



Zentralinstitut
für Seelische
Gesundheit

Mechanisms of sleep disturbance in ME/CFS

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Relevance of sleep disturbance in ME/CFS:

- As a risk factor for developing a post-acute infection syndrome (PAIS)
- As a severely distressing symptom (and essential diagnostic criterion for ME/CFS)
- Due to its interaction with other key symptoms (fatigue, cognitive impairment, etc.)
- As a „window“ to impaired brain function

Pre-existing sleep disorder as a risk factor for post-COVID

- **EPILOC phase 1-data** (n=11.720): Strongest predictor for case status: acute disease severity; second strongest predictor: **pre-existing sleep disorder!** (Adjusted **OR 2,7** – higher than the effect of all other pre-existing conditions, age, gender, BMI, lifestyle factors)

Schilling et al., J Sleep Res. 2023

- **UK-Biobank study:** 1.581 adults with SARS-CoV-2 infection, asked about their health behaviours in the previous month: -> **subjectively poor sleep quality: OR 3,53** for self-reported long COVID

Paul and Fancourt, BMJ Public Health 2022

- **ICOSS-II study:** 2.311 respondents with SARS-CoV-2 infection: in cases with **pre-pandemic insomnia: relative risk 1,33** for long COVID

Chen et al., Sleep Medicine 2023; 112: 2016-222

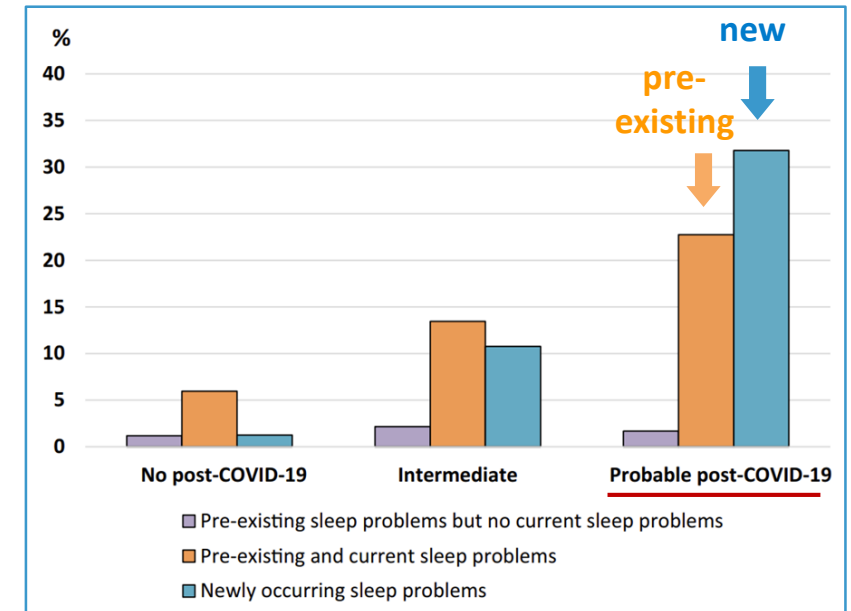
- **Berezin et al., 2023:** 2.508 people with SARS-CoV-2 infection: risk for long-COVID **x 29,5** among **short sleepers (< 6 hours)** with another comorbidity

Berezin et al., J Clin Sleep Med 2023

EPILOC study:

Questionnaire-based prevalence study
n = **11.720 with SARS-CoV-2 infection** (26,5 % „probable post-COVID“)

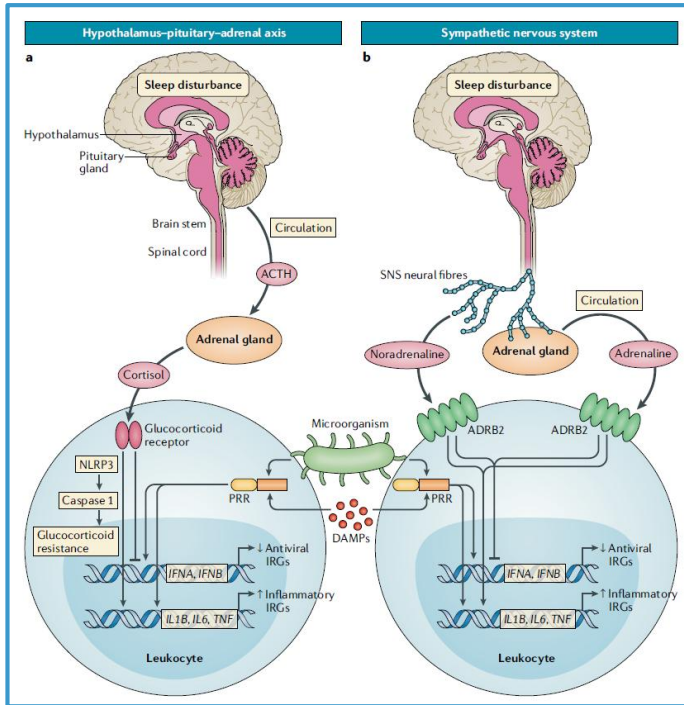
- Sleep disorders (new + ongoing) 54,6 %
- **But: Majority of newly developed sleep disturbances**



Schilling et al., J Sleep Res. 2023;e13949

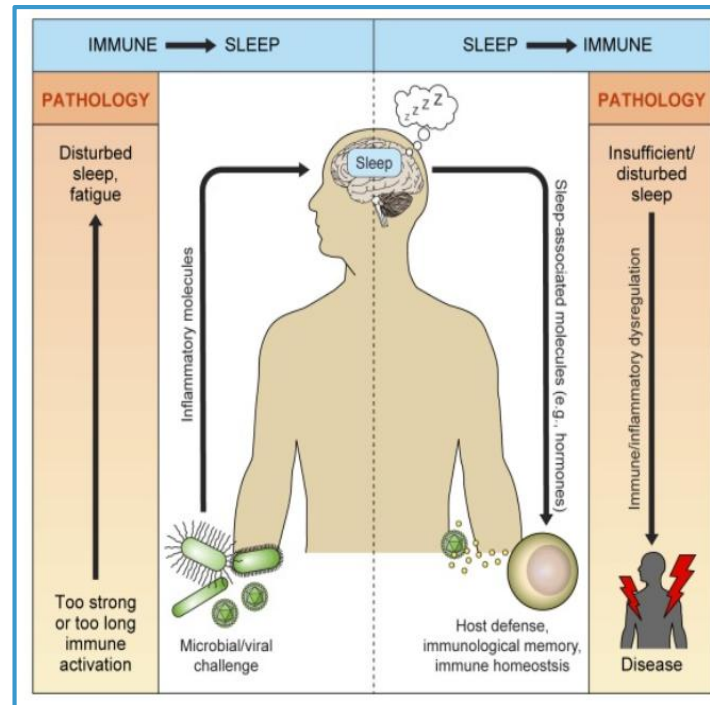
Sleep and inflammation – a bidirectional relationship

Effect of sleep disturbance on immune function

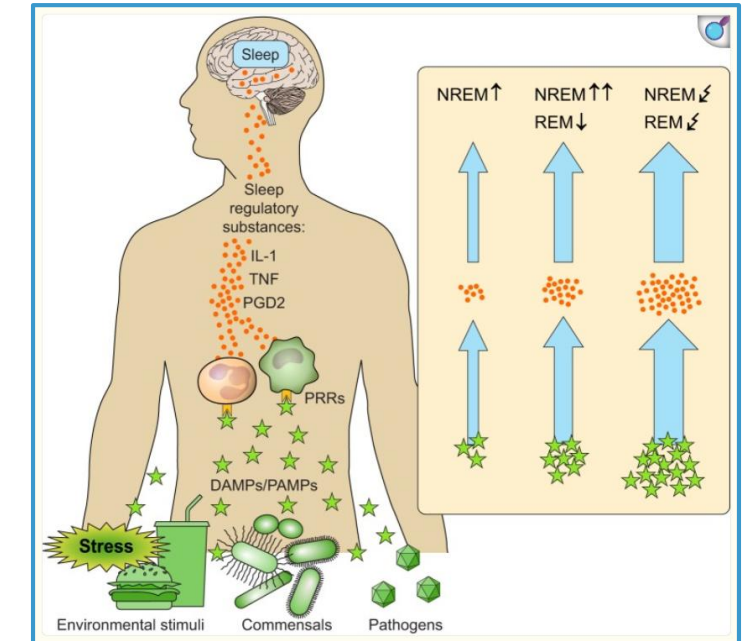


- via activation of sympathetic nervous system and adrenal gland stimulation -> adrenergic stimulation ($\beta 2$) of leukocytes
- chronic cortisol release -> loss of suppression of pro-inflammatory pathways

Bidirectional relationship



Effect of inflammation on sleep



- by pro-inflammatory mediators (cytokines, prostaglandins) acting on the CNS
- depending on the magnitude of inflammatory process

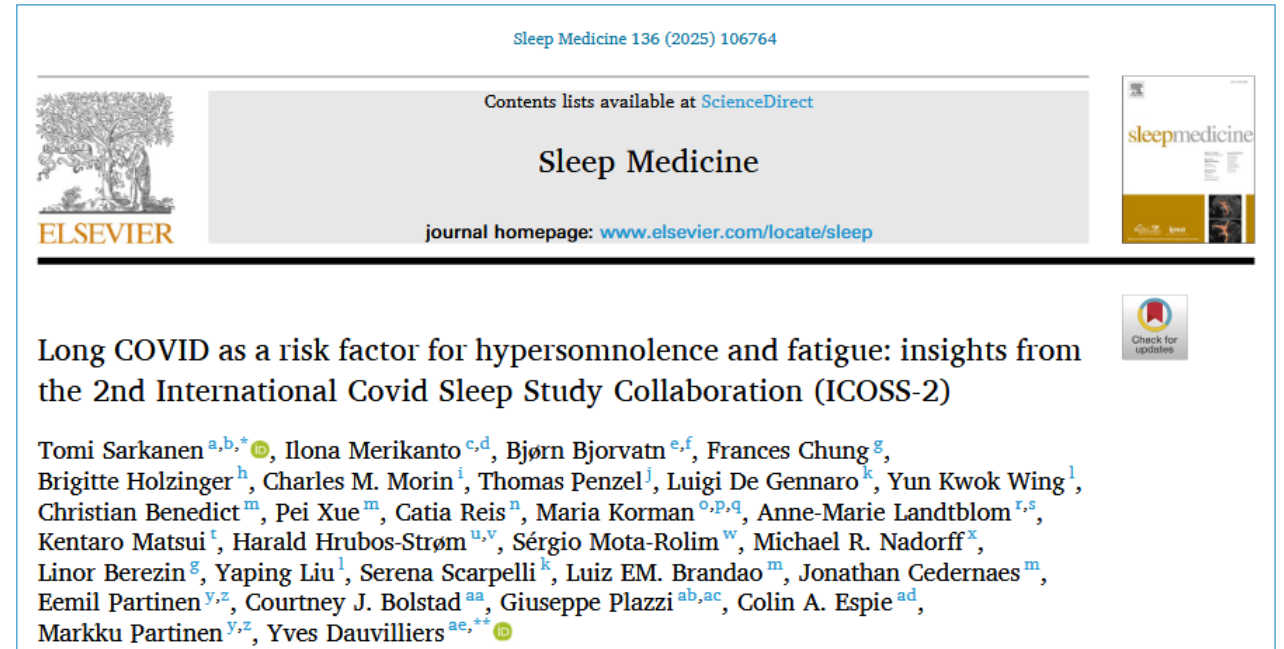
Daytime sleepiness as a symptom of long-COVID: ICOS-2 study

13.656 participants:

- 10.945 (80,1%) COVID-negative
- 1.688 (12,4%) recovered in 4 Wo. (SC)
- 1.023 (7,5%) Long-COVID (LC)

Online questionnaire:

- Daytime sleepiness (ESS)
- Fatigue (FSS)
- Total sleep duration in 24 h



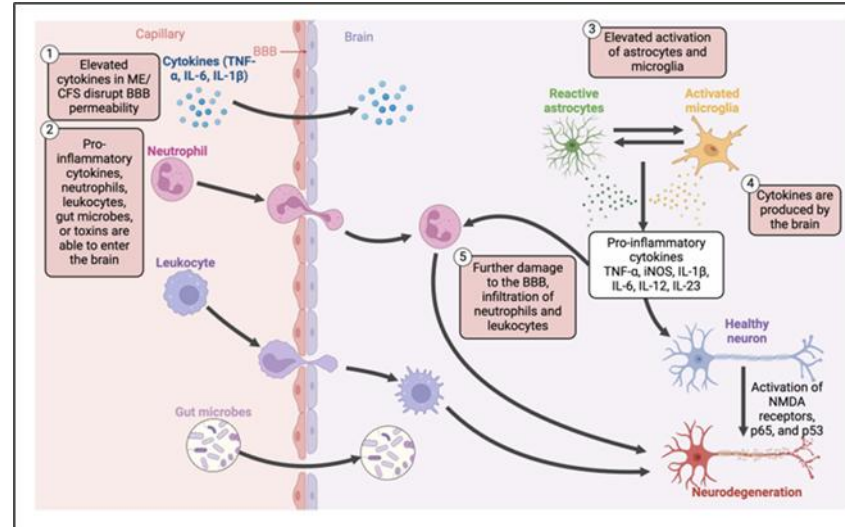
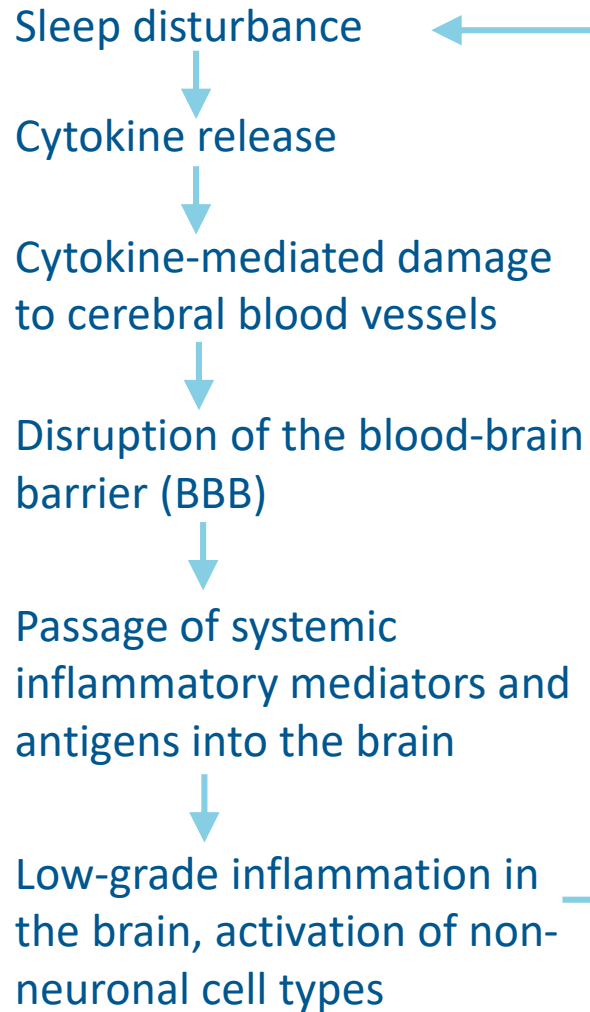
Sarkanen et al., Sleep Medicine 136 (2025) 106764

Results:

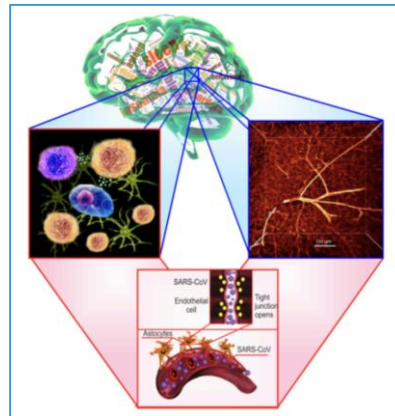
- Daytime sleepiness (ESS score): LC > SC > COVID-negative (9,16 vs 7,26 vs 6,53) → more daytime sleepiness and excessive sleep duration in long-COVID compared to recovered and COVID-negative
- ESS score >10: more in LC than in SC (OR 1,58)
- Excessive sleep duration (> 10 h/day): LC > COVID-negative

Mechanisms of sleep disturbance in ME/CFS

-> role of blood-brain barrier dysfunction



Arron HE, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: the biology of a neglected disease. *Front Immunol.* 2024 Jun 3;15:1386607



Semyachkina-Glushkovskaya et al., Brain Mechanisms of COVID-19-Sleep Disorders. *Int. J. Mol. Sci.* 2021, 22, 6917

Conditions associated with blood-brain barrier dysfunction:

- insomnia
- sleep deprivation
- sleep apnoea
- neurocognitive long-COVID

Article <https://doi.org/10.1038/s41593-024-01576-9>

Blood-brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment

- Dynamic contrast-enhanced MR imaging revealing BBB disruption
- Increased adhesion of PBMCs to brain endothelial cells

Greene et al., *Nature Neuroscience* 2024

Investigation of neuronal mechanisms of sleep disturbance in ME/CFS / PAIS

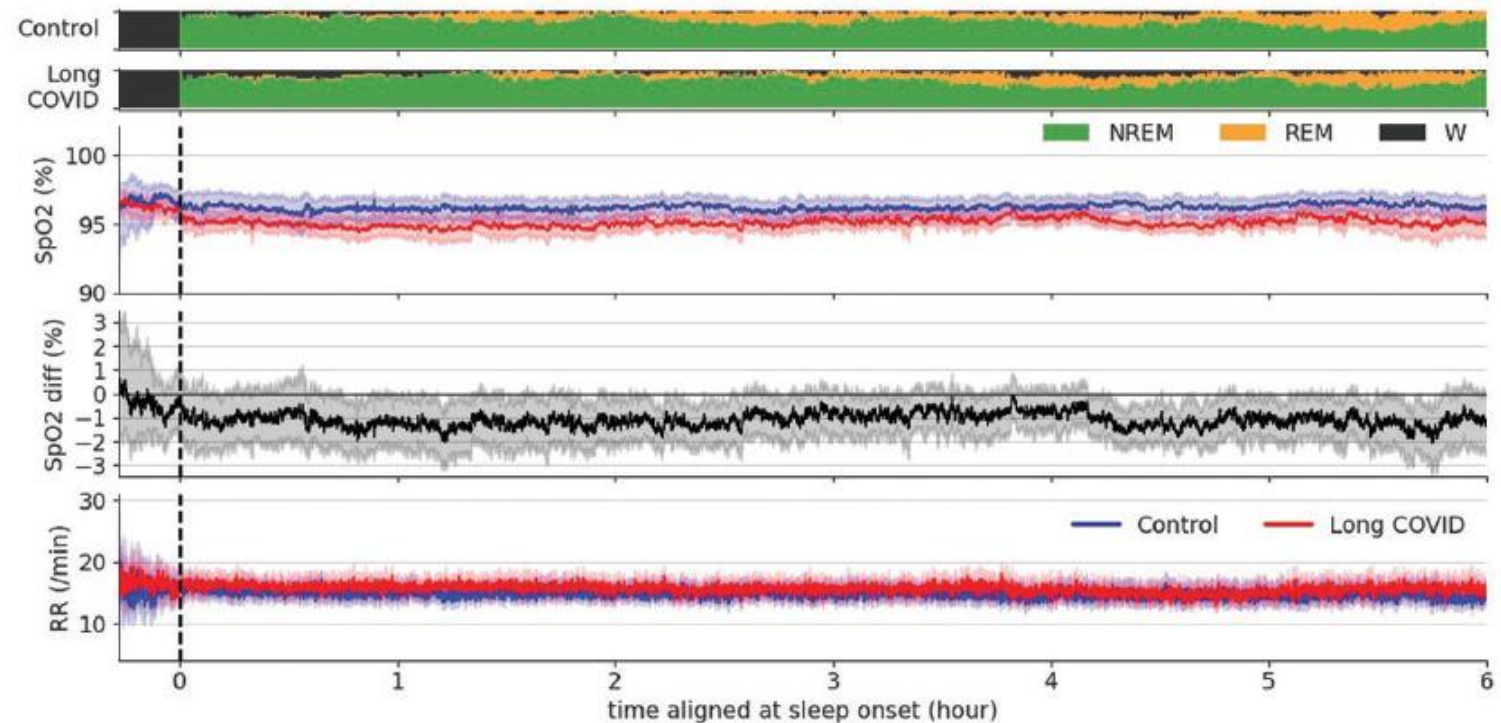
- Sleep pathology may be indicative of distinctive brain network dysfunction
 - thalamo-cortical network
 - arousal-regulating brainstem networks
- Sleep investigation enables neuronal network investigation unbiased by behaviour
- Disease-relevant functions are subject to specific regulation during sleep
 - sleep stage-dependent regulation of sympathovagal balance
 - ventilation and blood oxygenation are more vulnerable during sleep

Facility-measured nocturnal hypoxemia and sleep among adults with long COVID versus age- and sex-matched healthy adults: a preliminary observational study

Haoqi Sun^{1,*}, Rammy Dang¹, Monika Haack¹, Kristine Hauser², Jennifer Scott-Sutherland¹, M. Brandon Westover¹, Sairam Parthasarathy³, Susan Redline⁴, Robert J. Thomas⁵ and Janet M. Mullington^{1,*}

↑ vulnerability of ventilation and blood oxygenation during sleep

- N=25/25 long-COVID / controls
- Age 38 y., 68% women, time since infection 1,3 y., BMI 28
- Ø AHI in both groups 1,9/h
- Sign. ↓ SpO₂ (also after removing desaturations) beginning 5-10 min after sleep onset (- 1,0% - 1,3%, in REM + NREM)
- Increased respiratory rate (+1,4/Min.)



-> Long-COVID: Subclinical nocturnal hypoxia despite increased respiratory rate

-> Marker of long-COVID-associated organ dysfunction ? (e.g. endothelial dysfunction, ↓ gas diffusion capacity, ventilation-perfusion mismatch)

Sleep architecture and rapid eye movement sleep without atonia in post-COVID-19 insomnia

Abubaker Ibrahim ¹, Matteo Cesari ¹, Qi Tang¹, Merve Aktan Süzgün ¹, Elisabeth Brandauer¹, Evi Holzknecht¹, Alexander Wachter¹, Victoria Anselmi¹, Anna Heidbreder ², Ambra Stefani ¹ and Birgit Högl ^{1,*}

Aim: Characterisation of post-COVID insomnia versus chronic insomnia without COVID-19 background

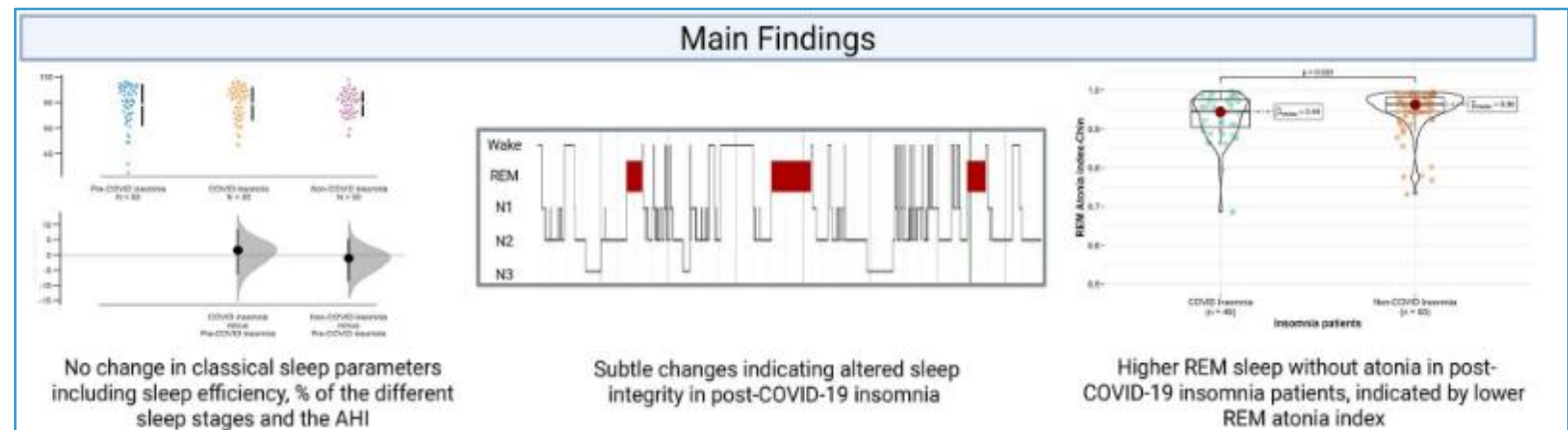
3 groups:

- N = 50 post-COVID with insomnia
- N = 50 chronic insomnia during pandemic without COVID-19 infection
- N = 50 pre-pandemic chronic insomnia

1 night PSG

Results:

- No differences in standard PSG parameters
- However: ↑ REM without atonia (at levels similar to untreated OSAS), ↑ sleep fragmentation (shorter N3 phases, unstable REM, ↑ sleep stage transitions) and ↑ heart rate during sleep (dysautonomia) in post-COVID insomnia
- Results point to neural CNS mechanisms going beyond pandemic-related stress

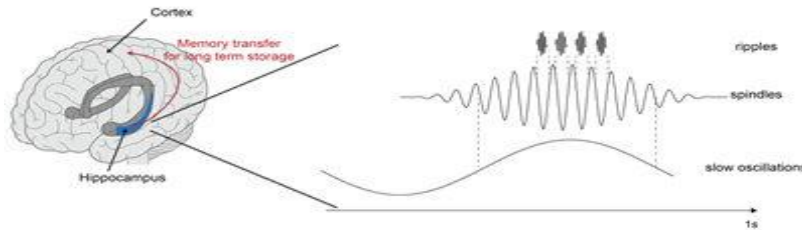


Facility-Measured Sleep Electroencephalographic Microstructures in Long COVID

Haoqi Sun¹, Rammy Dang¹, Peng Li², Wenzhong Xiao², Jennifer Scott-Sutherland³,
Kenneth C Sassower⁴, M Brandon Westover¹, Donna Felsenstein⁵, Robert J Thomas⁶,
Monika Haack¹, Janet M Mullington¹

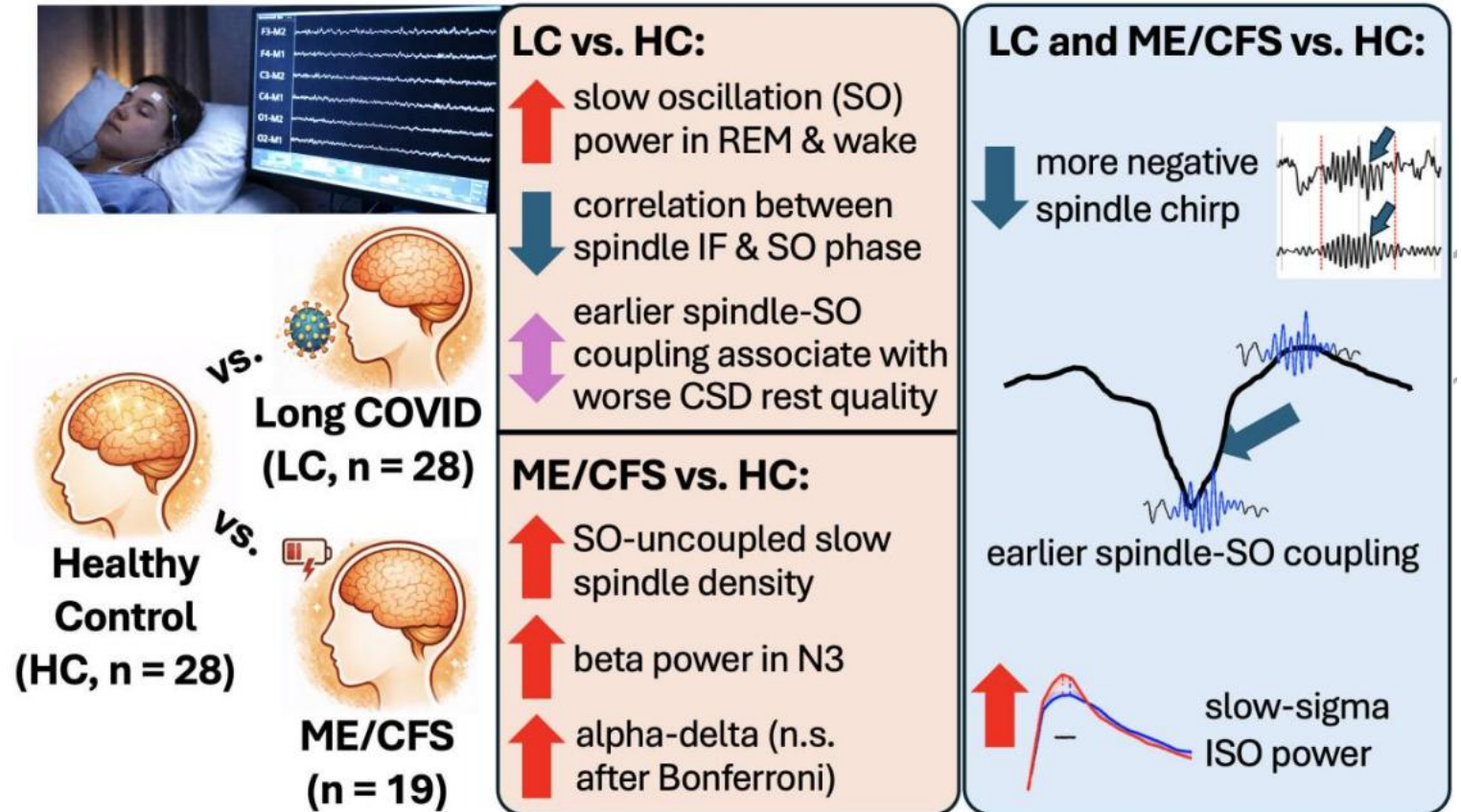
Affiliations + expand

PMID: 42017829 DOI: [10.1093/sleep/zsag090](https://doi.org/10.1093/sleep/zsag090)



Diekelmann and Born (2010) The memory function of sleep.
Nat Rev Neurosci 11: 114-126

-> candidates for electrophysiological biomarkers associated with disturbed sleep in post-COVID



Sleep. 2026 Apr 22:zsag090. doi: 10.1093/sleep/zsag090. Online ahead of print.

Alterations in cortical excitation/inhibition balance?

- Established role of excitation/inhibition (E/I) balance in sleep regulation and hyperarousal
- Transmission of glutamate and GABA in the CNS controls the neural E/I balance
- Chronic insomnia:
 - Evidence from neuroimaging studies suggests altered cortical GABAergic neurotransmission

Jones BE. Arousal and sleep circuits. *Neuropsychopharmacology*. 2020 Jan;45(1):6-20

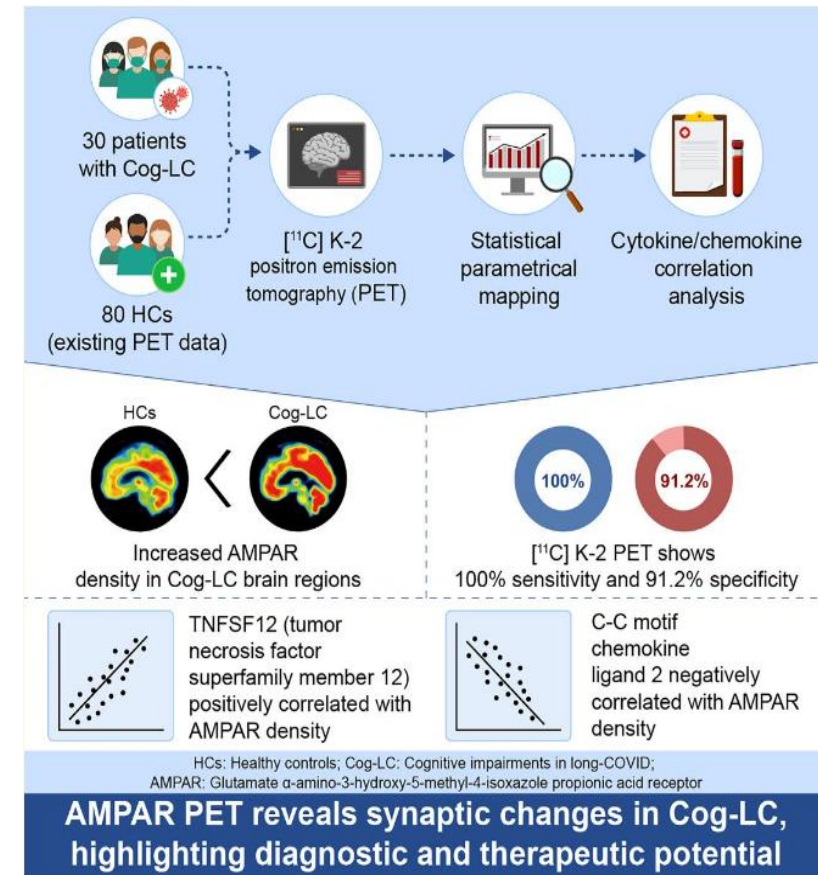
- Preliminary evidence (heterogenous data) for reduced cortical GABA levels in post-COVID

Marinkovic, K., et al. (2023). Cortical GABA Levels Are Reduced in Post-Acute COVID-19 Syndrome. *Brain Sciences*, 13(12), 1666

- Long-COVID-associated insomnia may partly reflect alterations in cortical E/I balance, potentially involving impaired GABAergic inhibitory regulation and/or increased excitatory neurotransmission

Systemic increase of AMPA receptors associated with cognitive impairment of long COVID

Yu Fujimoto,^{1,*} Hiroki Abe,^{1,*} Tsuyoshi Eiro,^{2,*} Sakiko Tsugawa,¹ Meiro Tanaka,¹ Mai Hatano,¹ Waki Nakajima,¹ Sadamitsu Ichijo,¹ Tetsu Arisawa,³ Yuuki Takada,¹ Kimito Kimura,¹ Akane Sano,¹ Koichi Hirahata,⁴ Nobuyuki Sasaki,⁵ Yuichi Kimura,⁶ and Takuya Takahashi¹



↑ density of postsynaptic AMPA receptors In patients with neurocognitive long-COVID

Fujimoto Y, et al. Systemic increase of AMPA receptors associated with cognitive impairment of long COVID. *Brain Commun*. 2025 Oct 1;7(5):fcaf337

Conclusion and summary

Mechanisms of sleep disturbance in ME/CFS / PAIS

- Immunological effects on sleep, especially in the context of BBB dysfunction
- Sleep micro-structural abnormalities point to neural mechanisms involving functional networks that regulate sleep
- Altered E/I balance may contribute to neuropsychiatric symptoms including insomnia

What can we learn from investigation of sleep in ME/CFS ?

- Source of insights into impairments of functional networks / pathomechanisms
- Sleep disorders in PAIS are clinically heterogeneous -> require diagnosis to identify specific treatment options
- Neurophysiology of sleep disturbance may give indications for differential effectiveness of treatment strategies

