

Beyond the Symptom: The Biology of Fatigue

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Electroencephalography of non-refreshing sleep

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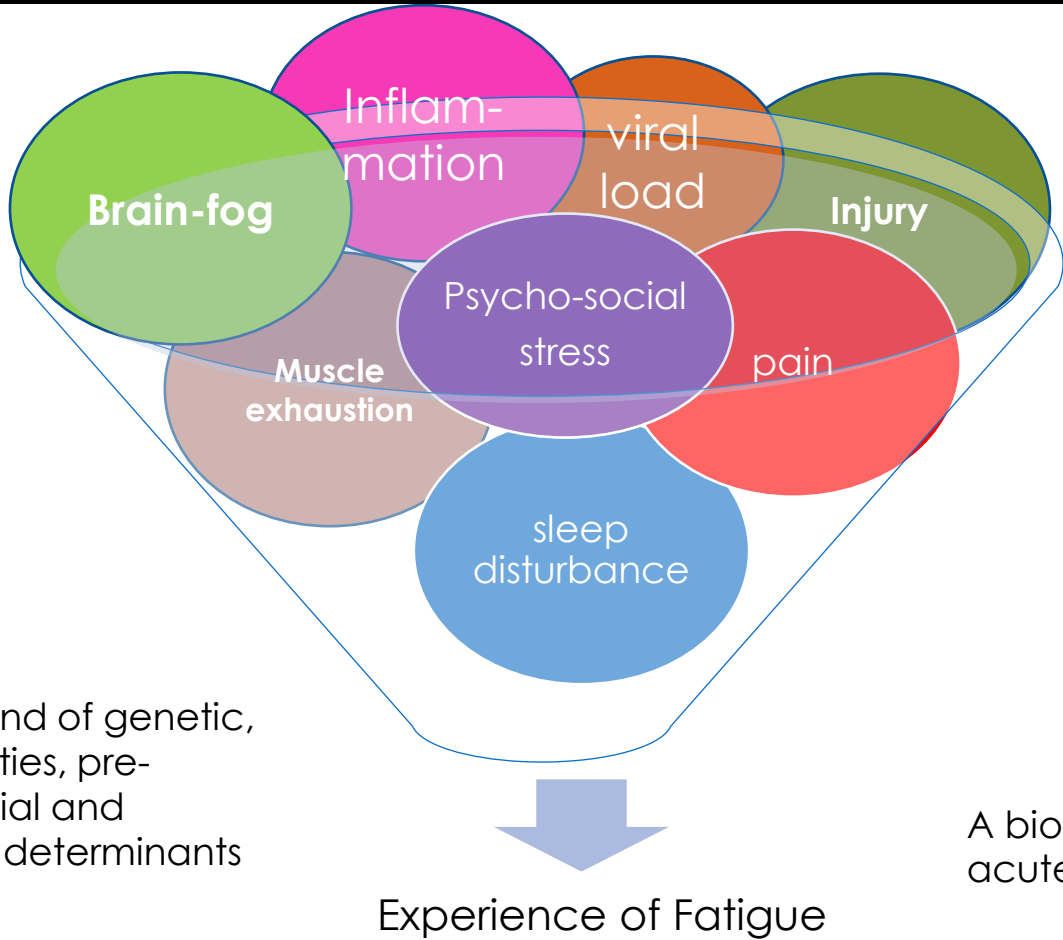


Disclaimer

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Other research funding is NIH based



The symptom of fatigue may have many causes but be experienced quite similarly



Fatigue is experienced on a background of genetic, epigenetic, systems biology vulnerabilities, pre-existing comorbid disease burden, social and environmental factors including social determinants of health.

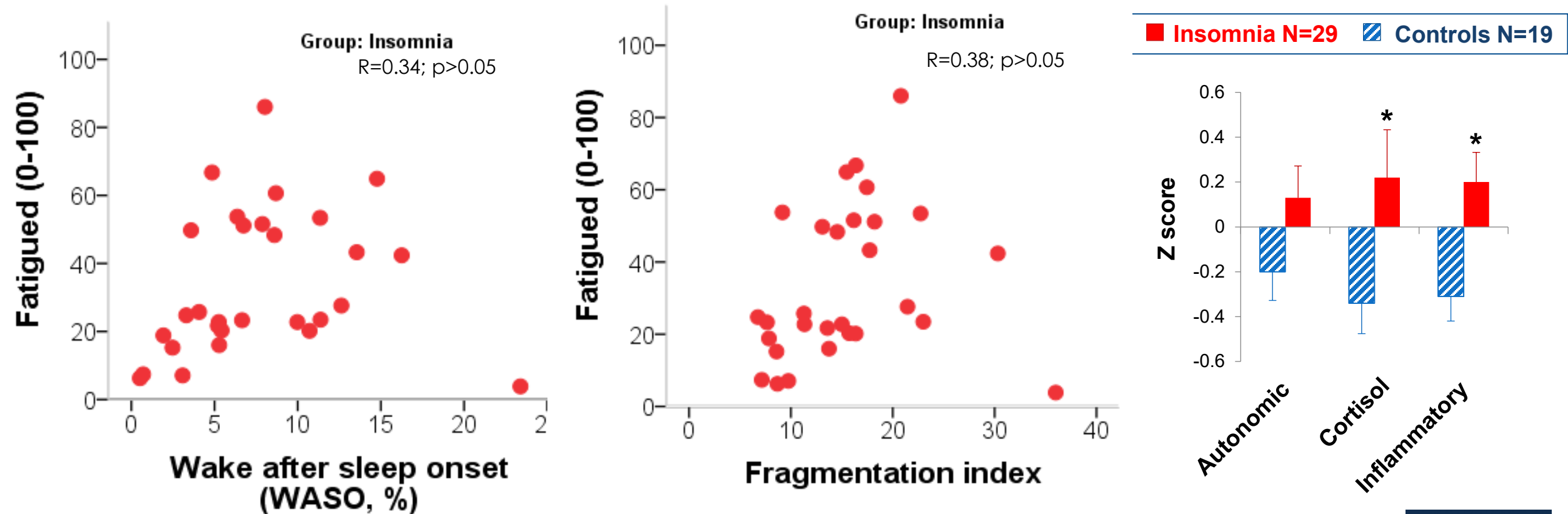
A biomarker would need to consider: acute/chronic; injury/stress/illness and severity





Chronic sleep disorders cause sleepiness and fatigue

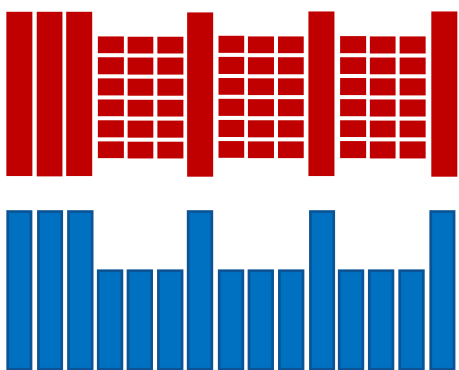
Insomnia disorder, sleep apnea, circadian rhythms disorder, narcolepsy, restless legs syndrome.



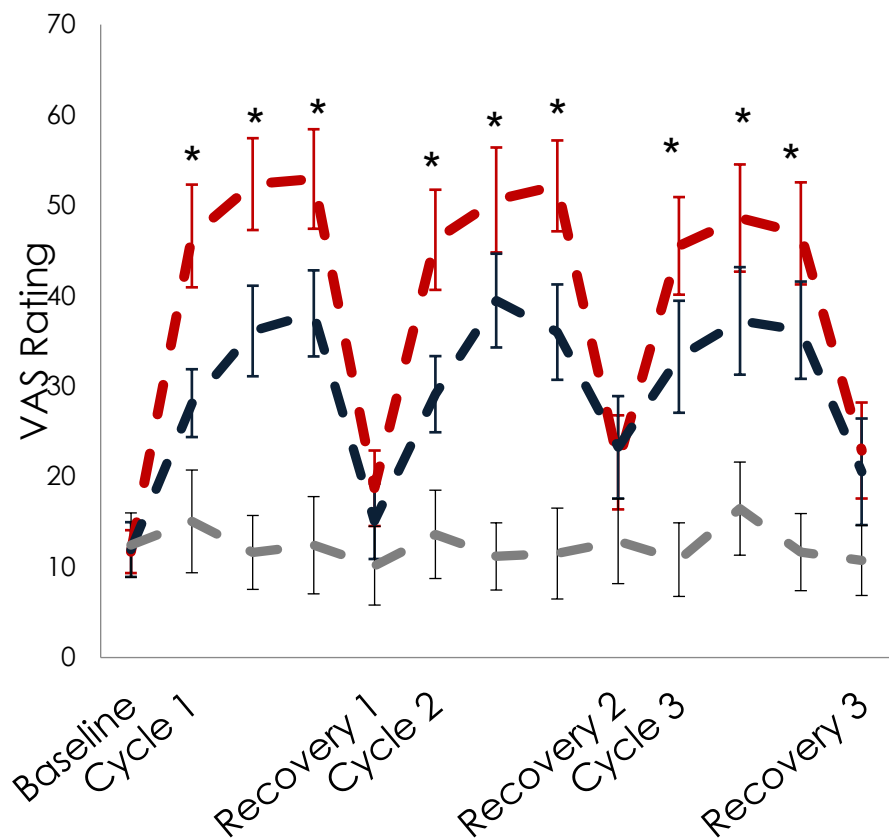
Floam et al., J. Sleep Res 2015



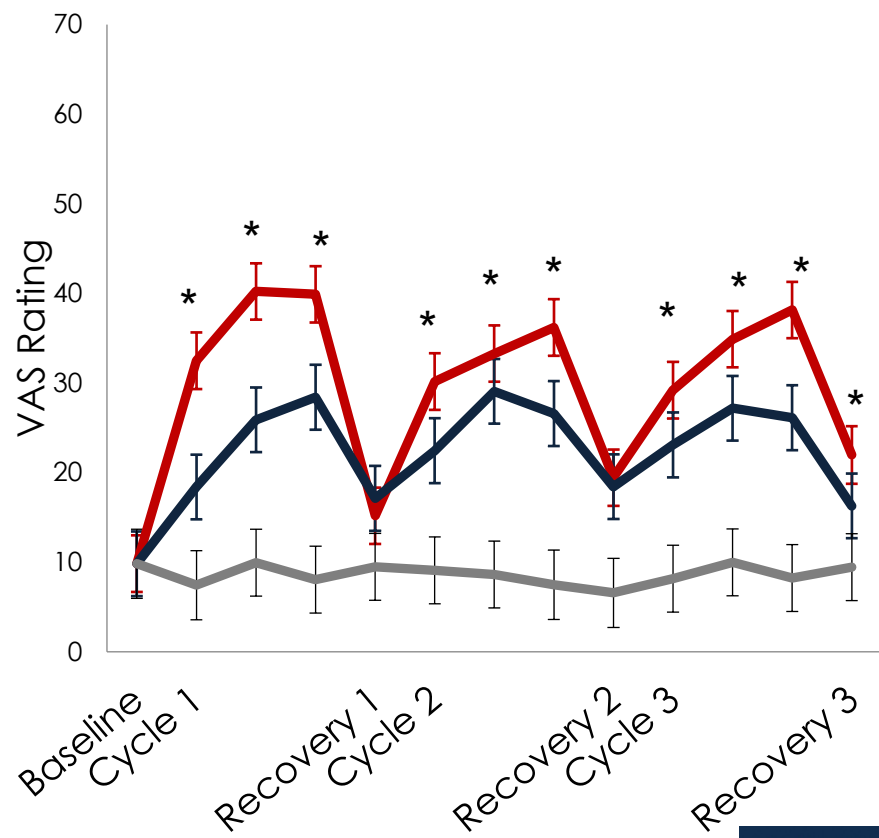
Experimental sleep disturbances in healthy sleepers cause sleepiness and fatigue



Sleepiness



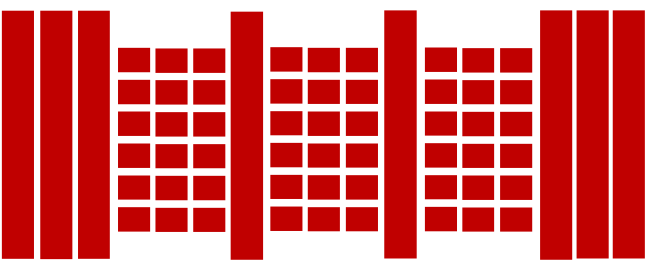
Fatigue



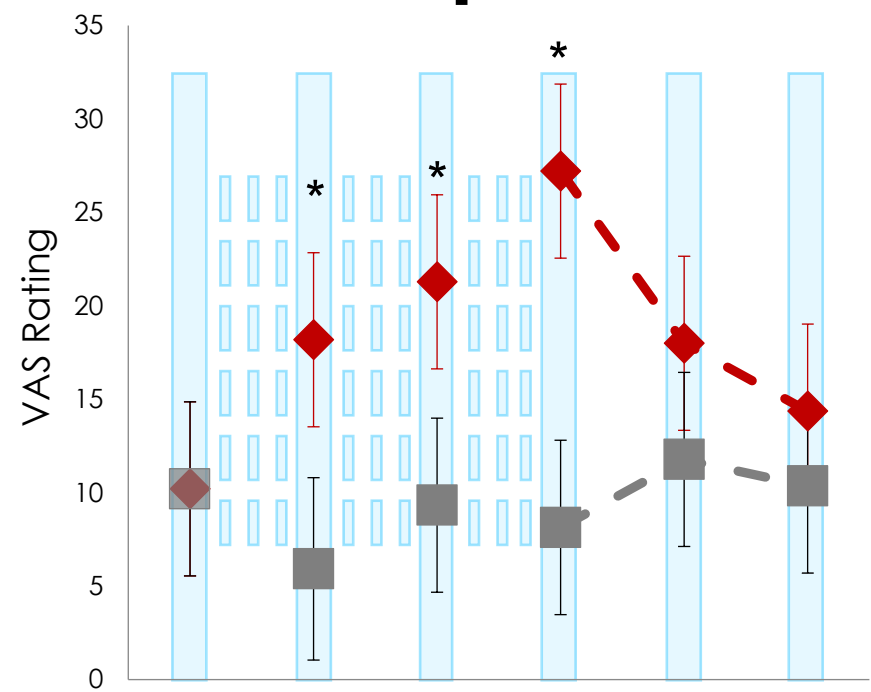
Devine et al Sleep 2017



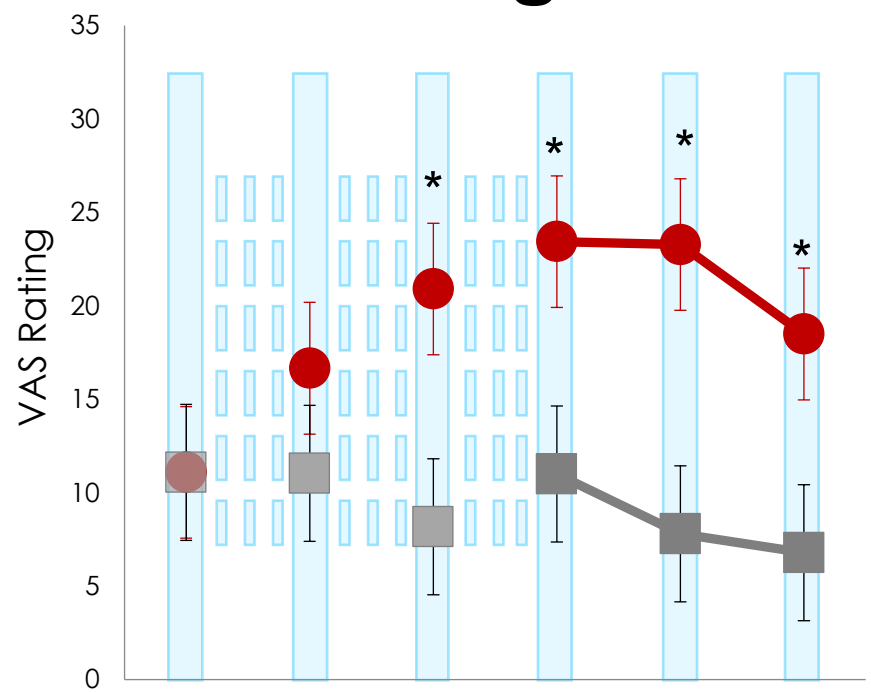
...and it takes multiple nights to recover



Sleepiness

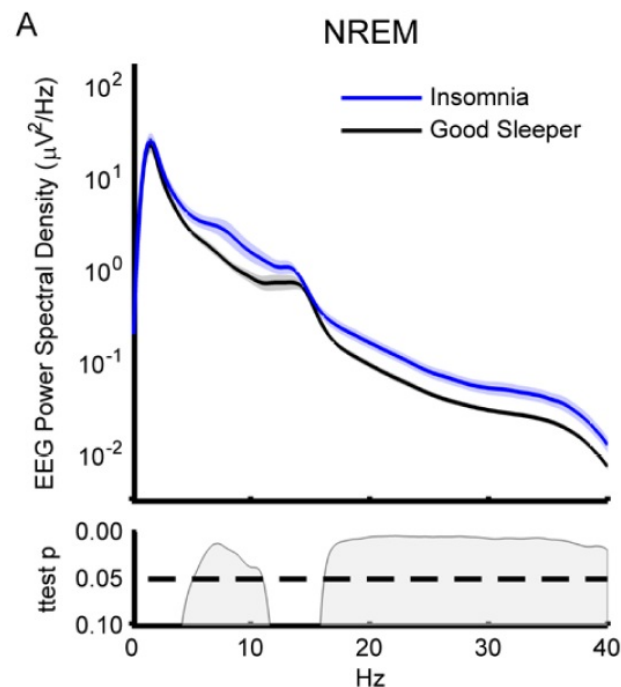
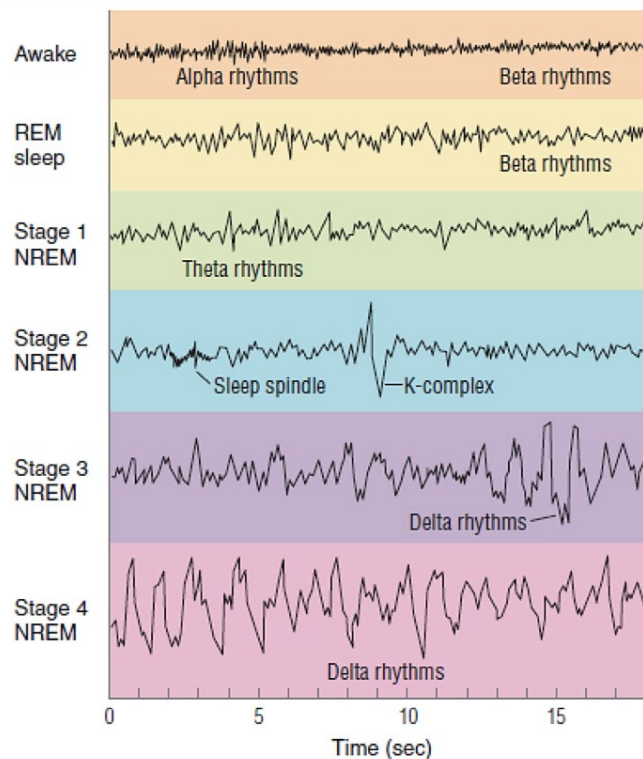


Fatigue





Electroencephalography of non-refreshing sleep



EEG around since 1929, discovered by Hans Berger in Germany who named it the "Elektrenkephalogramm", and the 10-20 system of electrode placements on the skull was published by Jasper in 1958.

Digitization has made for rich data and powerful modeling methods opened up many possibilities, including the search for an EEG biomarker of non-restorative sleep and fatigue.

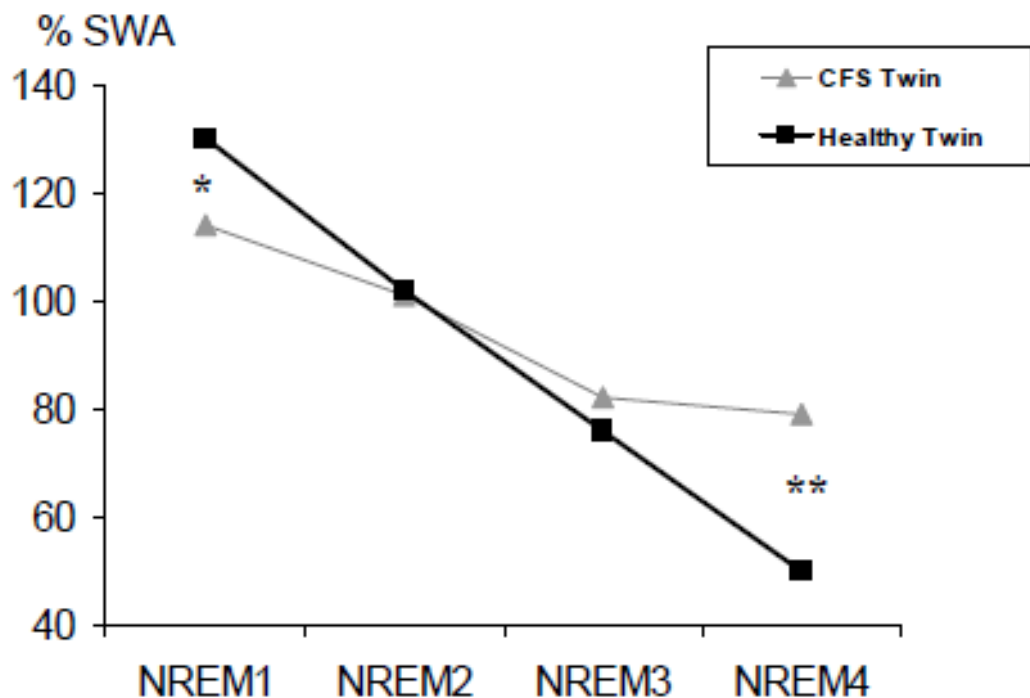


Investigation of sleep electrophysiology in ME/CFS has not led to a biomarker of fatigue

SHORT NOTE

The Impact of a 4-Hour Sleep Delay on Slow Wave Activity in Twins Discordant for Chronic Fatigue Syndrome

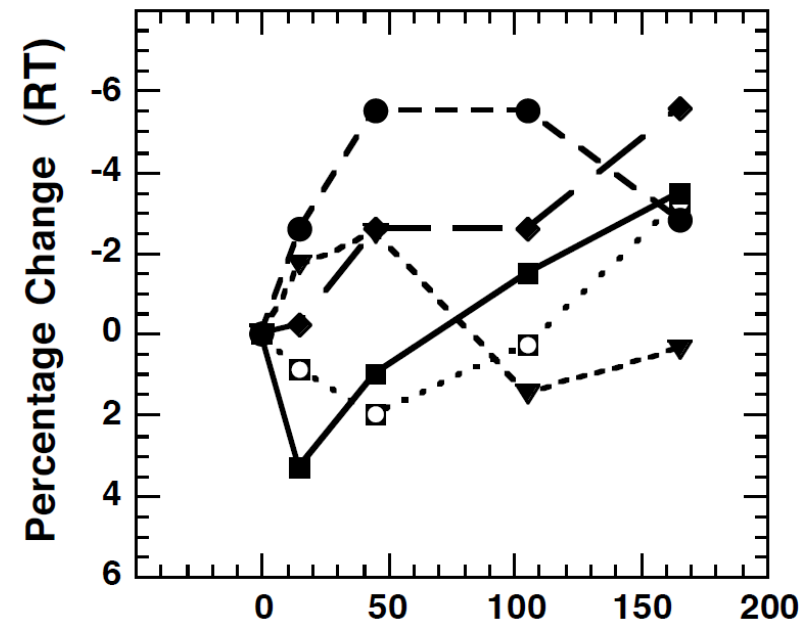
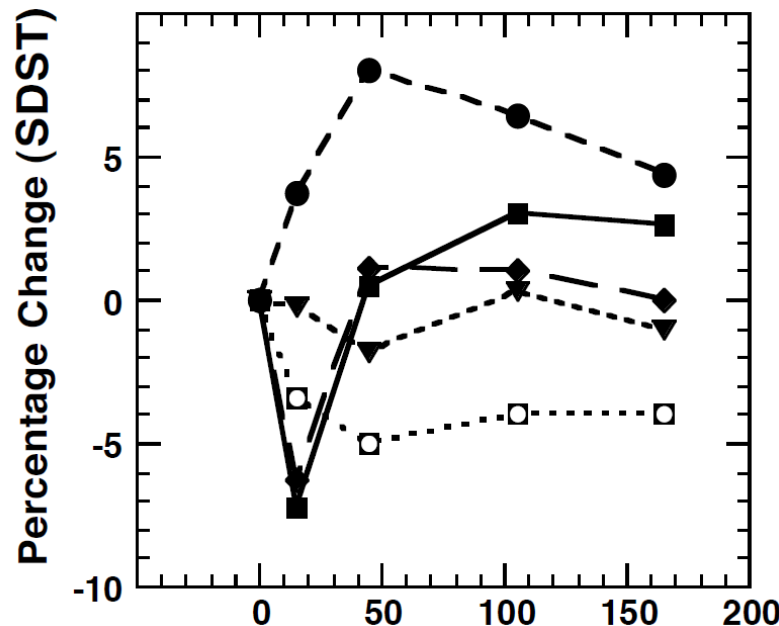
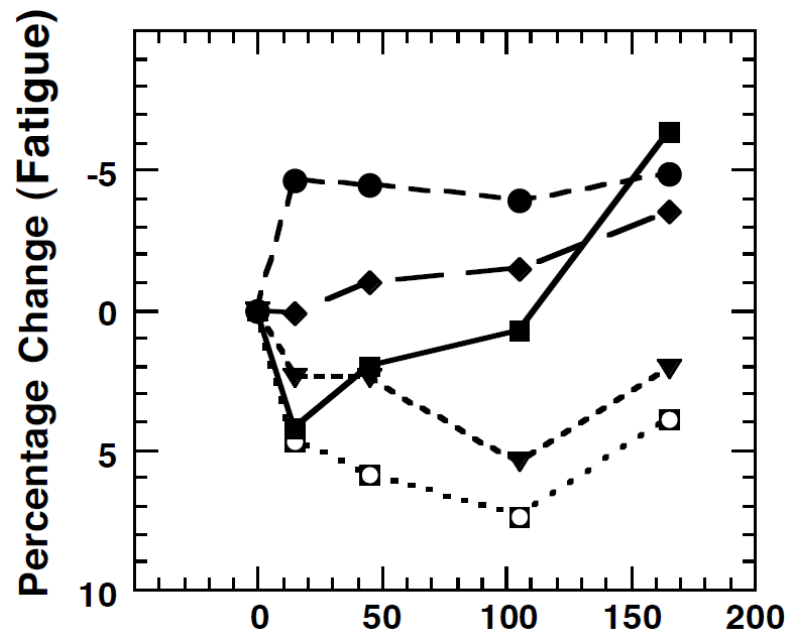
Roseanne Armitage, PhD¹; Carol Landis, DNSc, RN²; Robert Hoffmann, PhD¹; Martha Lentz, PhD, RN²; Nathaniel F. Watson, MD³; Jack Goldberg, PhD⁴; Dedra Buchwald, MD⁵



- This group of investigators found no substantial differences in the sleep architecture, frequency spectra, including spindle and delta frequencies.
- ME/CFS studies have even been conducted with monozygotic twins.
- There they found that ME/CFS is associated with a blunted SWA response to sleep deprivation challenge, suggesting that the basic sleep drive and homeostatic response are impaired.



Unrefreshing and non-restorative? Or is it subjectively unrefreshing but none-the-less restorative?



Legend:

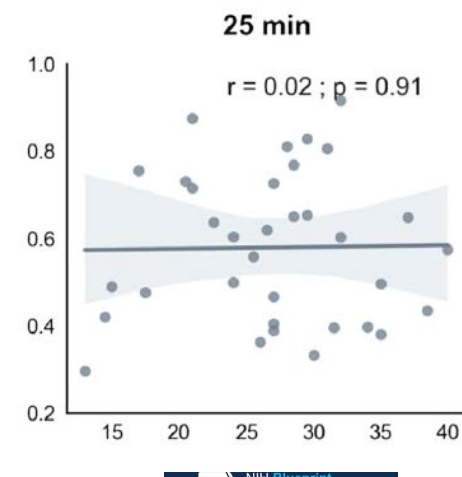
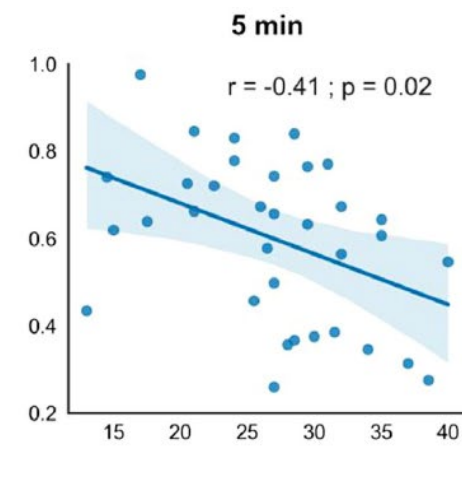
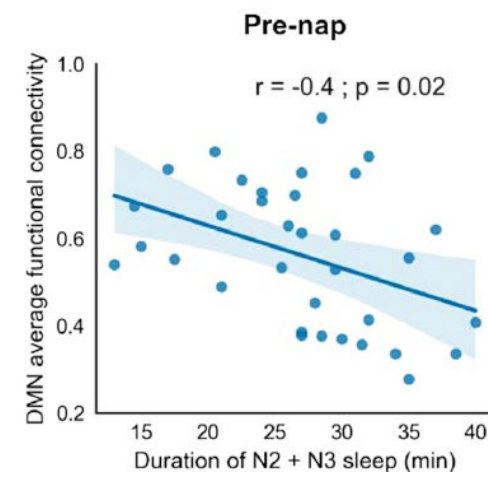
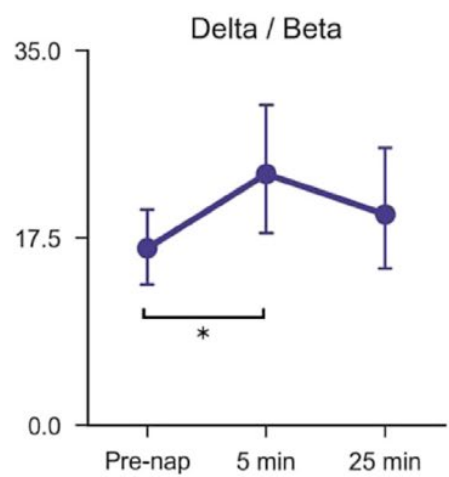
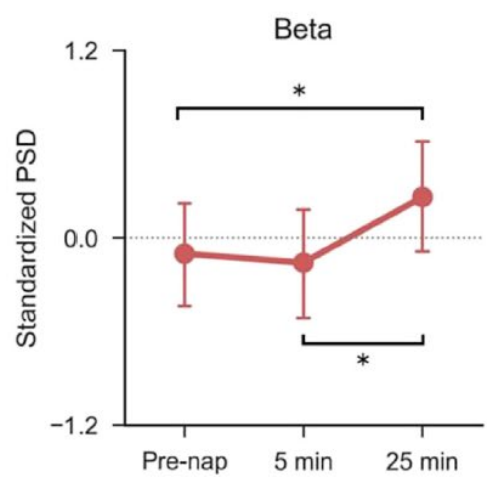
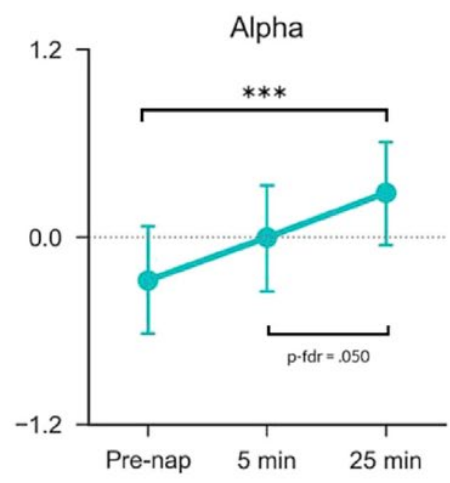
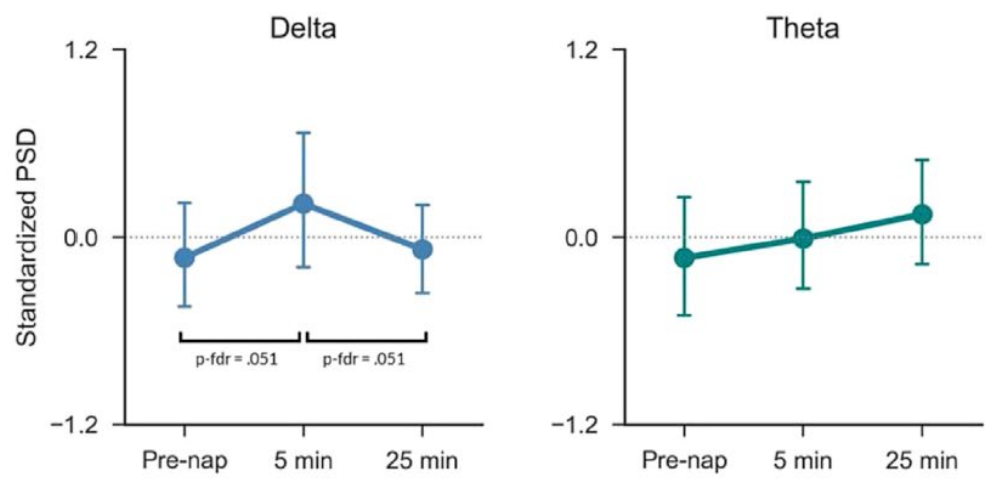
- no nap (dotted line, open squares)
- 5-min (dashed line, inverted triangles)
- 10-min (dashed line, circles)
- 20-min (solid line, diamonds)
- 30-min (solid line, squares)

Post-nap testing at 5, 35, 95 and 155 min after a nap that began at between 2:30 and 3:00pm

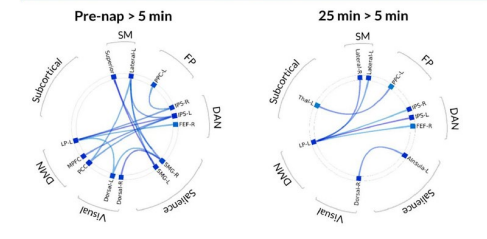
Brooks & Lack Sleep, 2006



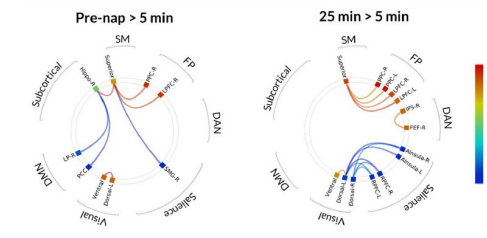
Unrefreshing and non-restorative? Can sleep inertia inform this question?



A) Participants awakened in N3 sleep (n=20)



B) Participants awakened in N2 sleep (n=14)



Vallat et al Neuroimage, 2019



The search for a biomarker of non-restorative sleep and fatigue, unrefreshing sleep, must include sleep and wake EEG

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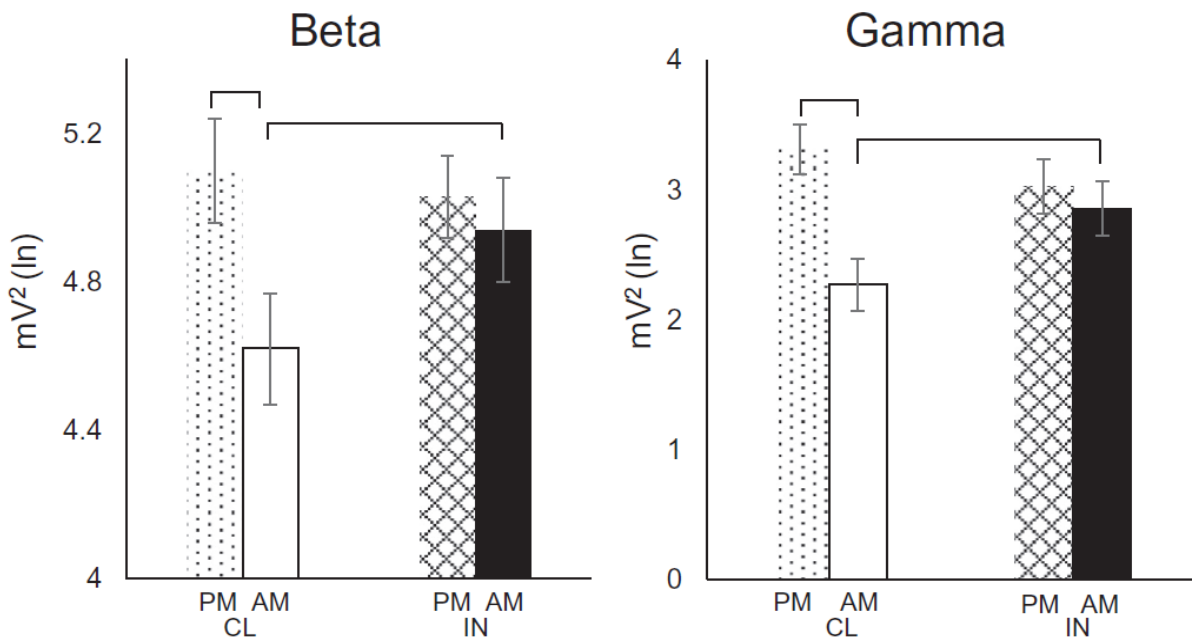


Waking EEG signs of non-restoring sleep in primary insomnia patients

María Corsi-Cabrera^{a,*}, Olga A. Rojas-Ramos^{a,b}, Yolanda del Río-Portilla^{a,b}

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New methods of EEG analysis show promise for use in discovering a fatigue biomarker



Sleep
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SLEEPJ, 2021, 1–13

doi: 10.1093/sleep/zsaa274

Advance Access Publication Date: 9 December 2020

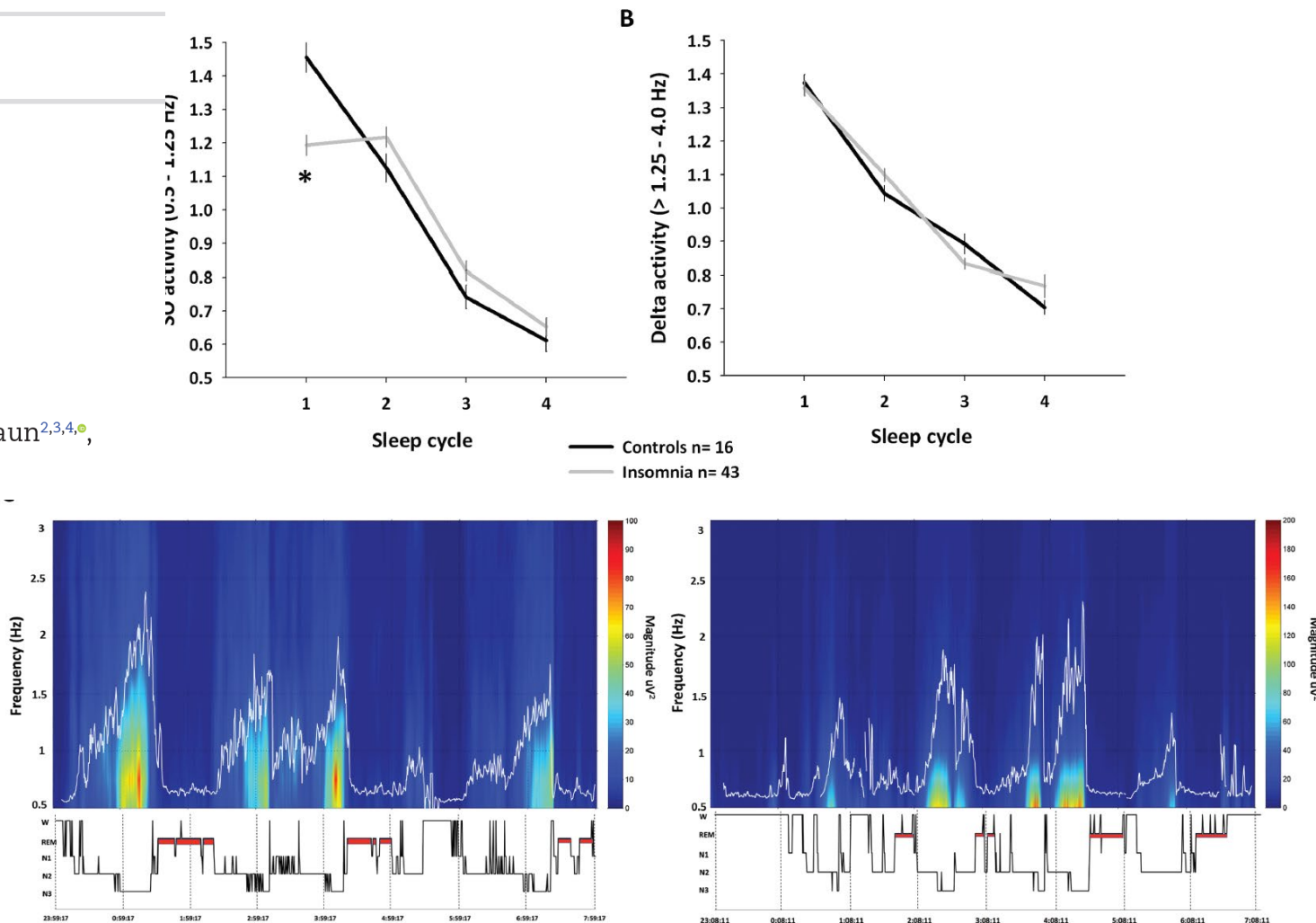
Original Article

ORIGINAL ARTICLE

Autonomic dysregulation and sleep homeostasis in insomnia

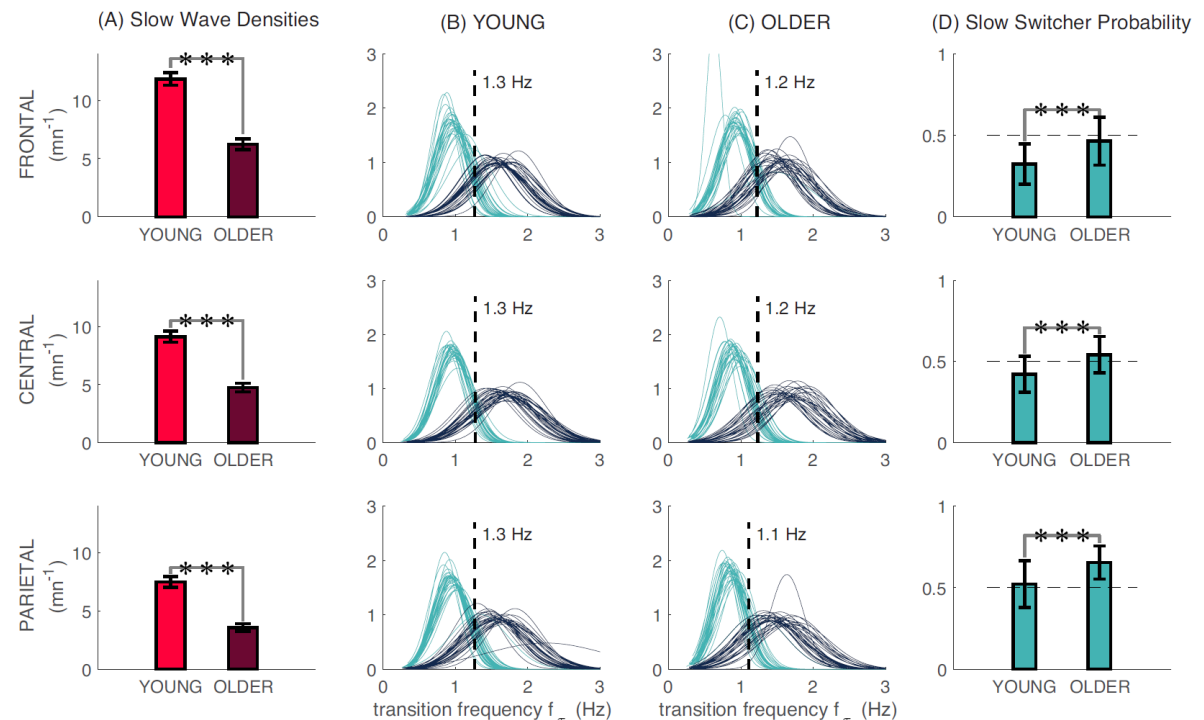
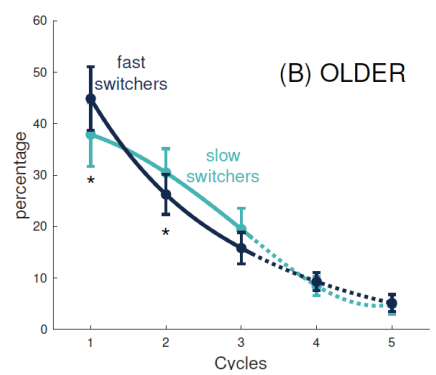
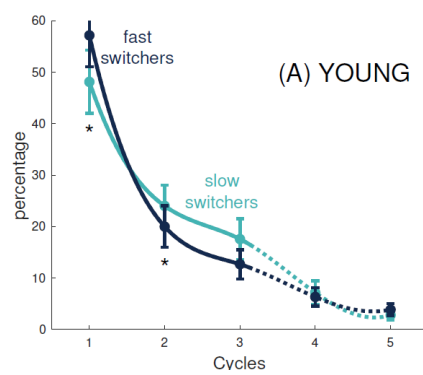
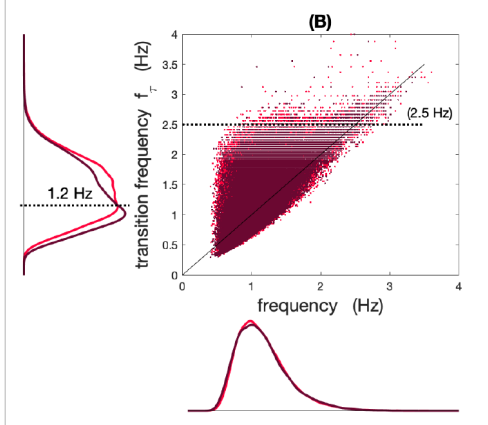
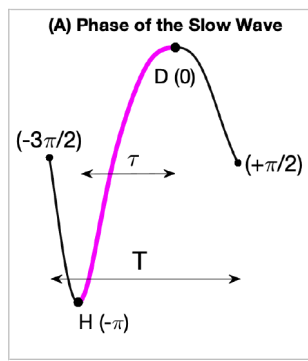
Daniela Grimaldi¹, Kathryn J. Reid¹, Nelly A. Papalambros¹, Rosemary I. Braun^{2,3,4,5}, Roneil G. Malkani¹, Sabra M. Abbott^{1,6}, Jason C. Ong^{1,6} and Phyllis C. Zee^{1,*}

Also found that 24h cortisol was elevated in insomnia and that NE was lower. Controls showed a correlation between NE during the day and SO in first cycle, but this was not seen in insomnia





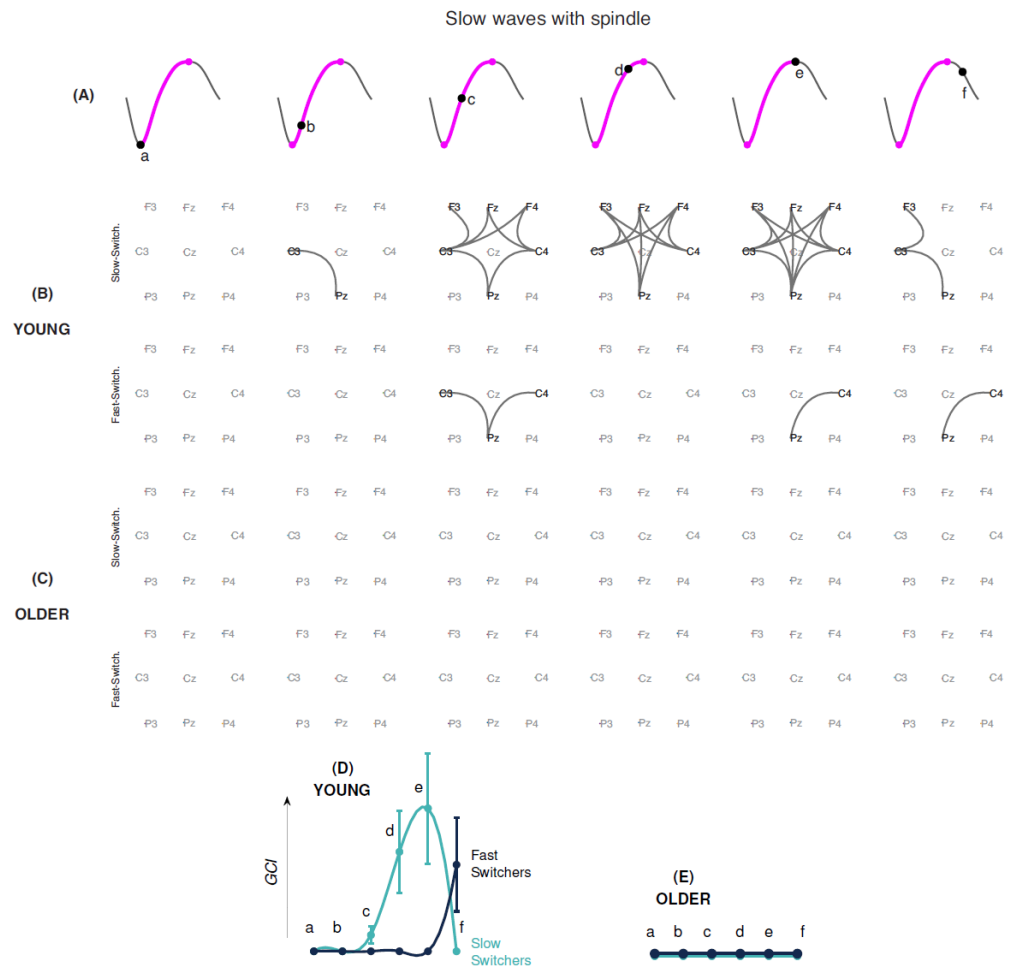
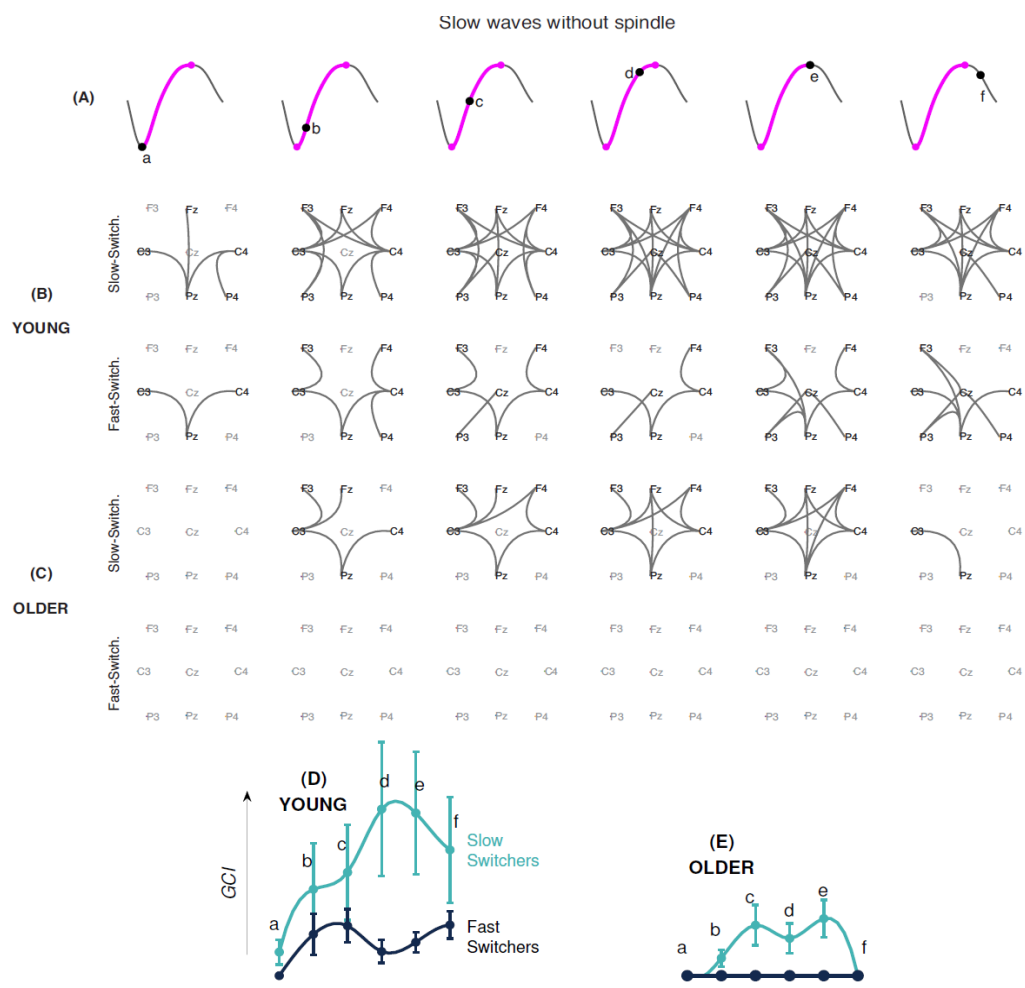
Dissecting slow waves



Bouchard et al., eLife 2021



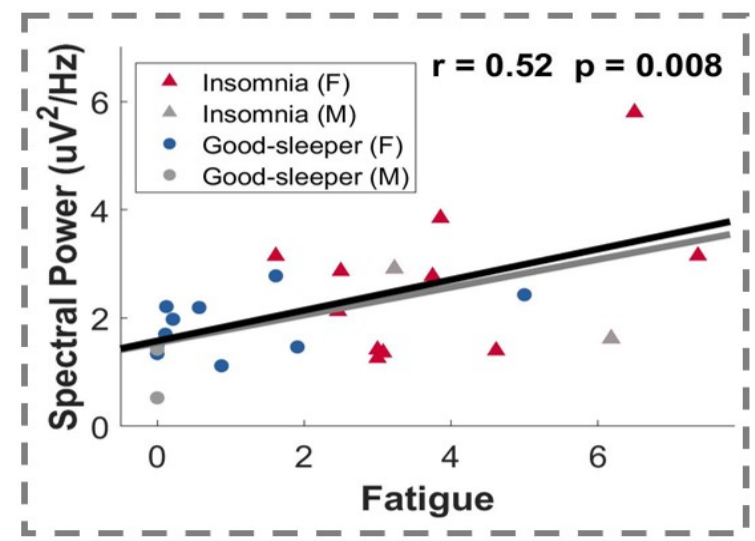
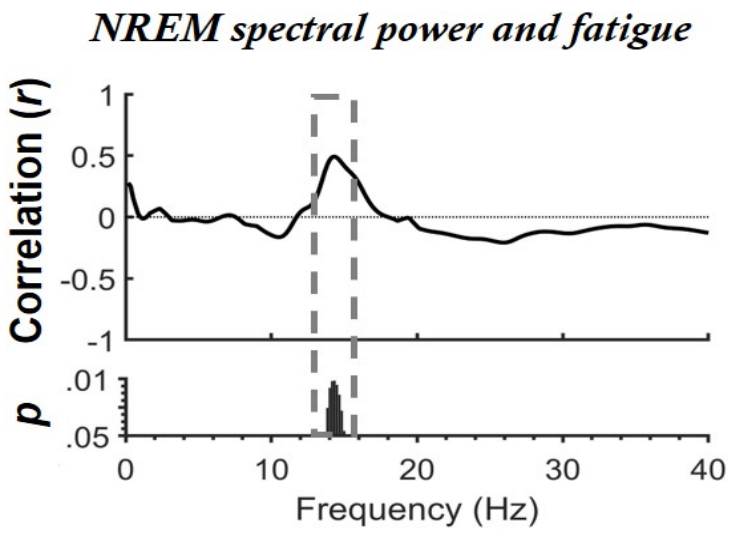
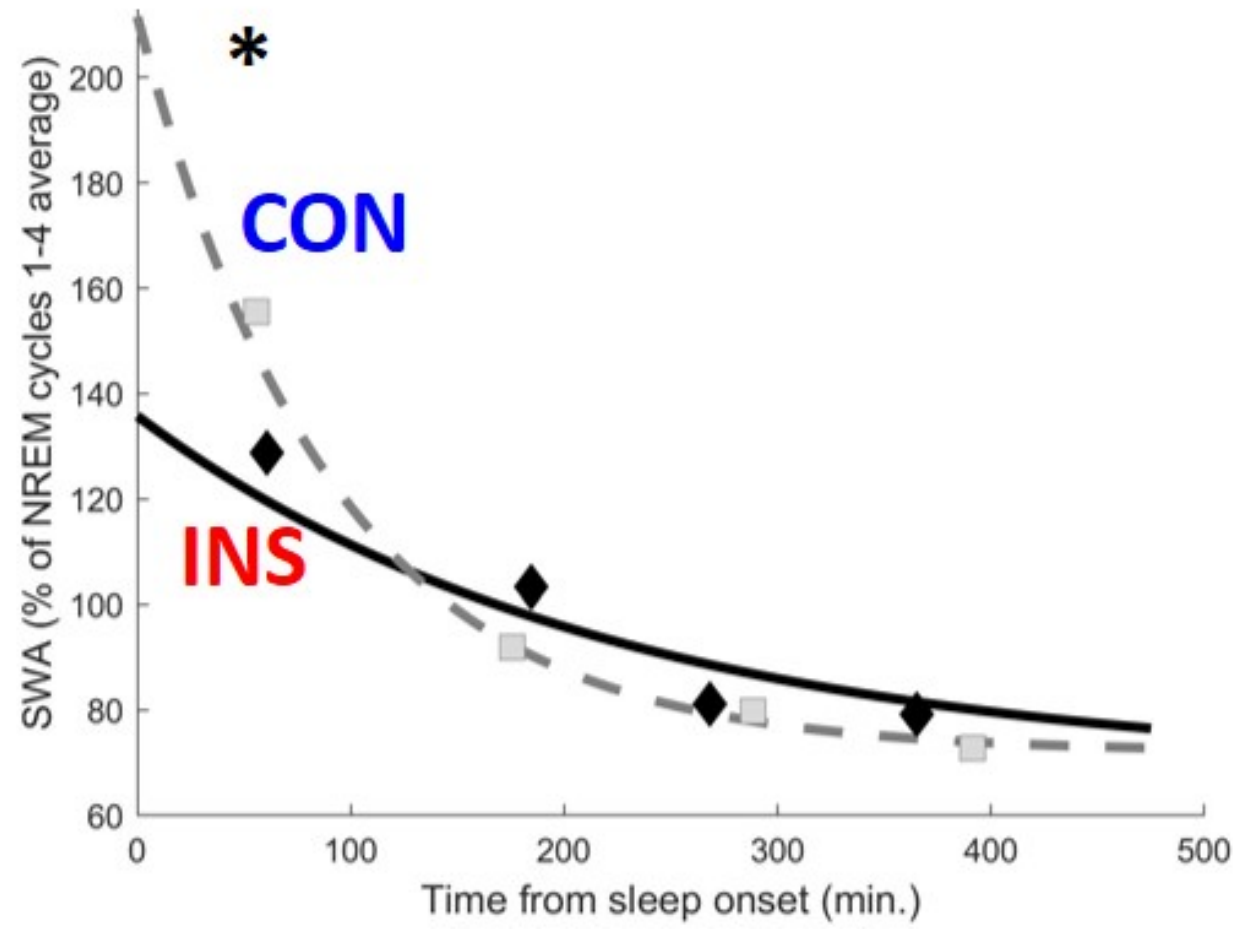
Dissecting slow waves



Bouchard et al., eLife 2021



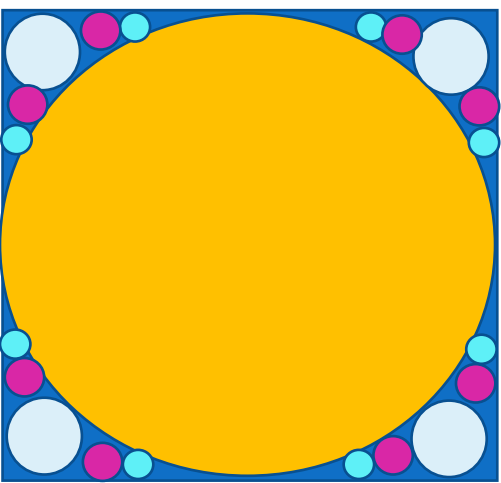
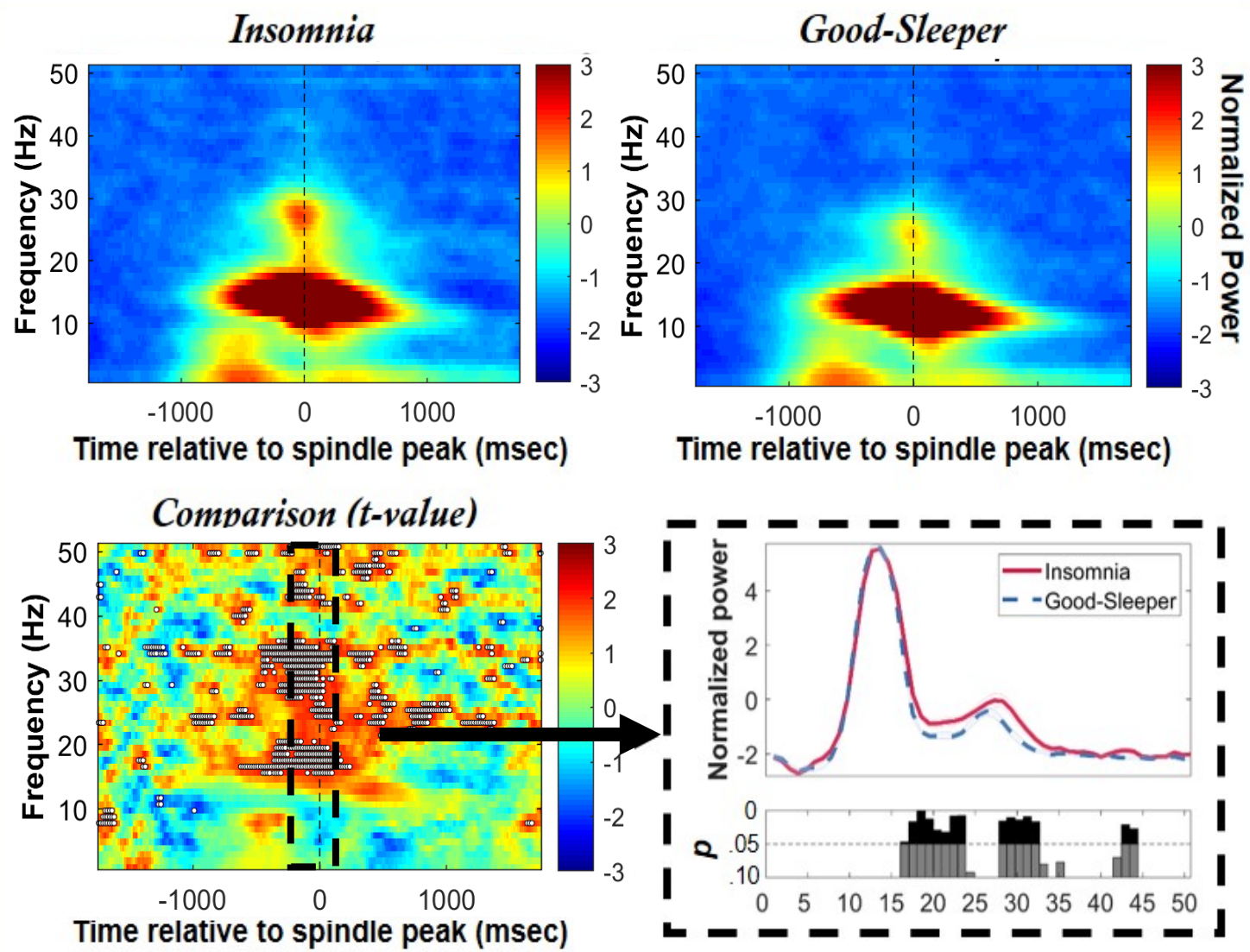
New methods of EEG analysis show promise for use in discovering a fatigue biomarker



Goldstein MR, Haack M, Mullington JM (2021). Sleep spindle harmonics in insomnia. *Sleep*, 44:A29.



New methods of EEG analysis may lead to discovery of a fatigue biomarker



Goldstein MR, Haack M, Mullington JM (2021). Sleep spindle harmonics in insomnia. *Sleep*, 44:A29.



Key Points

- Restorative sleep may be a necessary but not sufficient condition to provide subjective refreshment from sleep
- Non-refreshing sleep may be assessed subjectively; aspects of restorativeness must be physiologically and behaviorally measured
- Within-&-between participant designs with special attention to rate of change and individual differences; EEG across states and in conjunction with neurobehavioral as well as subjective evaluation
- Unprecedented opportunity and obligation, with PASC, to improve understanding of restorativeness of sleep and its refreshing quality; and role in recovery
- Biomarker potential with innovative analysis approaches

