronic fatigue syndrome. *Physiol Rep*. 2019;**7**:e14138. doi:10.14814/phy2.14138.
63. Meeus M, *et al*. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. *J Rehabil Med*. 2010;**42**:884–890. doi:10.2340/16501977-0595.
64. De Doncker W, *et al*. Exploring the relationship between effort perception and poststroke fatigue. *Neurology*. 2020;**95**:e3321–e3330. doi:10.1212/WNL.0000000000010985.
65. Kuppuswamy A. The neurobiology of pathological fatigue: new models, new questions. *Neuroscientist*. 2022;**28**:238–253. doi:10.1177/1073858420985447.
66. Hornig M, *et al*. Cytokine network analysis of cerebrospinal fluid in myalgic encephalomyelitis/chronic fatigue syndrome. *Mol Psychiatr*. 2016;**21**:261–269.
67. Germain A, *et al*. Metabolic profiling of a myalgic encephalomyelitis/chronic fatigue syndrome discovery cohort reveals disturbances in fatty acid and lipid metabolism. *Mol Biosyst*. 2017;**13**:371–379. doi:10.1039/c6mb00600k.
68. Naviaux RK, *et al*. Metabolic features of chronic fatigue syndrome. *P Natl Acad Sci USA*. 2016;**113**:E5472–E5480.
69. Yamano E, *et al*. Index markers of chronic fatigue syndrome with dysfunction of TCA and urea cycles. *Sci Rep*. 2016;**6**:34990.
70. Giloteaux L, *et al*. Cytokine profiling of extracellular vesicles isolated from plasma in myalgic encephalomyelitis/chronic fatigue syndrome: a pilot study. *J Transl Med*. 2020;**18**(1):387. doi:10.1186/s12967-020-02560-0.
71. Mandarano AH, *et al*. Myalgic encephalomyelitis/chronic fatigue syndrome patients exhibit altered T cell metabolism and cytokine associations. *J Clin Invest*. 2020;**130**(3):1491–1505. doi:10.1172/JCI132185.
72. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci*. 2002;**3**:655–666.
73. Craig AD. Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol*. 2003;**13**:500–505. doi:10.1016/s0959-4388(03)00090-4.
74. Gogolla N. The insular cortex. *Curr Biol*. 2017;**27**:R580–R586. doi:10.1016/j.cub.2017.05.010.
75. Koren T, *et al*. Insular cortex neurons encode and retrieve specific immune responses. *Cell*. 2021;**184**:5902–5915.e17. doi:10.1016/j.cell.2021.10.013.
76. Seidner G, *et al*. Identification of neurons with a privileged role in sleep homeostasis in *Drosophila melanogaster*. *Curr Biol*. 2015;**25**:2928–2938. doi:10.1016/j.cub.2015.10.006.
77. Vaccaro A, *et al*. Sleep loss can cause death through accumulation of reactive oxygen species in the gut. *Cell*. 2020;**181**:1307–1328.e15. doi:10.1016/j.cell.2020.04.049.
78. Cryan JF, *et al*. The microbiota-gut-brain axis. *Physiol Rev*. 2019;**99**(4):1877–2013.
79. García-Cabrerizo R, *et al*. Microbiota-gut-brain axis as a regulator of reward processes. *J Neurochem*. 2021;**157**(5):1495–1524.
80. Kennedy PJ, *et al*. Kynurenine pathway metabolism and the microbiota–gut–brain axis. *Neuropharmacology*. 2017;**112**(Pt B):399–412. doi:10.1016/j.neuropharm.2016.07.002.
81. Giloteaux L, *et al*. Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome. *BMC Microbiome*. 2016;**4**:30.
82. Guo C, *et al*. Deficient butyrate-producing capacity in the gut microbiome of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients is associated with fatigue symptoms. *Cell Host Microbe*. 2021;**31**(2):288–304. https://arxiv.org/abs/10.27.21265575, preprint.
83. Magistretti PJ, *et al*. A cellular perspective on brain energy metabolism and functional imaging. *Neuron*. 2015;**86**(4):883–901. doi:10.1016/j.neuron.2015.03.035.
84. Suzuki A, *et al*. Astrocyte-neuron lactate transport is required for long-term memory formation. *Cell*. 2011;**144**(5):810–823. doi:10.1016/j.cell.2011.02.018.
85. Carrard A, *et al*. Role of adult hippocampal neurogenesis in the antidepressant actions of lactate. *Mol Psychiatr*. 2021;**26**(11):6723–6735.
86. Grossberg AJ, *et al*. Tumor-associated fatigue in cancer patients develops independently of IL1 signaling. *Cancer Res*. 2018;**78**:695–705. doi:10.1158/0008-5472.CAN-17-2168.
87. Olivadoti MD, *et al*. Sleep and fatigue in mice infected with murine gammaherpesvirus 68. *Brain Behav Immun*. 2011;**25**:696–705. doi:10.1016/j.bbi.2011.01.010.
88. Hart BL. Biological basis of the behavior of sick animals. *Neurosci Biobehav Rev*. 1988;**12**:123–137.
89. Lasselin J, *et al*. Comparison of bacterial lipopolysaccharide-induced sickness behavior in rodents and humans: Relevance for symptoms of anxiety and depression. *Neurosci Biobehav Rev*. 2020;**115**:15–24. doi:10.1016/j.neubiorev.2020.05.001.
90. Lasselin J, *et al*. Lipopolysaccharide alters motivated behavior in a monetary reward task: a randomized trial. *Neuropsychopharmacology*. 2017;**42**(4):801–810.
91. Draper A, *et al*. Effort but not reward sensitivity is altered by acute sickness induced by experimental endotoxemia in humans. *Neuropsychopharmacology*. 2018;**43**(5):1107–1118.
92. Capuron L, *et al*. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Arch Gen Psychiatr*. 2012;**69**:1044–1053.
93. Eisenberger NI, *et al*. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. *Biol Psychiatry*. 2010;**68**:748–754.
94. Harrison NA, *et al*. A neurocomputational account of how inflammation enhances sensitivity to punishments versus rewards. *Biol Psychiatry*. 2016;**80**:73–81.
95. Salamone JD, *et al*. Complexities and paradoxes in understanding the role of dopamine in incentive motivation and instrumental action: exertion of effort vs. anhedonia. *Brain Res Bull*. 2022;**182**:57–66. doi:10.1016/j.brainresbull.2022.01.019.

96. Salamone JD, *et al*. The psychopharmacology of effort-related decision making: dopamine, adenosine, and insights into the neurochemistry of motivation. *Pharmacol Rev.* 2018;**70**(4):747–762. doi:10.1124/pr.117.015107.
97. Osterhout JA, *et al*. A preoptic neuronal population controls fever and appetite during sickness. *Nature.* 2022;**606**(7916):937–944. doi:10.1038/s41586-022-04793-z.
98. Ilanges A, *et al*. Brainstem ADCYAP1+ neurons control multiple aspects of sickness behaviour. *Nature.* 2022;**609**(7928):761–771. doi:10.1038/s41586-022-05161-7.
99. Toda H, *et al*. A sleep-inducing gene, nemuri, links sleep and immune function in *Drosophila*. *Science.* 2019;**363**:509–515. doi:10.1126/science.aat1650.
100. Sinner MP, *et al*. Innate immunity promotes sleep through epidermal antimicrobial peptides. *Curr Biol.* 2021;**31**:564–577.e12. doi:10.1016/j.cub.2020.10.076.
101. Lenz O, *et al*. FMRFamide signaling promotes stress-induced sleep in *Drosophila*. *Brain Behav Immun.* 2015;**47**:141–148. doi:10.1016/j.bbi.2014.12.028.
102. Nelson MD, *et al*. FMRFamide-like FLP-13 neuropeptides promote quiescence following heat stress in *Caenorhabditis elegans*. *Curr Biol.* 2014;**24**:2406–2410. doi:10.1016/j.cub.2014.08.037.
103. Yetish G, *et al*. Natural sleep and its seasonal variations in three pre-industrial societies. *Curr Biol.* 2015;**25**:2862–2868. doi:10.1016/j.cub.2015.09.046.
104. Hrvatin S, *et al*. Neurons that regulate mouse torpor. *Nature.* 2020;**583**(7814):115–121. doi:10.1038/s41586-020-2387-5.
105. Takahashi TM, *et al*. A discrete neuronal circuit induces a hibernation-like state in rodents. *Nature.* 2020;**583**(7814):109–114. doi:10.1038/s41586-020-2163-6.
106. Saper CB, *et al*. Flipping the switch on the body's thermoregulatory system. *Nature.* 2020;**583**:34–35. doi:10.1038/d41586-020-01600-5.
107. Charvet LE, *et al*. Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: results from a randomized, sham-controlled trial. *Mult Scler.* 2018;**24**:1760–1769.
108. Palotai M, *et al*. Brain anatomical correlates of fatigue in multiple sclerosis. *Mult Scler.* 2020;**26**:751–764. doi:10.1177/1352458519876032.
109. Choi-Kwon S, *et al*. Fluoxetine is not effective in the treatment of post-stroke fatigue: a double-blind, placebo-controlled study. *Cerebrovasc Dis.* 2007;**23**:103–108. doi:10.1159/000097045.
110. Karaiskos D, *et al*. Duloxetine versus citalopram and sertraline in the treatment of poststroke depression, anxiety, and fatigue. *J Neuropsych Clin Neurosci.* 2012;**24**:349–353.
111. Dobryakova E, *et al*. Neural correlates of cognitive fatigue: cortico-striatal circuitry and effort-reward imbalance. *J Int Neuropsychol Soc.* 2013;**19**:849–853.
112. Critchley HD. Neural mechanisms of autonomic, affective, and cognitive integration. *J Comp Neurol.* 2005;**493**:154–166. doi:10.1002/cne.20749.
113. Genova HM, *et al*. Examination of cognitive fatigue in multiple sclerosis using functional magnetic resonance imaging and diffusion tensor imaging. *PLoS One.* 2013;**8**(11):e788111–e788110. doi:10.1371/journal.pone.0078811.
114. Wylie GR, *et al*. Using functional connectivity changes associated with cognitive fatigue to delineate a fatigue network. *Sci Rep.* 2020;**10**(21927):1–12.
115. Pedersen NP, *et al*. Supramammillary glutamate neurons are a key node of the arousal system. *Nat Commun.* 2017;**8**(1):1405. doi:10.1038/s41467-017-01004-6.
116. Greenhalgh AD, *et al*. Immune cell regulation of glia during CNS injury and disease. *Nat Rev Neurosci.* 2020;**21**:139–152.
117. Han RT, *et al*. Astrocyte-immune cell interactions in physiology and pathology. *Immunity.* 2021;**54**:211–224. doi:10.1016/j.immuni.2021.01.013.
118. Liddelow S, *et al*. Astrocytes in health and disease. *Cell.* 2015;**162**:1170–1170. e1171.
119. Liddelow SA, *et al*. Microglia and astrocytes in disease: dynamic duo or partners in crime? *Trends Immunol.* 2020;**41**:820–835. doi:10.1016/j.it.2020.07.006.
120. Gibson EM, *et al*. Bad wrap: Myelin and myelin plasticity in health and disease. *Dev Neurobiol.* 2018;**78**:123–135. doi:10.1002/dneu.22541.
121. Xie L, *et al*. Sleep drives metabolite clearance from the adult brain. *Science.* 2013;**342**(6156):373–377. doi:10.1126/science.1241224.
122. Eide PK, *et al*. Sleep deprivation impairs molecular clearance from the human brain. *Brain.* 2021;**144**(3):863–874.
123. Mestre H, *et al*. Periarteriolar spaces modulate cerebrospinal fluid transport into brain and demonstrate altered morphology in aging and Alzheimer's disease. *Nat Commun.* 2022;**13**(1):3897.
124. Helakari H, *et al*. Human NREM sleep promotes brain-wide vasomotor and respiratory pulsations. *J Neurosci.* 2022;**42**(12):2503-2515. doi: 10.1523/JNEUROSCI.0934-21.2022.
125. Fultz NE, *et al*. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science.* 2019;**366**(6465):628–631. doi:10.1126/science.aax5440.
126. Lewis LD. The interconnected causes and consequences of sleep in the brain. *Science.* 2021;**374**(6567):564–568. doi:10.1126/science.abi8375.