17th Annual Sleep Medicine Virtual Course

Saturday, March 22, 2025

Sleep Function, an evolutionary perspective

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Conflict of Interest Disclosures for Speakers

Jerome Siegel has no relevant financial relationships with ineligible companies to disclose.

Learning Objectives

- Upon completion of this course, attendees should be able to…
  - Update 1: Understand the function of REM and nonREM sleep in the context their phylogenetic evolution.
  - Update 2: Appreciate that the claim that a primary function of sleep is “memory consolidation” is based on weak evidence.
  - Update 3: Understand sleep in the “natural” environment, as seen in hunter gatherers.
  - Update 4: Understand that longer sleep time is not correlated with longer lifespan.

THE FUNCTION AND EVOLUTION OF SLEEP

Jerome Siegel, University of California, Los Angeles

Sleep deprivation studies of learning and memory are difficult to interpret

- **Interference from the subject's learning during the deprivation period degrades subjects recall of the items learned prior to start of the deprivation.**
- **Cortisol release increases during sleep deprivation and waking stress. Elevated cortisol level is known to decrease recall.**
- Most sleep deprivation studies have **not controlled for these factors**.

Cortisol release blocks learning

1. Gribbin,C.E., Watamura,S.E., Cairns,A., Harsh,J.R., & Lebourgeois,M.K. The cortisol awakening response (CAR) in 2- to 4-year-old children: effects of acute nighttime sleep restriction, wake time, and daytime napping. Dev. Psychobiol. 54, 412-422 (2012).

2. Dinse,H.R., Kattenstroth,J.C., Lenz,M., Tegenthoff,M., & Wolf,O.T. The stress hormone cortisol blocks perceptual learning in humans. Psychoneuroendocrinology 77, 63-67 (2017). Our data show that a single dose of cortisol not only disrupts memory in the hippocampus, but it also has a substantial effect on the plasticity of sensory areas of the brain

3. Brunner,R.O.M.U. et al. Effect of high-dose cortisol on memory functions. Ann NY Acad Sci 1071, 434-437 (2006).

4. Lee,B.K. et al. Associations of salivary cortisol with cognitive function in the Baltimore memory study. Archives of General Psychiatry 64, 810-818 (2007).

5. Crowley,S.J. et al. A longitudinal assessment of sleep timing, circadian phase, and phase angle of entrainment across human adolescence. PLoS ONE 9, e112199 (2014).

Papers showing effects of sleep deprivation on learning and memory, to my knowledge, have never controlled for, or measured, cortisol levels, making it impossible to distinguish sleep loss effects from cortisol effects caused by sleep deprivation.

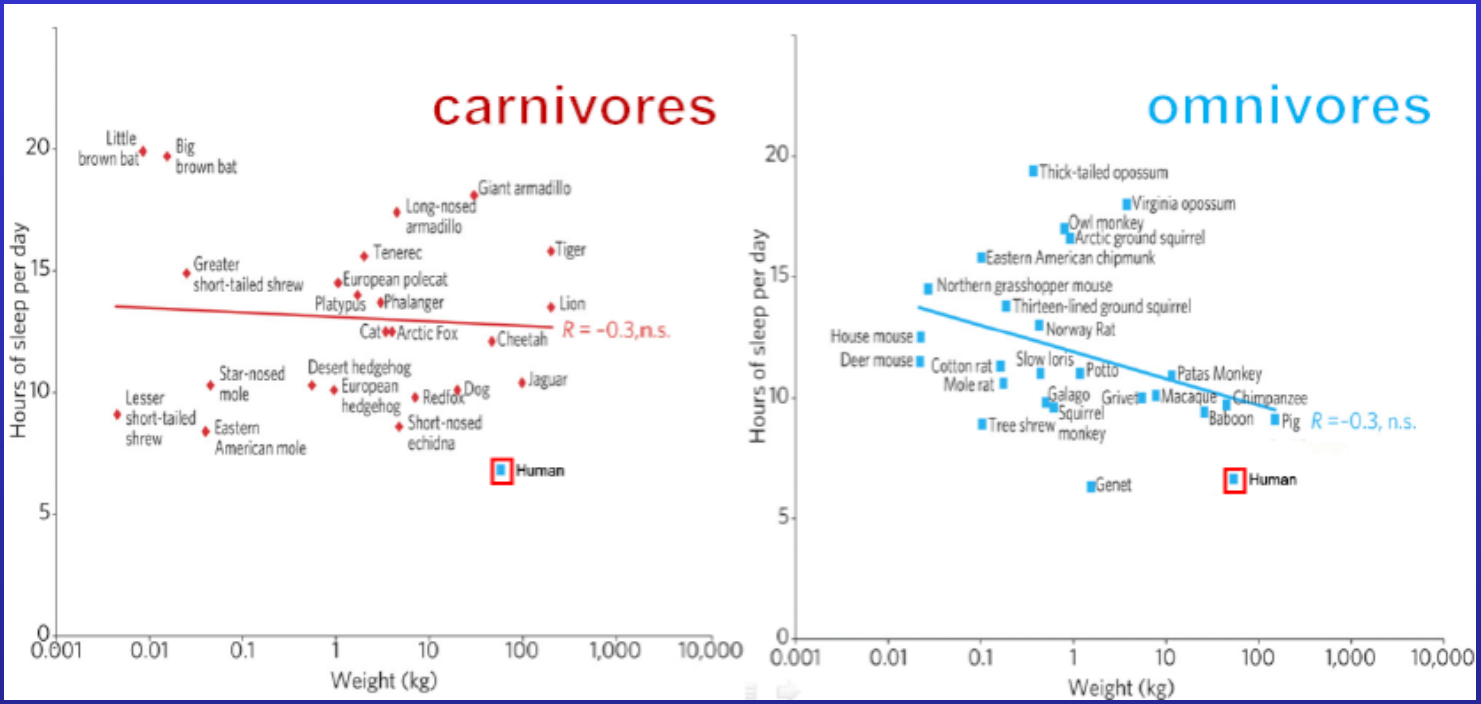
As an alternative to human sleep deprivation studies, animal studies of baseline sleep duration can provide insights into sleep function because REM and non-REM sleep amounts vary over more than an order of magnitude between species. These differences can be correlated with cognitive, behavioral, neurologic, and dietary variables without introducing any stress. Which of these variables is sleep most strongly correlated with?

Across placental mammalian species:

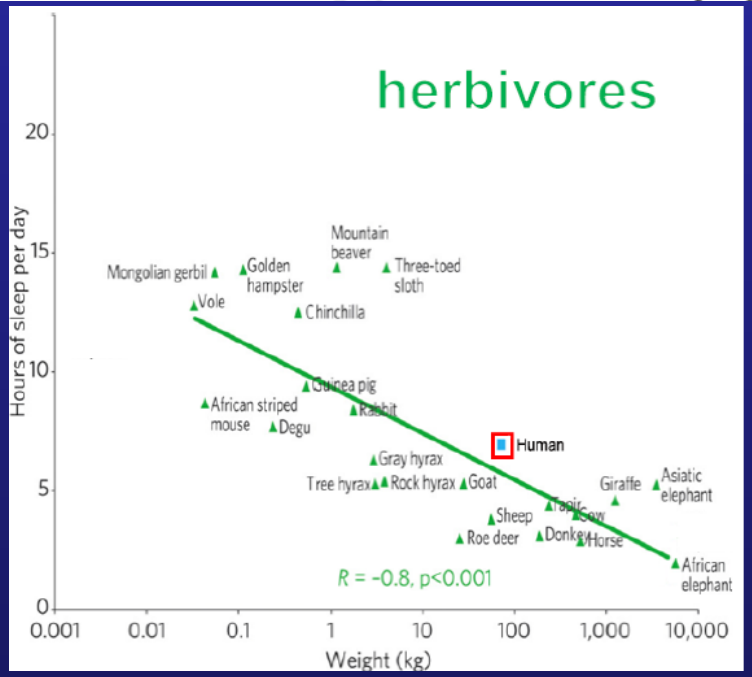
- Carnivores have the greatest amount of sleep and herbivores the least.

- Herbivore sleep duration is negatively correlated with body mass, with big herbivores sleeping the least (and spending most of their waking time eating).

- Humans have a low amount of sleep, lower than that in other primates, comparable to that in herbivores, and less than that in carnivores and most omnivores.



Hunter-gatherers main food is plants. Finding food takes most of their day. The growth of agriculture has greatly reduced food acquisition time and created “free time” in developed economies.



Siegel, Lancet Neurology 2022
Siegel, Nature 2005

Sleep in the wild provides insights not available under zoo or constant laboratory conditions. Although we tend to think of sleep duration as constant once animals reach adulthood, sleep varies with:

- Season/temperature
- Migration
- Feeding
- Mating
- Predator-Prey related conditions

Lyamin and Siegel, Current Biology, 2024

African elephants in Botswana

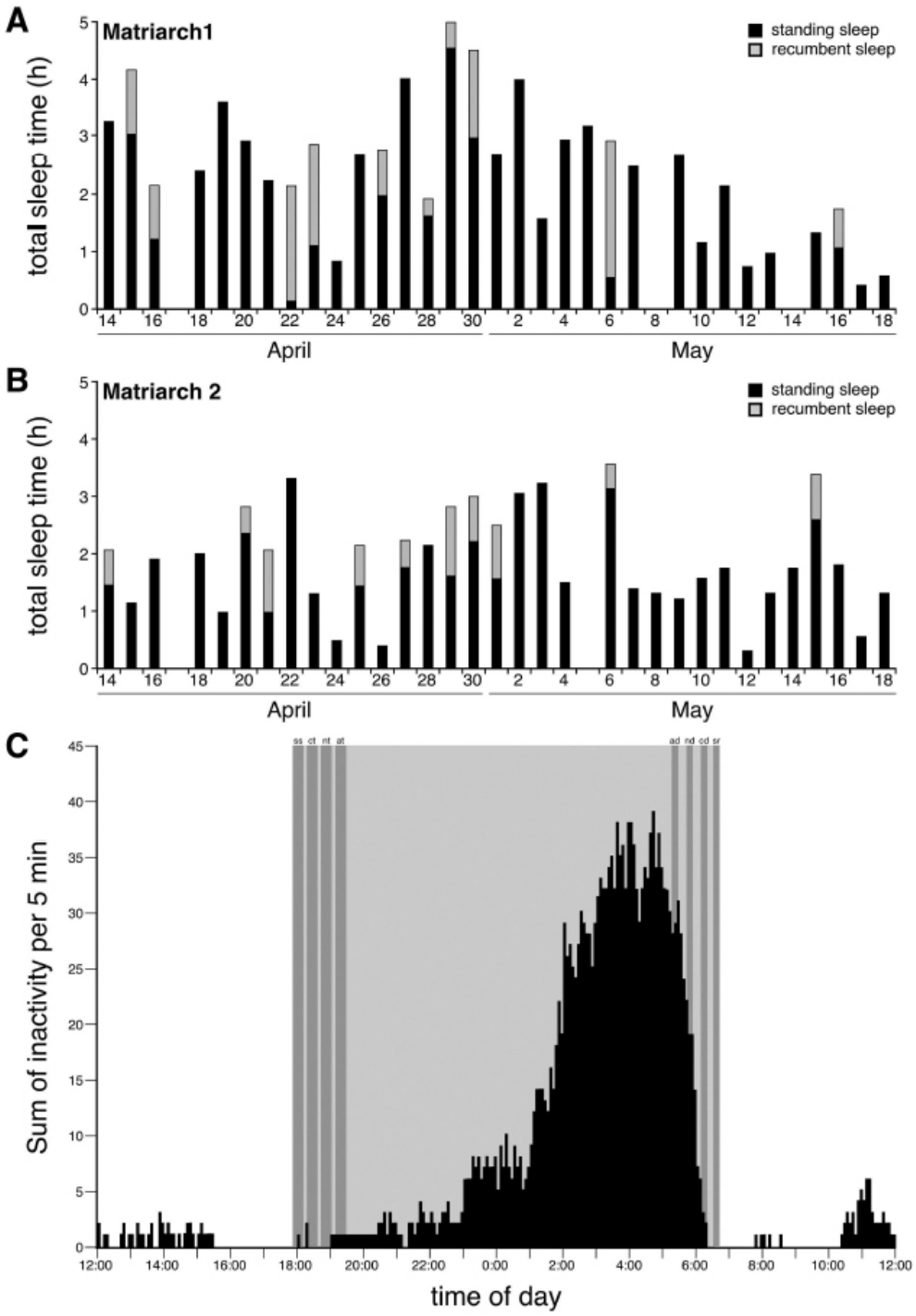
- **Although African elephants <u>in zoos</u> sleep 4-5 Hours/day, the average sleep duration of African elephants in the wild is 2.1 hours/day, <u>the lowest of any land mammal</u>.**

- **<u>Wild elephants are healthier and live much longer than elephants in captivity. Elephants have impressive cognitive abilities</u>.**

- **Days without sleep are not unusual and are not followed by rebound.**

- **Most sleep occurs towards the end of the night: energy savings.**

Gravett, Bhagwandin, Sutcliffe, Landen, Lyamin, Siegel, Manger, PLOS One 2017



Little Brown Bat sleeps 20 h/day, the highest of any mammal. Waking is synchronized to prey availability. It can be adaptive to be inactive.

Siegel, Nature Reviews Neuroscience 2009

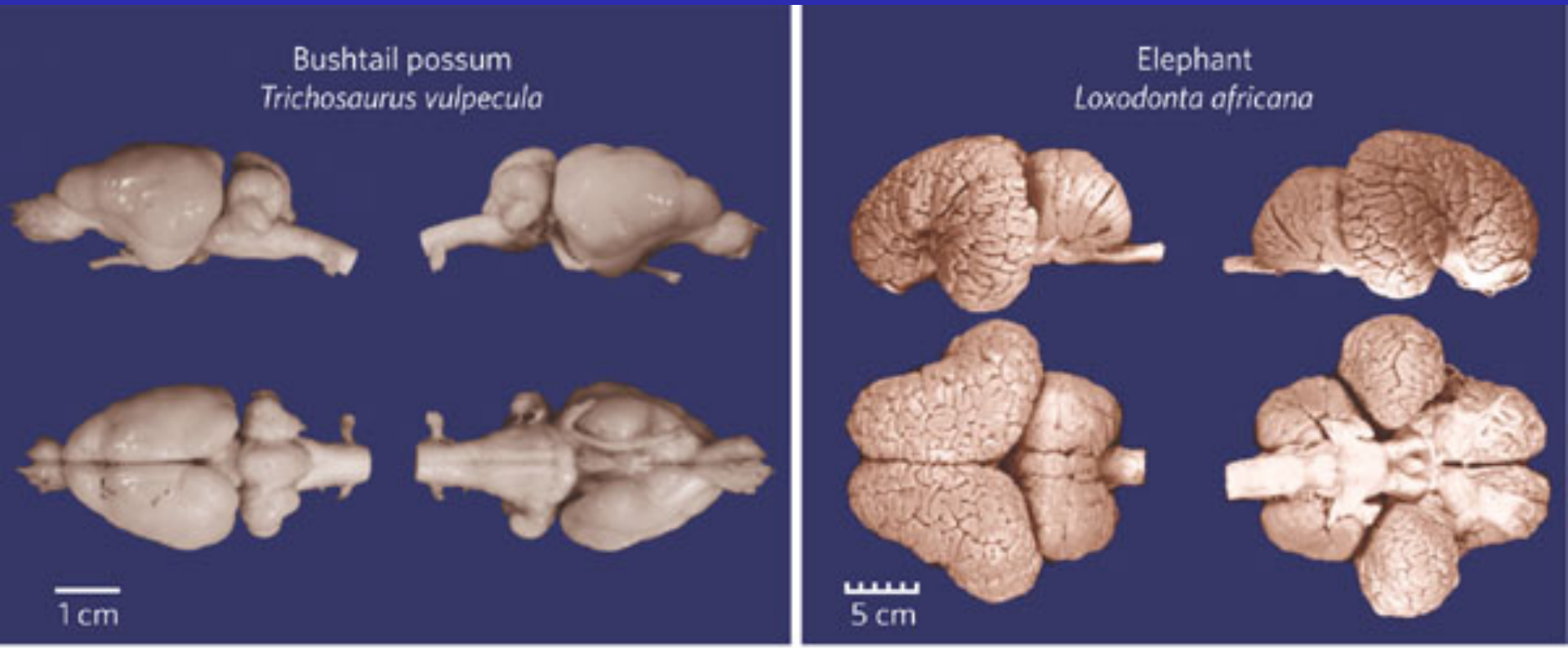
Is sleep for the brain?

INSIGHT COMMENTARY NATURE|Vol 437|27 October 2005|doi:10.1038/nature04283

Sleep is of the brain, by the brain and for the brain

J. Allan Hobson[1]

Brain size and brain/body weight ratio are not correlated with total sleep time. Very weakly and negatively correlated with REM sleep time (R^2 =.04)



18 hours of sleep, 6.6 hours of REM sleep

2.1 hours of sleep

Siegel, Lancet Neurology, 2022; Nature, 2005, Gravett et al. 2017

Brain size vs. total sleep and REM sleep (hours/day)

- **Neither REM nor nonREM sleep time sleep time is correlated with brain size, brain/body weight ratio or presumed cognitive capabilities.**

- **REM sleep time is maximal in the platypus and echidna, both monotreme mammals.**

- **Cetaceans (whales and porpoises) do not have REM sleep.**

Siegel, 2023, Revue Neurologique

High REM Sleep

≥ 3 hours of REM sleep/day

Siegel, Lancet Neurology 2022, Science, 2001

Platypus
Ornithorhynchus anatinus

8 REM, 14 Total

Thick-tailed Opossum
Lutreolina crassicaudata

6.6 REM, 18 Total

Ferret
Mustela nigripes

6 REM, 14.5 Total

Big Brown Bat
Eptesicus fuscus

3.9 REM, 19.7 Total

Armadillo
Dasypus novemcinctus

3 REM, 17 Total

European Hedgehog
Erinaceus europaeus

3.5 REM, 10.1 Total

Human
Homo sapiens

2 REM, 7 Total

Low REM Sleep

≤ 1 hour of REM sleep/day

Guinea Pig
Cavia porcellus

1 REM, 9.5 Total

Guinea Baboon
Papio papio

1 REM, 9.5 Total

Sheep
Ovis aries

0.6 REM, 5.9 Total

Horse
Equus caballus

0.5 REM, 3 Total

Giraffe
Giraffa camelopardalis

0.5 REM, 4.5 Total

Bottlenose Dolphin
Tursiops truncatus

0 REM, 4 Total

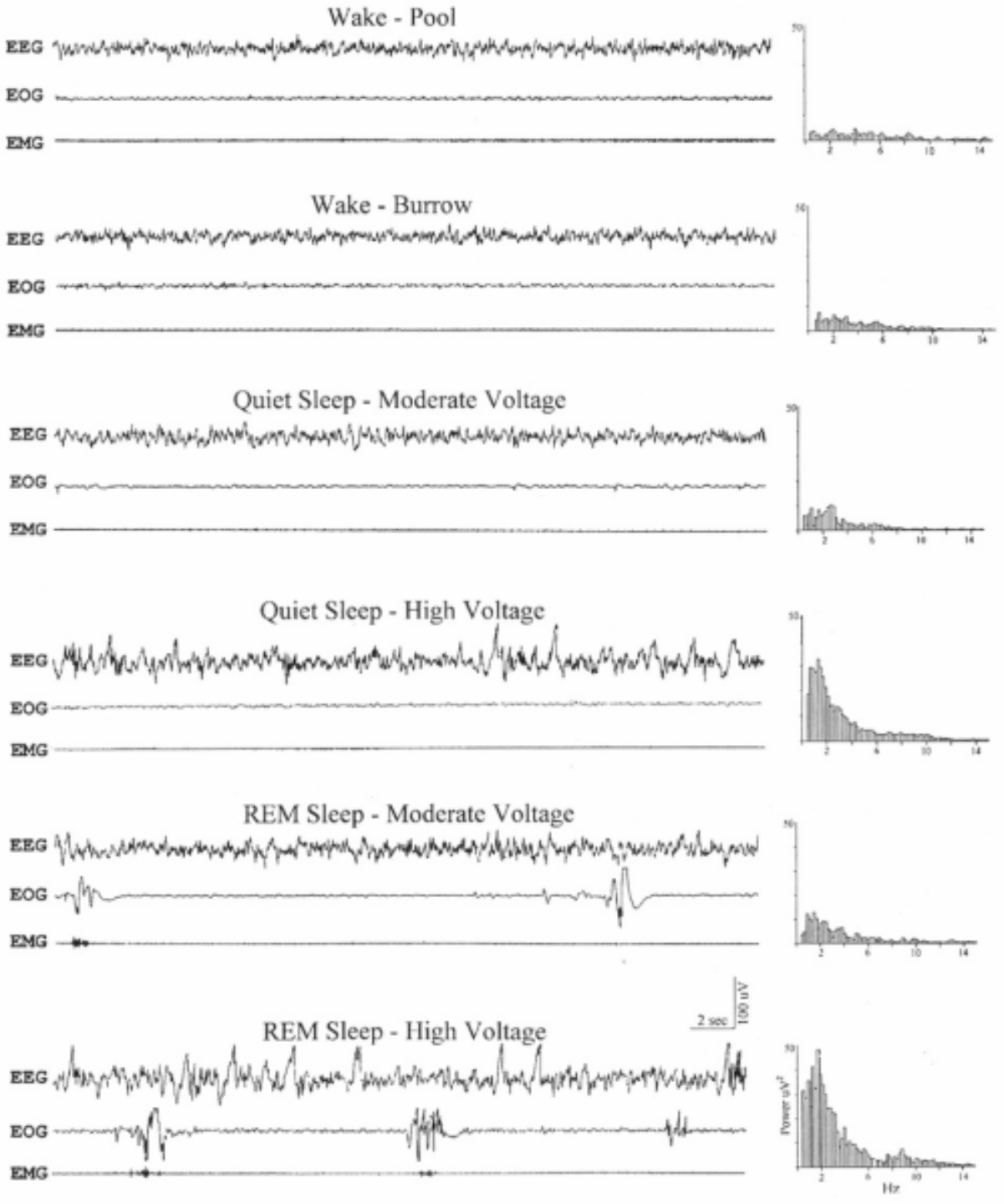
Platypus, an egg laying (monotreme) mammal

(Ornithorhynchus anatinus) Siegel et al., 1999

The platypus has very large amounts (8h/day) of REM sleep,' frequently with slow wave EEG activity.

Platypus and echidna (the other monotreme mammal) have more REM sleep than any other mammals.

Siegel et al., Neuroscience, 1999

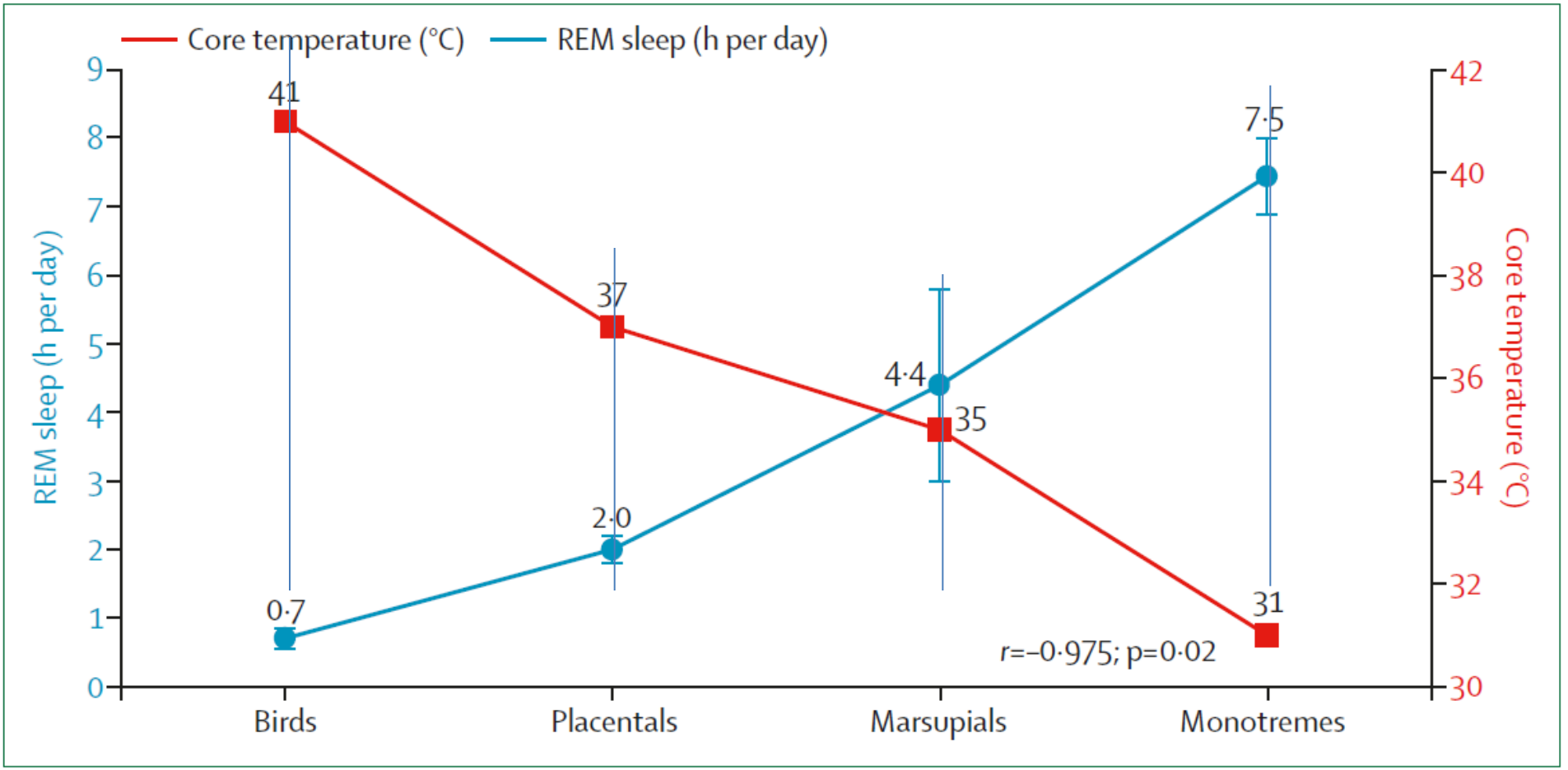



Platypus
(Ornithorynchus anatus)

REM sleep in the platypus and echidna

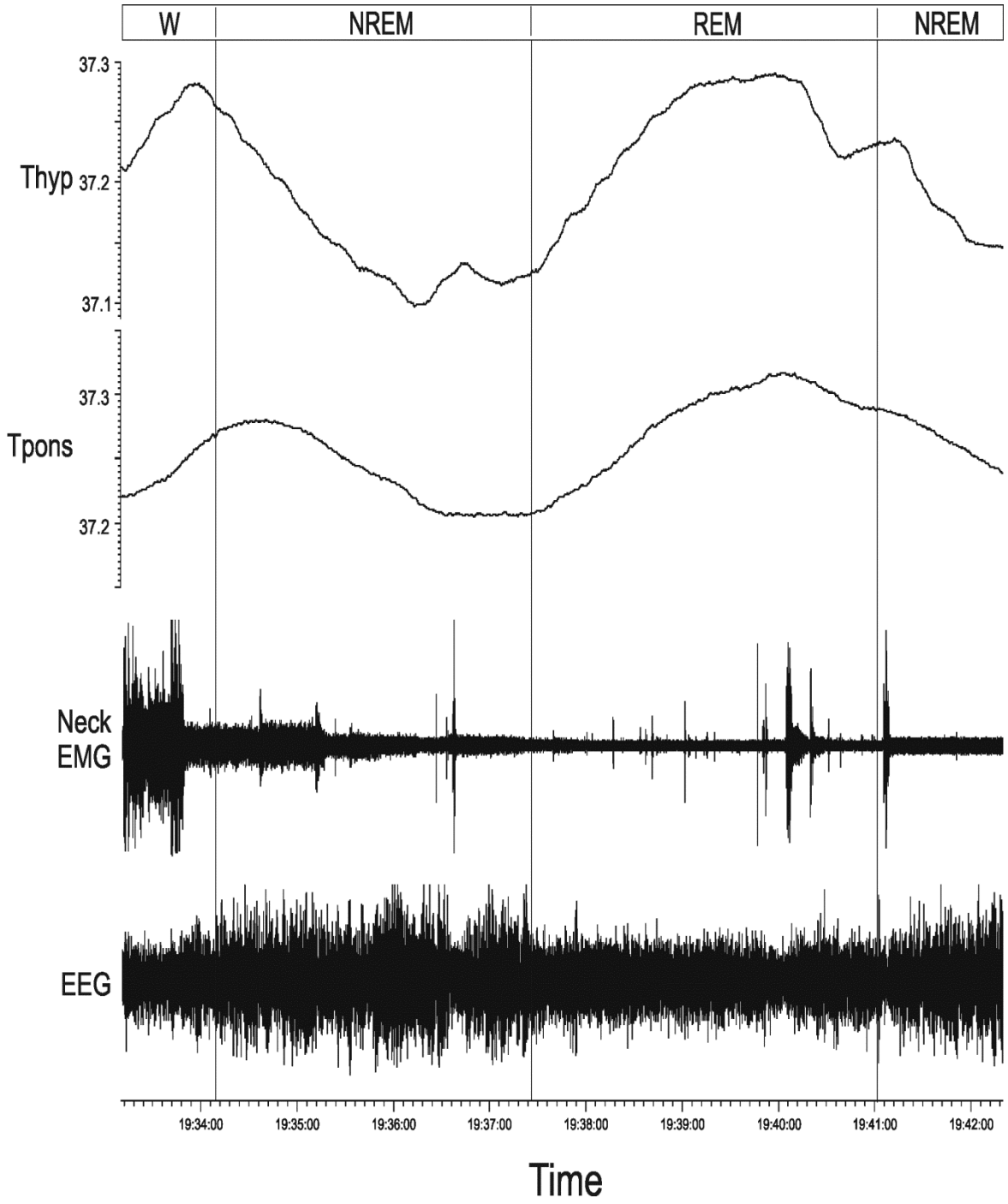
- Why do monotremes, “primitive” egg laying mammals, have so much REM sleep (Siegel et al., 1999)?
- Brain is roughly the size of the rat brain.
- But body (and brain) temperature is only 31°C. Could brain temperature be inversely correlated with REM sleep amount?
- Sleep deprived rats get very cold and when allowed to sleep have huge rebound of REM sleep regardless of whether they have been deprived of REM or nonREM (Rechtschaffen et al., 1989).

Across all homoeothermic orders -



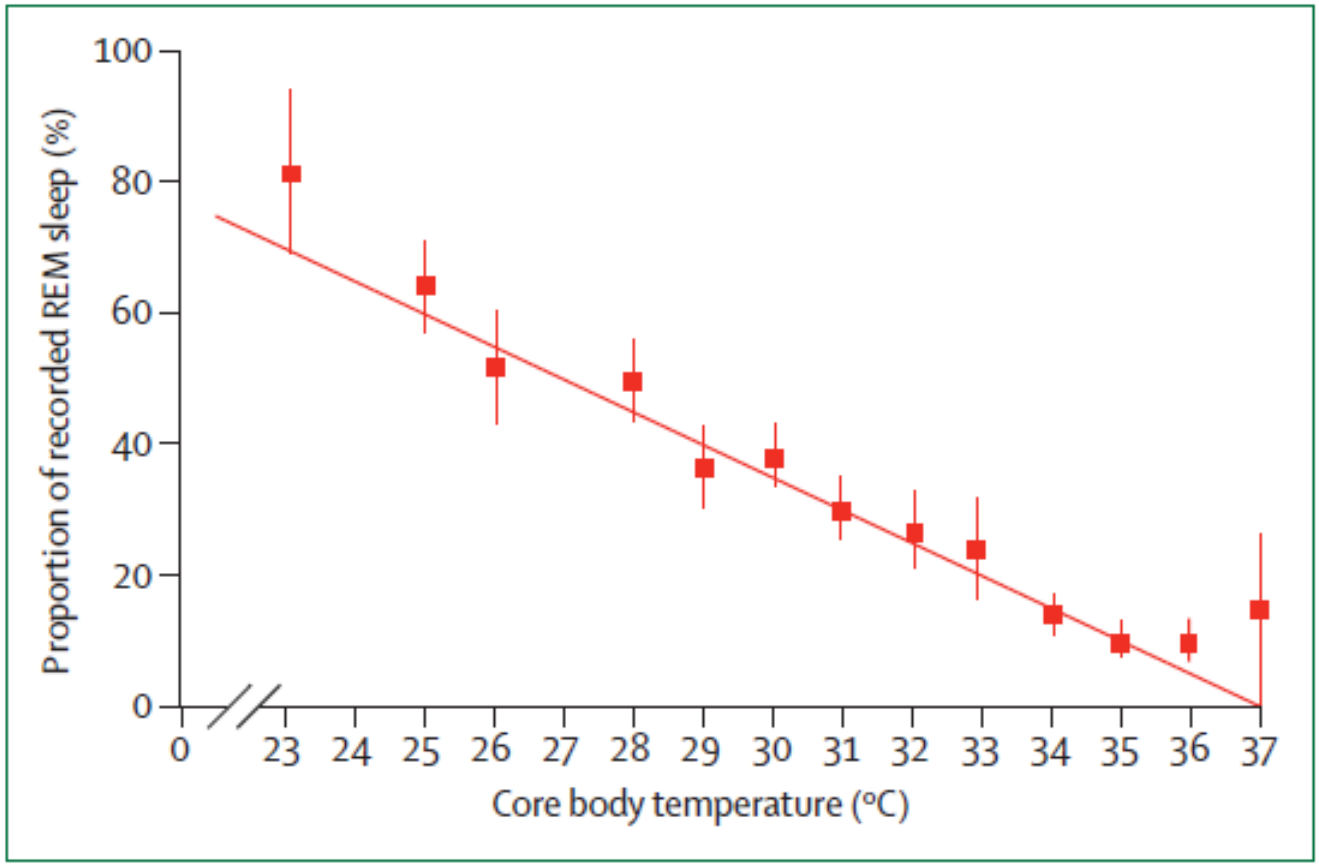
REM sleep hours per day in homeotherm orders is negatively correlated r=-0.975 with core (body-brain) temperature of homeotherms (106°F - 88°F core temp).

Siegel, Lancet Neurology, 2022



REM sleep reverses the temperature decrease of nonREM sleep.

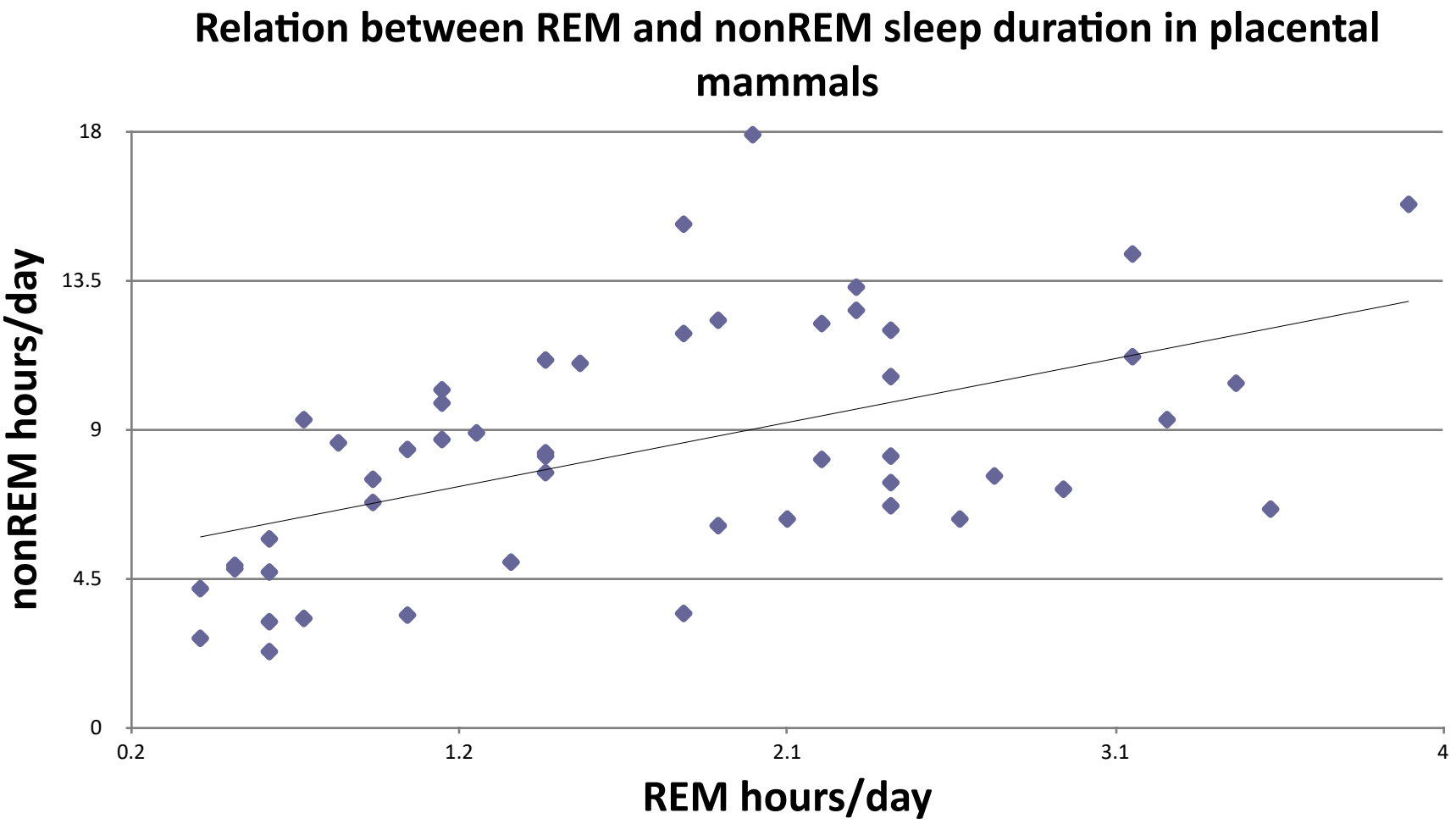
Rechtschaffen et al., 1965
Wu and Siegel, 2025



Effect of brain temperature on REM sleep duration. A decerebrate cat (brainstem disconnected from hypothalamus) does not thermoregulate, because the hypothalamic temperature sensor mechanisms are disconnected from brainstem effector systems. As body temperature falls to 23°C REM sleep percentage rises from 15% to 80%.

REM sleep is increased as brainstem cools Jouvet et al., 1990

Cold monotremes and cold brainstems generate lots of REM sleep.



REM sleep duration is significantly correlated with nonREM sleep duration across mammalian species (r=0.5, p=0.0002). REM sleep typically follows nonREM sleep.

Siegel, Lancet Neurology, 2022

Is REM sleep amount positively correlated with memory?

Rasch et al., 2009, Nature Neuroscience

No Associations between Interindividual Differences in Sleep Parameters and Episodic Memory Consolidation

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Study Objectives: Sleep and memory are stable and heritable traits that strongly differ between individuals. Sleep benefits memory consolidation, and the amount of slow wave sleep, sleep spindles, and rapid eye movement sleep have been repeatedly identified as reliable predictors for the amount of declarative and/or emotional memories retrieved after a consolidation period filled with sleep. These studies typically encompass small sample sizes, increasing the probability of overestimating the real association strength. In a large sample we tested whether individual differences in sleep are predictive for individual differences in memory for emotional and neutral pictures.

Design: Between-subject design.

Setting: Cognitive testing took place at the University of Basel, Switzerland. Sleep was recorded at participants' homes, using portable electroencephalograph-recording devices.

Participants: Nine hundred-twenty-nine healthy young participants (mean age 22.48 ± 3.60 y standard deviation).

Interventions: None.

Measurements and results: In striking contrast to our expectations as well as numerous previous findings, we did not find any significant correlations between sleep and memory consolidation for pictorial stimuli.

Conclusions: Our results indicate that individual differences in sleep are much less predictive for pictorial memory processes than previously assumed and suggest that previous studies using small sample sizes might have overestimated the association strength between sleep stage duration and pictorial memory performance. Future studies need to determine whether intraindividual differences rather than interindividual differences in sleep stage duration might be more predictive for the consolidation of emotional and neutral pictures during sleep.

Keywords: declarative memory, rapid eye movement sleep, sample size, sleep EEG, slow wave sleep

Citation: Ackermann S, Hartmann F, Papassotiropoulos A, de Quervain DJF, Rasch B. No associations between interindividual differences in sleep parameters and episodic memory consolidation. *SLEEP* 2015;38(6):951–959.

No evidence for intra-individual correlations between sleep-mediated declarative memory consolidation and slow-wave sleep

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Sleep, 2020, 2021

Abstract

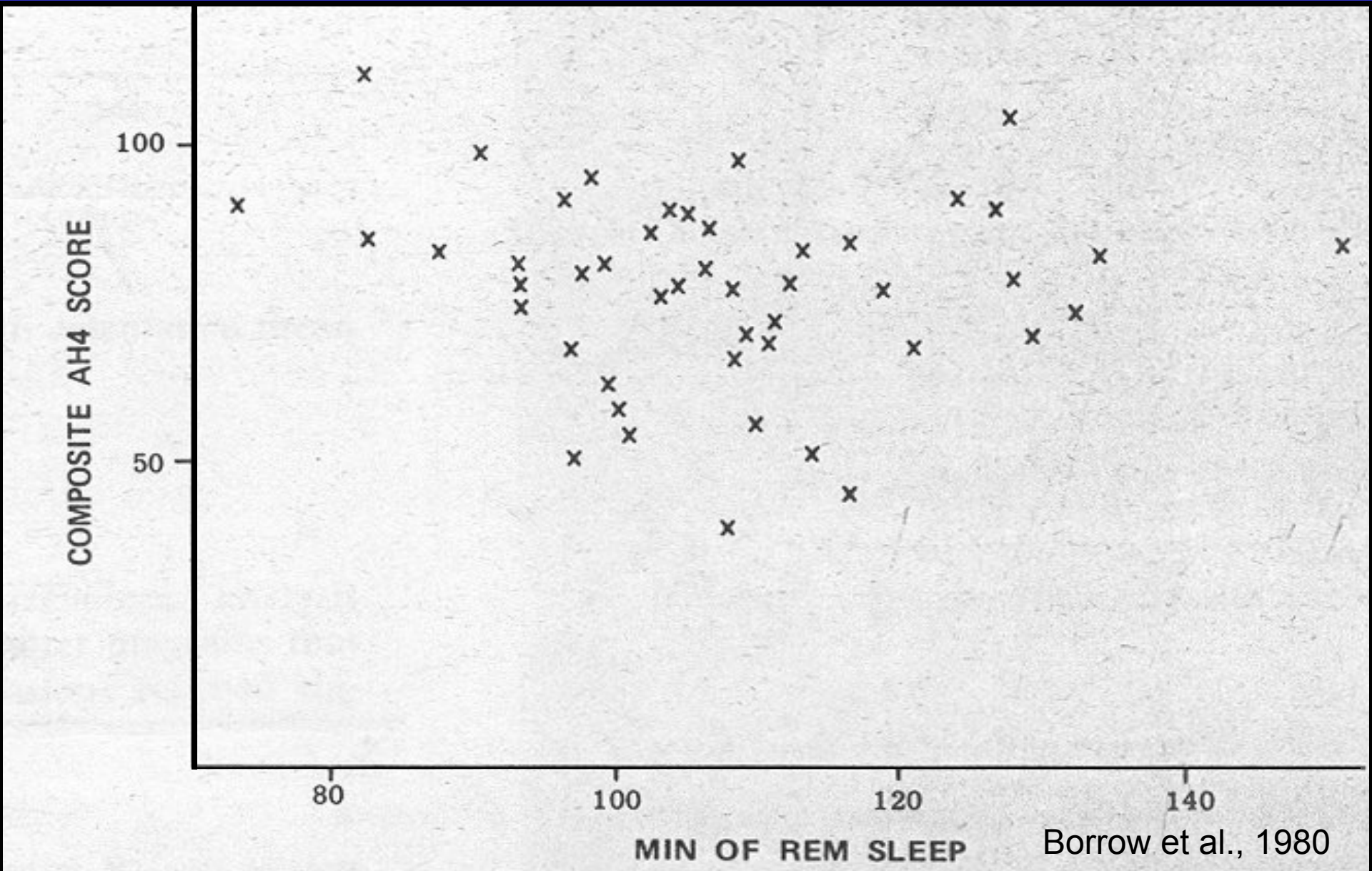
Study Objectives: Memory consolidation benefits from a retention period filled with sleep. Several theoretical accounts assume that slow-wave sleep (SWS) contributes functionally to processes underlying the stabilization of declarative memories during sleep. However, reports on correlations between memory retention and the amount of SWS are mixed and typically rely on between-subject correlations and small sample sizes. Here we tested for the first time whether the amount of SWS during sleep predicts the effect of sleep on memory consolidation on an intra-individual level in a large sample.

Methods: One hundred and fifty-nine healthy participants came to the lab twice and took a 90 min nap in both sessions. Sleep-mediated memory benefits were tested using the paired associates word-learning task in both sessions.

Results: In contrast to the theoretical prediction, intra-individual differences in sleep-mediated memory benefits did not significantly correlate with differences in SWS or SWA between the two naps. Also between subjects, the amount of SWS did not correlate with memory retention across the nap. However, subjective ratings of sleep quality were significantly associated with the amount of SWS.

Conclusion: Our results question the notion that the amount of SWS per se is functionally related to processes of memory consolidation during sleep. While our results do not exclude an important role of SWS for memory, they suggest that "more SWS" does not necessarily imply better memory consolidation.

REM sleep time in humans is not correlated with IQ



Borrow et al., 1980

Fig. 1. Scatter diagram showing REM sleep and IQ.

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Brief Communication

2018

Near-total absence of REM sleep co-occurring with normal cognition: an update of the 1984 paper

Efrat Magidov [a, b], Hanna Hayat [a], Omer Sharon [a], Fani Andelman [c], Shlomit Katzav [d], Peretz Lavie [e], Riva Tauman [d], Yuval Nir [a, b, f, *]

After injury that greatly reduced REM sleep:

Subject above normal on all cognitive tests

Subject obtained law degree after injury

Was puzzle editor of Tel Aviv newspaper

nature neuroscience

Brief Communication

https://doi.org/10.1038/s41593-024-01638-y

Brain clearance is reduced during sleep and anesthesia

Received: 1 April 2022

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Check for updates

Andawei Miao[1,2,7], Tianyuan Luo[1,5,6,7], Bryan Hsieh[1,3], Christopher J. Edge[1], Morgan Gridley[1], Ryan Tak Chun Wong[1], Timothy G. Constandinou[4], William Wisden[1,2,3] ✉ & Nicholas P. Franks[1,2,3] ✉

It has been suggested that the function of sleep is to actively clear metabolites and toxins from the brain. Enhanced clearance is also said to occur during anesthesia. Here, we measure clearance and movement of fluorescent molecules in the brains of male mice and show that movement is, in fact, independent of sleep and wake or anesthesia. Moreover, we show that brain clearance is markedly reduced, not increased, during sleep and anesthesia.

Hypotheses on mammalian sleep

- The major determinant of sleep duration across species is ecological, an adaptive reduction in brain and body energy usage, constrained by the waking time needed for food acquisition. (Next to the heart, the brain uses the most energy of any organ).

- High amounts of REM sleep in monotremes (echidna and platypus) may be a consequence of their low body temperature. NonREM sleep likely evolved after REM sleep.

- REM sleep reverses the brain cooling and associated metabolic reduction that occurs in bilateral nonREM sleep.

- REM sleep follows, and its duration is correlated with prior nonREM period.

- No correlation of sleep parameters with memory consolidation or skill learning. Sleep deprivation effects on cognition are likely the result of stress & cortisol release.

- REM sleep increases before awakening and facilitates alert awakening.

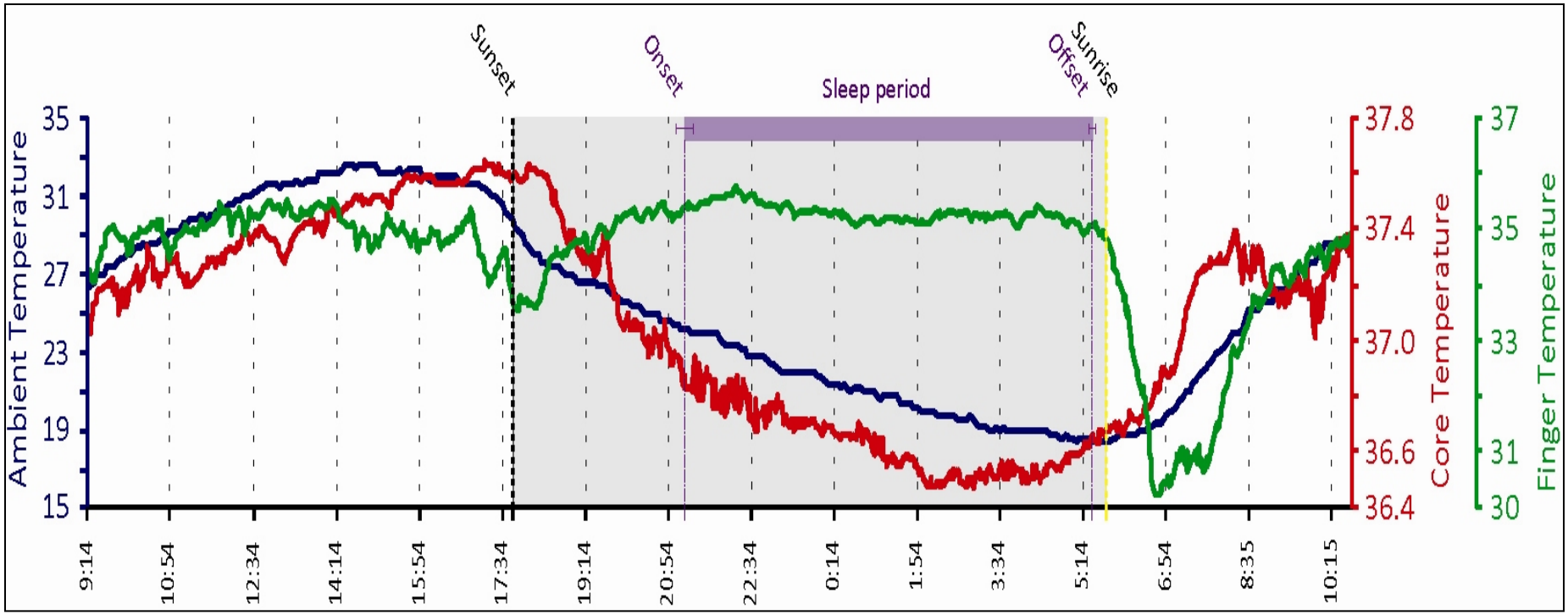
Sleep in Hunter-gatherers

Yetish, Kaplan, Gurven, Wood, Pontzer, Manger, Wilson, McGregor, Siegel, Current Biology, 2015

Recording sites

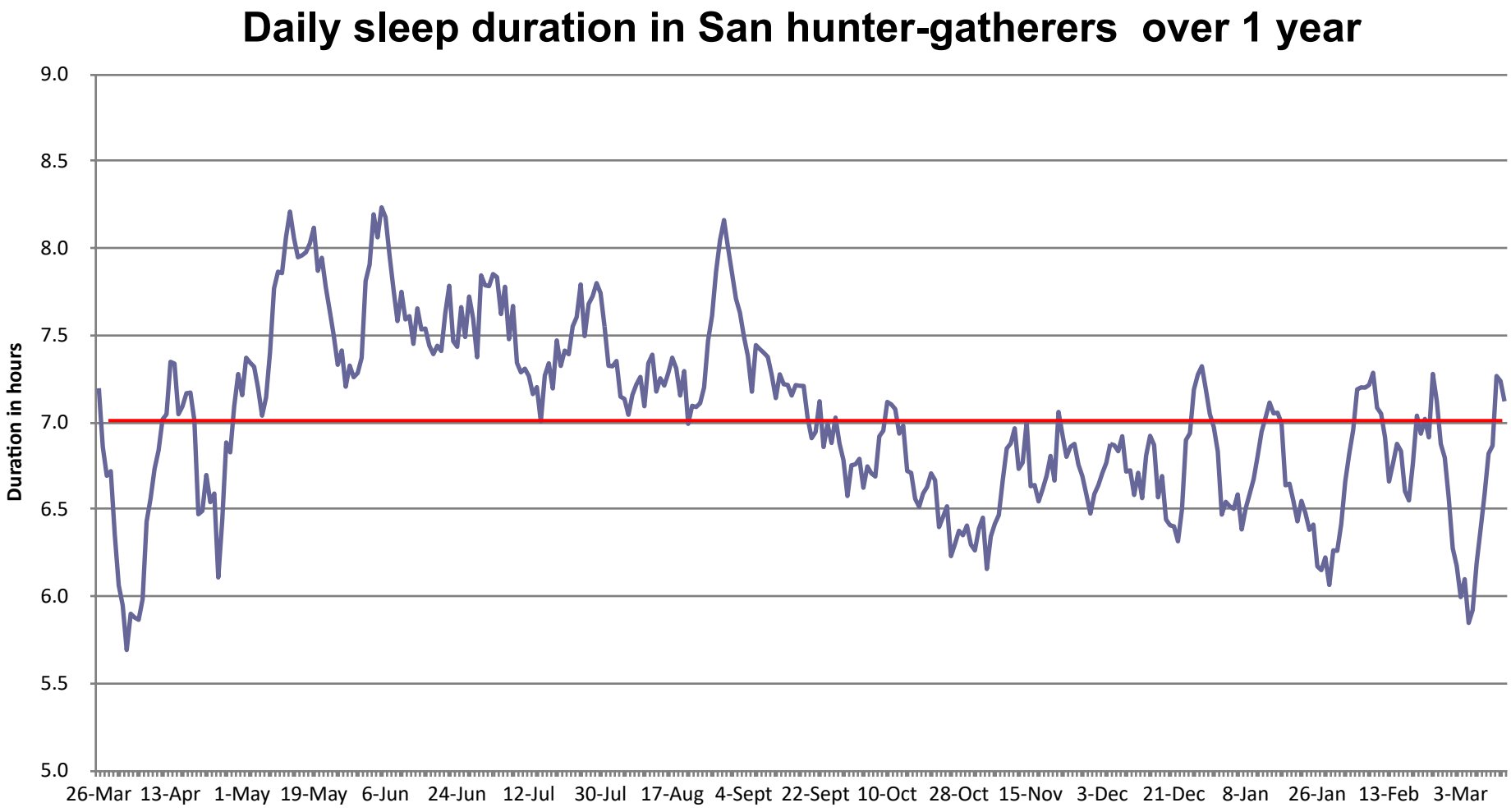
Study of 3 groups facilitates detection of common aspects of human sleep in “natural” conditions

Light, temperature and human sleep



Sunset-sunrise, sleep period, and ambient (blue), core (red) and finger (green) temperature (°C) averaged across 20 San hunter-gatherers for 1 week in the Fall in Namibia. Environmental temperature minimum is at sunrise, core temperature minimum is during sleep period and rises before wake onset. Finger temperature falls at awakening reflecting peripheral vasoconstriction. **Sleep does not start at sunset, but it regularly ends at sunrise, the time of minimal environmental temperature.**

Siegel et al., 2025



Sleep duration in 20 San hunter gatherers recorded for 365 consecutive days. Sleep duration is about 50 minutes longer in winter than in summer.

Siegel et al., 2025

Hunter-gatherer Summary

- 7, 28 or 365 day recordings, 104 subjects, 8,165 days of recordings.
- All 3 groups (San and Hadza in Africa and Tsimané in Bolivia) have similar sleep parameters.
- **No sleep onset at sunset**, even in the absence of electric light. Average onset is >3 h after sunset.
- Sleep duration in these societies averages 7h, the **same as, or less than,** that of industrial cultures and **lower than other diurnal primates**.
- **Little napping** in winter, low level (22%) in summer.
- **No consistent interruption of nighttime sleep**.
- 50 minute difference between summer and winter sleep duration.

Lifespan does not increase with sleep time. 7 h is optimal for lifespan in the U.S.

Kripke, 2003

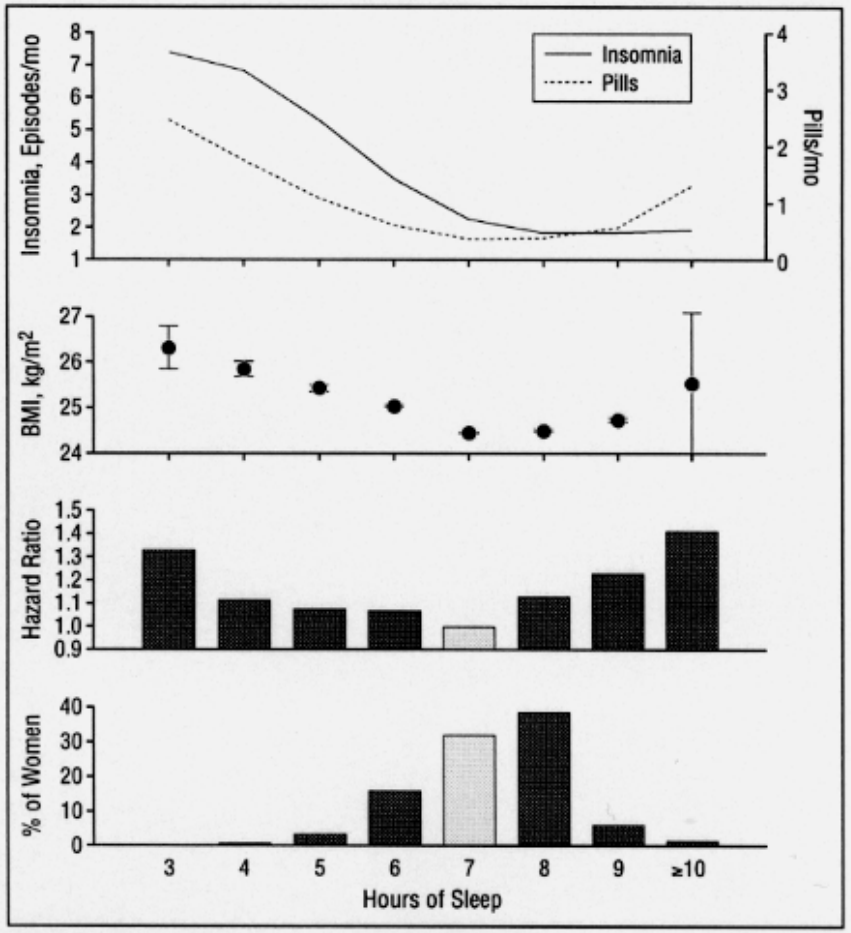


Figure 1. For 636 095 women, the average reported frequency of insomnia, the average number of sleeping pills used per month, and the mean body mass index (BMI) according to reported hours of sleep. The 95% confidence intervals of the BMI are shown. Also shown are the hazard ratios from the 32-covariate Cox models and the percentage of women reporting each sleep duration. The reference duration of 7 hours is represented by the lighter bars.

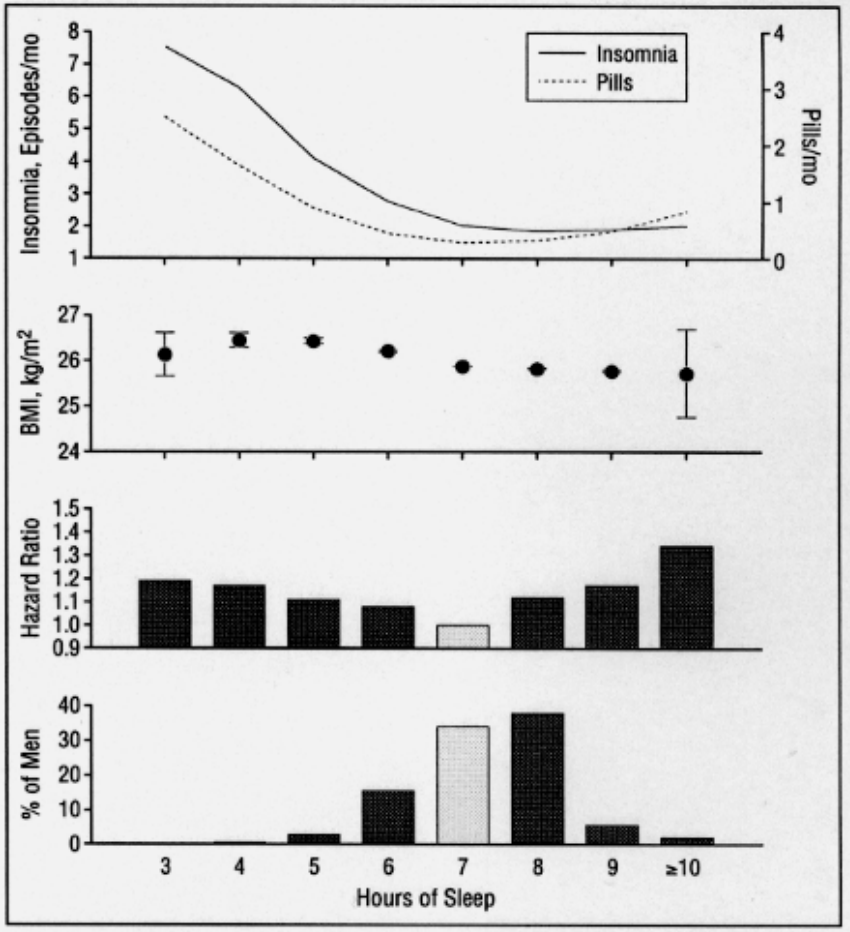


Figure 2. For 480 841 men, data comparable to those shown in Figure 1. BMI indicates body mass index.

According to CDC, obesity epidemic began 25-50 YA < 1985 (30 YA)