Neural and fluid dynamics of sleep

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Disclaimer
This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure
This certifies that I, Laura Lewis, have no financial relationship that is relevant to the subject matter of this presentation.

I, Laura Lewis, have a pending patent application on a technique for CSF flow imaging.
Multiple forms and origins of fatigue

- Sleep deprivation
- Multiple sclerosis
- Chronic fatigue
- Depression
- Stroke

• In addition to many other conditions
Persistent fatigue in Long COVID

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Acute COVID-19 phase</th>
<th>Post-COVID-19 follow-up</th>
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<tbody>
<tr>
<td>Fatigue</td>
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<td>Dyspnea</td>
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<td>Joint pain</td>
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<td>Chest pain</td>
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<td>Cough</td>
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<td>Anosmia</td>
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<td>Sickle syndrome</td>
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<td>Rhinitis</td>
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<td>Red eyes</td>
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<tr>
<td>Dysgeusia</td>
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<td>Headache</td>
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<td>Sputum production</td>
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<tr>
<td>Lack of appetite</td>
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<td>Sore throat</td>
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<td>Vertigo</td>
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<td>Myalgia</td>
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<td>Diarrhea</td>
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</tbody>
</table>

Carfi et al., JAMA. 2020

Davis et al., medRxiv, 2021
Sleep in individuals with fatigue

• Fatigue can result from sleep disturbances

• Patients with fatigue can have disturbed sleep or may spend as much or more time asleep as is typical (Mariman et al., 2013)
Sleep serves diverse functions for the brain and body

• Cognitive
Sleep serves diverse functions for the brain and body

• Cognitive

• Electrophysiological

**Human EEG in NREM:**

- Wakefulness
- NREM (stage 1)
- NREM (stages 2/3) with Sleep spindle and K-complex
- NREM (stage 4)

Brown et al., *Physiol Rev*, 2012
Sleep serves diverse functions for the brain and body

- Cognitive
- Electrophysiological
- Metabolic

Buchsbaum et al., 2001
Sleep serves diverse functions for the brain and body

- Cognitive
- Electrophysiological
- Metabolic

Buchsbaum et al., 2001

Holth et al., 2019
Sleep serves diverse functions for the brain and body

- Cognitive
- Electrophysiological
- Metabolic
- Waste clearance

Xie et al., 2013
Sleep serves diverse functions for the brain and body

• Cognitive

• Electrophysiological

• Metabolic

• Waste clearance

• Immune/inflammatory

Besedvosky et al., 2017
What neurobiological factors could cause arousal dysregulation?

• Is sleep less restorative?

• Are arousal regulatory circuits disordered?

• Is waste removal impaired?

• Is there a widespread dysregulation of neural activity/inflammation?
Subcortical circuits regulate arousal state

Saper et al., 2005
Sleep-defining EEG rhythms reflect thalamocortical oscillations

Adamantidis et al., 2019
Heightened clearance during states with neural slow wave activity

Xie et al., *Science*, 2013

Hablitz et al. *Science Advances*, 2019
Cerebrospinal fluid flow in sleep
CSF flow waves appear during sleep

Fultz et al., 2019
Cerebrospinal fluid flow is coupled to hemodynamic waves during sleep

Fultz et al., 2019
CSF waves are coupled to neural slow waves
Coupled hemodynamic and CSF flow waves during sleep
Multiple points of vulnerability in sleep

• Sleep loss or fragmentation could impair restorative effects of sleep

• The neural, metabolic, and fluid consequences of sleep are coupled

• Sleep with disrupted neural, glial, vascular, or fluid dynamics may have distinct outcomes for CSF and clearance

• Direct impairment of arousal regulatory circuits as a parallel pathway

• Sleep serves multiple functions and affect multiple components of brain physiology
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