



«Sonno e salute»

Andrea Romigi

IRCCS Neuromed Centro di Medicina del Sonno Pozzilli (IS)
International Medical University UNICAMILLUS Roma



European Network
for Workplace Health
Promotion
ENWHP



Bambino Gesù
OSPEDALE PEDIATRICO

**EUROPEAN MEETING
AND SCHOOL ON
WORKPLACE HEALTH
PROMOTION
VII EDIZIONE**



INAIL

ISTITUTO NAZIONALE PER L'ASSICURAZIONE
CONTRO GLI INFORTUNI SUL LAVORO

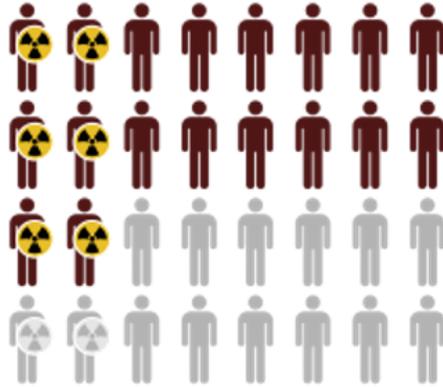


The need to promote sleep health in public health agendas across the globe

Lancet Public Health 2023;
8: e820-26

Diane C Lim*, Arezu Najafi*, Lamia Afifi, Claudio LA Bassetti, Daniel J Buysse, Fang Han, Birgit Högl, Yohannes Adama Melaku, Charles M Morin, Allan I Pack, Dalva Poyares, Virend K Somers, Peter R Eastwood†, Phyllis C Zee†, Chandra L Jackson†, on behalf of the World Sleep Society Global Sleep Health Taskforce

PAF population of attributable fraction represents the **percentage of disease that would be eliminated if exposure to the risk factor is completely eliminated** from the population.



The economic cost of inadequate sleep

David Hillman^{1,2,*}, Scott Mitchell³, Jared Streatfeild³,
Chloe Burns³, Dorothy Bruck⁴ and Lynne Pezzullo³

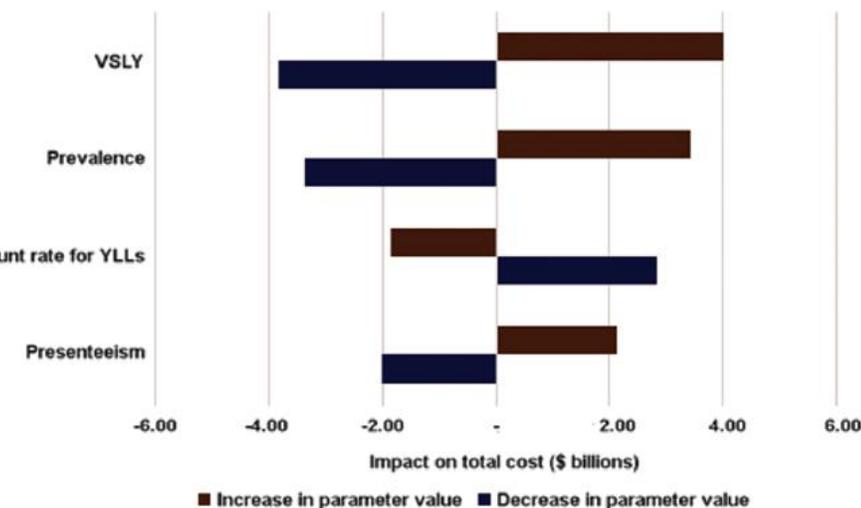


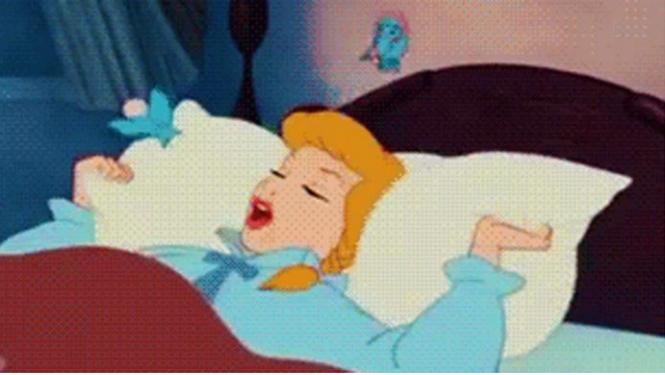
Table 1. Linkages between various categories of inadequate sleep and associated conditions

Condition	Prevalence or Annual Rate (%)	EDS-SD			EDS-Other		Insufficient Sleep	
		Type of EDS-SD	Odds ratio	PAF (%)	Odds ratio	PAF (%)	Odds ratio	PAF (%)
Congestive heart failure	1.9 [70]	OSA	1.6 [71]	1.5	—	—	—	—
Coronary artery disease	4.9 [70]	OSA	3.2 [72]	4.8	—	—	—	—
Cerebrovascular disease	1.6 [73]	OSA	2.9 [74]	4.8	1.4 [75]	5.0	—	Stroke 9.8%
Type 2 diabetes	8.9 [39]	OSA	1.63 [76]	1.7	—	—	—	—
Depression	6.2 [77]	OSA	2.6 [78]	3.6	1.87 [79]	9.4	—	Depression 13%
		Insomnia	2.1 [80]	2.4	—	—	—	—
		RLS	1.9 [81]	0.5	—	—	—	—
Workplace injury	1.4 [43]	OSA	1.5 [82]	1.3	2.2 [83]	13.7	1.4 [84]	5.5 20.5%
		Insomnia	2.4 [85]	3.3	—	—	—	—
Motor vehicle accident	1.3 [43]	OSA	2.5 [86]	3.8	1.9 [87]	10.3	1.5 [88]	11.0 23.2%

EDS = Excessive daytime sleepiness; SD = sleep disorders; PAF = population attributable fraction; OSA = obstructive sleep apnea; RLS = restless legs syndrome. Data sources for prevalence and odds ratios are indicated in the table.

The lowest estimate is **\$41.38 billion** and the **highest is \$49.21 billion**. Inadequate sleep represents a **huge economic and social cost**.

This ranking indicates that **public health strategies aimed at enhancing sleep habits and extending sleep duration** could significantly alleviate the societal impact of inadequate sleep.



Waking up to the importance of sleep

Editorial

Lancet 2022



Sleep Medicine: From Cinderella Branch to Growing Recognition

Historical Neglect: For decades, sleep health and sleepiness have been considered a "**Cinderella branch of medicine**," receiving little attention in undergraduate education, training, or research funding.

Why? the **disparate nature of sleep conditions** (e.g., sleep apnea, restless legs syndrome handled by different specialists), a **lack of understanding of their causes, and sparsity of treatment options.**



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See **Series** page 1033, 1047 and 1061
All papers in the **Series** are available at [thelancet.com/series/sleep-disorders](https://www.thelancet.com/series/sleep-disorders)

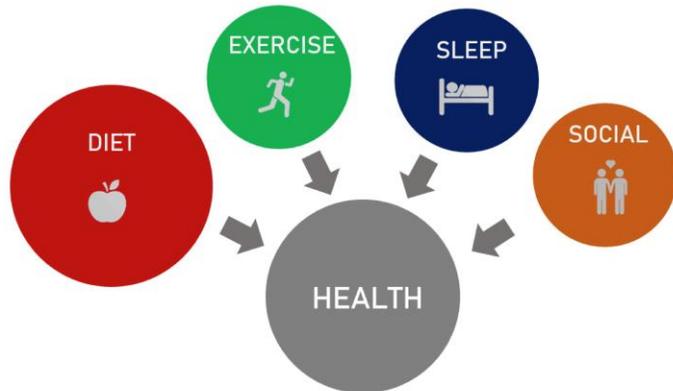
Sleep is presented as **a critical pillar of health**, on par with nutrition and physical activity. **It is not merely a passive state but a complex neurobehavioral process essential for complete physical, mental, and social well-being.**



«The big four»

- **Optimal Food Consumption -56%** all-cause mortality – **Risk increasing food +200%** all-cause mortality
- **Highly active men -22%** all-cause mortality vs mildly active men
- **Social participation -16%** all-cause mortality
- **4 out of 5 favorable sleep patterns** (early chronotype, adequate sleep duration, absence of insomnia, snoring and excessive daytime sleepiness) **-24%** all-cause mortality

Lohela et al., 2022 Nat Rev

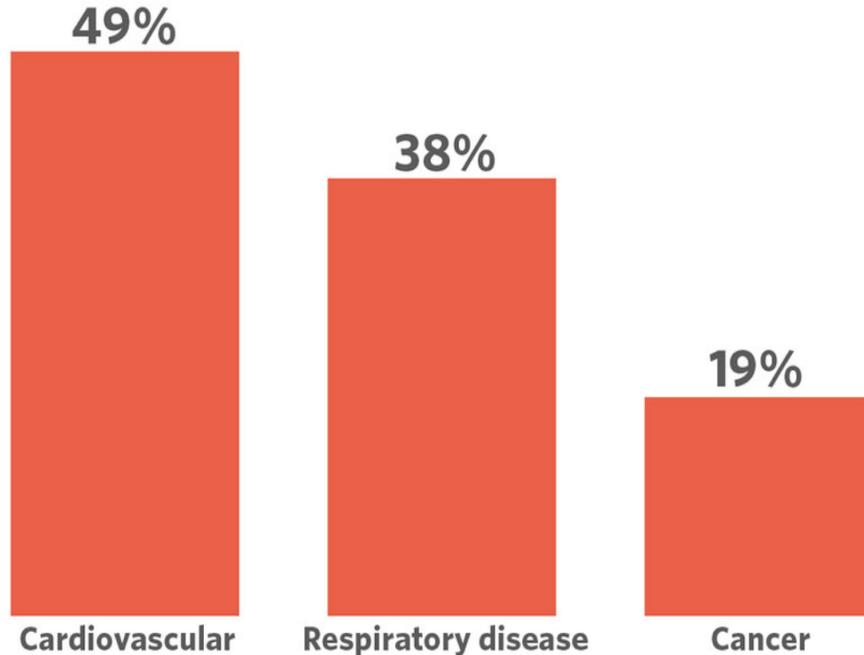


Pandemic

Obesity

How obesity increases your mortality

Mortality rates, by risk type



Note: Each percentage increase represents a five-unit increase in BMI as measured by a formula that divides your body weight by your height

Source: Harvard T.H. Chan School of Public Health and the University of Cambridge

COVID

Access 18th May 2024

7,047,741 **+425**
increase on previous 7 days
Reported COVID-19 deaths
World, 7 days to 5 May 2024



Globally, as of 3:49pm CEST, 10 May 2023, there have been 765,903,278 confirmed cases of COVID-19, including 6,927,378 deaths, reported to WHO. As of 9 May 2023, a total of 13,350,487,934 vaccine doses have been administered.

<https://covid19.who.int>
Access 13th May 2023

[:nce](#)

Obesity & sleep



Obesity Metabolic Syndrome

- Energy intake
- Physical exercise
- Insufficient sleep
- Circadian Misalignment

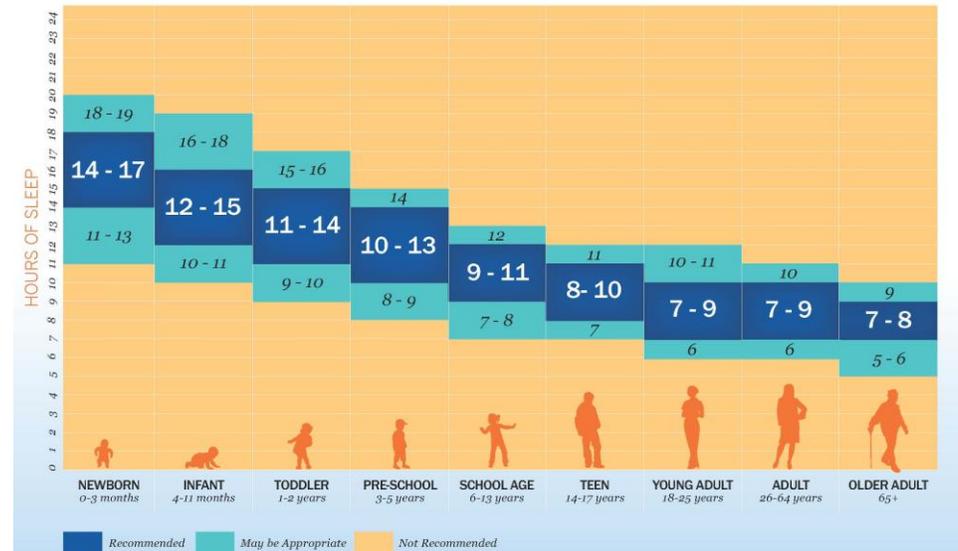
Key points

- Insufficient sleep and circadian misalignment are common in modern society.
- Insufficient sleep and circadian misalignment are important metabolic stressors and are associated with weight gain and obesity.
- Insufficient sleep increases energy expenditure by ~100 kcal per day but also increases energy intake by >250 kcal per day, resulting in a positive energy balance and weight gain.
- Sleep restriction increases the drive to eat, and excess food intake resulting from not sleeping enough is more related to cognitive control and reward mechanisms than to appetite hormones.
- Circadian misalignment reduces 24-h energy expenditure by ~3% (~55 kcal per day), alters the levels of appetite hormones and promotes unhealthier food choices than conditions of adequate sleep.

Chaput et al., 2023

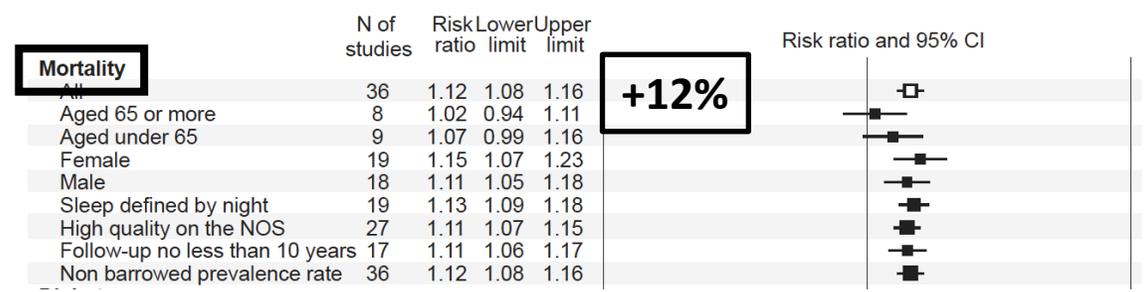
NATIONAL SLEEP FOUNDATION

SLEEP DURATION RECOMMENDATIONS



SLEEPFOUNDATION.ORG | SLEEP.ORG

Hirshkowitz M. The National Sleep Foundation's sleep time duration recommendations: methodology and results summary. Sleep Health (2015). <http://dx.doi.org/10.1016/j.sleh.2014.12.010>



«For clinical practice, the **effectiveness of psychoeducation or psychosocial intervention** to improve sleep in short sleepers on reducing mortality and the incidence of these health outcomes should be examined **in general community settings**.

Sleep Medicine 32 (2017) 246–256

Contents lists available at ScienceDirect

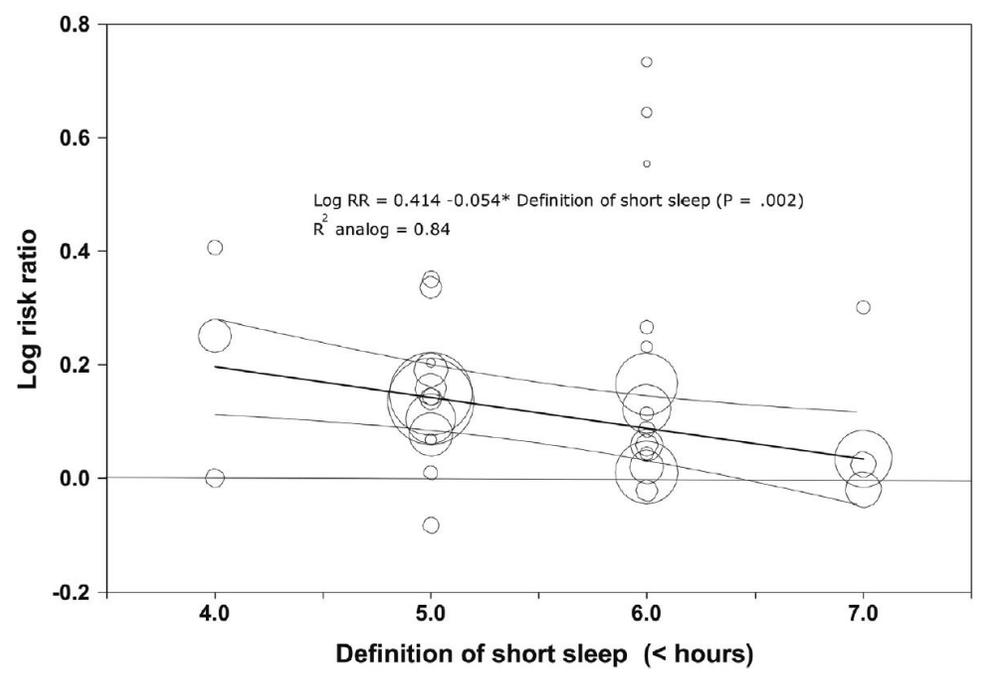
Sleep Medicine

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

Original Article

Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression

Osamu Itani ^{a,1}, Maki Jike ^{b,1}, Norio Watanabe ^{c,*}, Yoshitaka Kaneita ^a



But also not only **sleep duration** but **sleep fragmentation** and **poor sleep quality**

Association of Sleep Duration With All-Cause and Cardiovascular Mortality: A Prospective Cohort Study

Front Pub Health, 2022

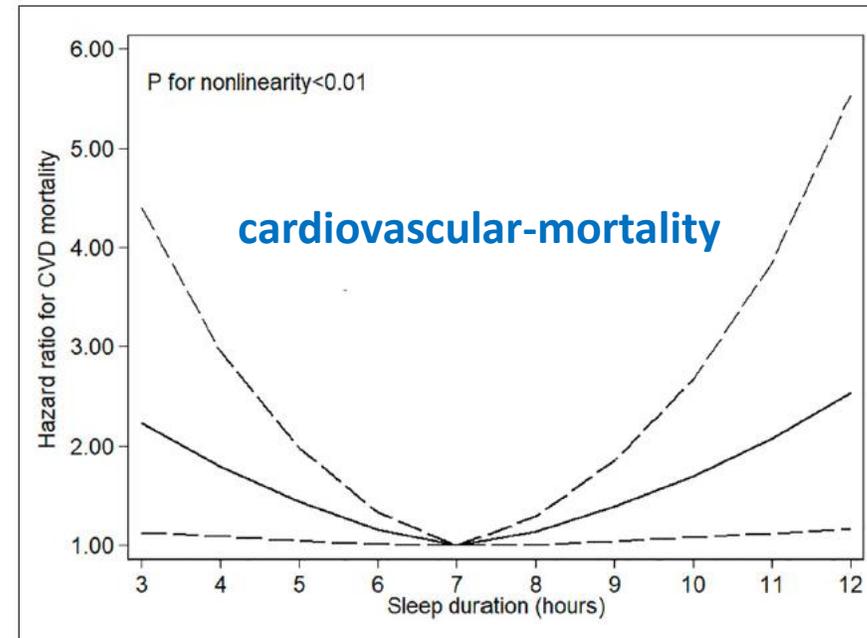
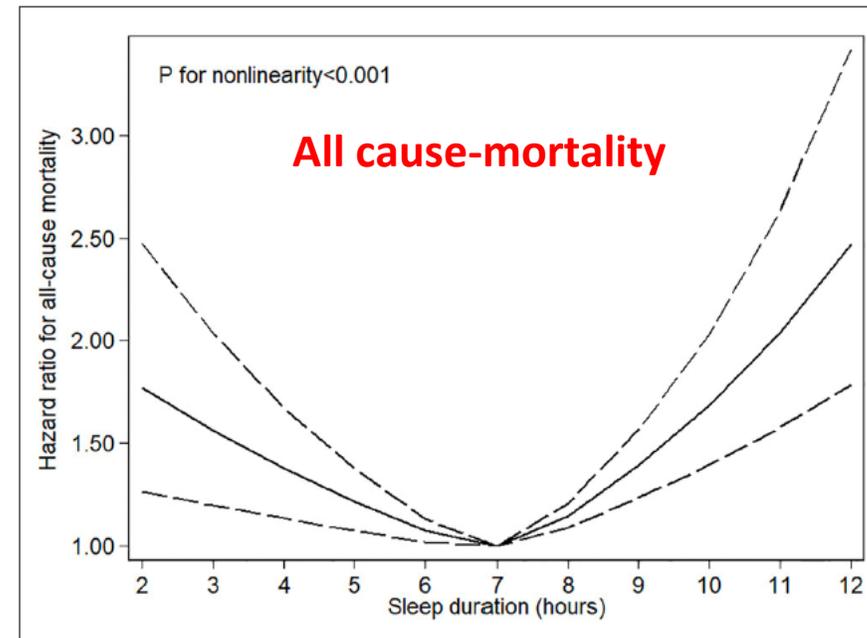
Qiman Jin¹, Niannian Yang¹, Juan Dai¹, Yuanyuan Zhao¹, Xiaoxia Zhang¹, Jiawei Yin^{2,3*} and Yaqiong Yan^{1*}

Short sleep duration (≤ 5 hours/day) and long sleep duration (≥ 9 hours/day) were significantly associated with increased cardiovascular mortality:

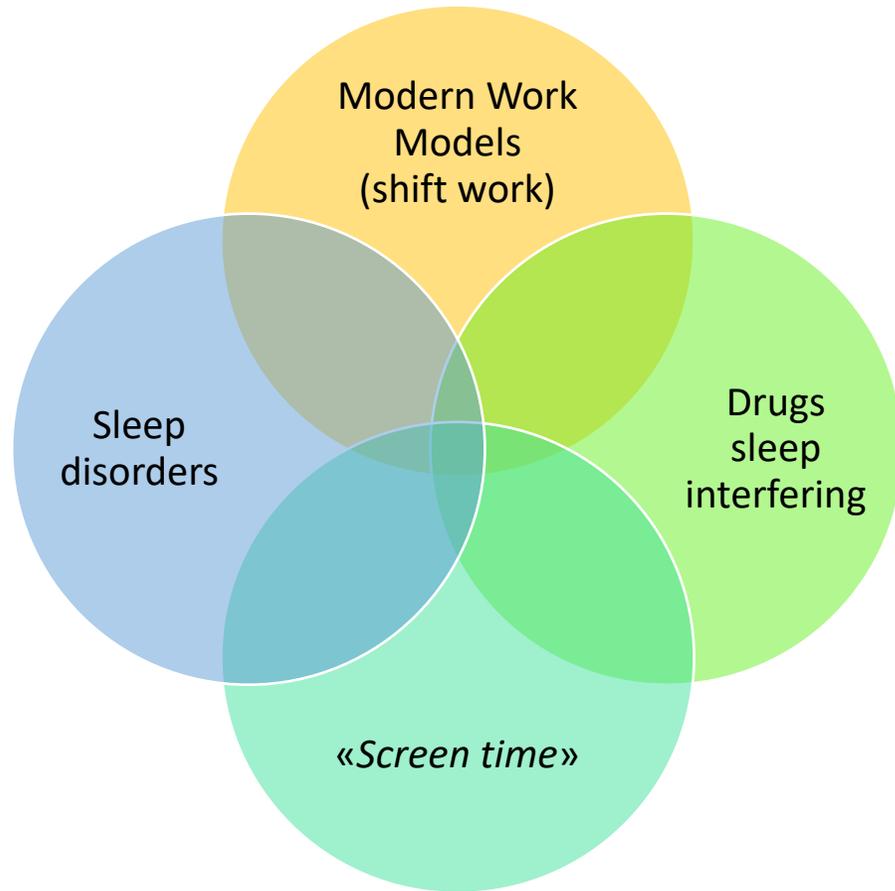
≤ 5 hours: **66% increased risk** (HR = 1.66, 95% CI: 1.02–2.72)

≥ 9 hours: **81% increased risk** (HR = 1.81, 95% CI: 1.09–3.02)

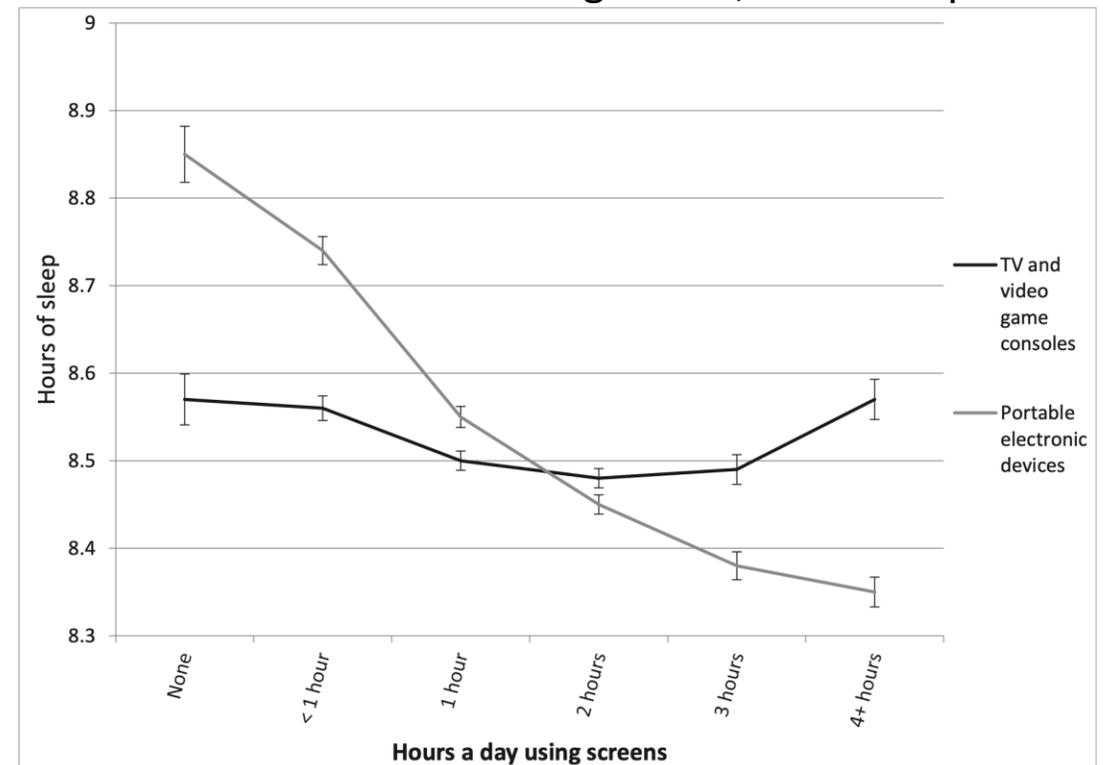
Optimal sleep duration (lowest CV risk) was around **7 hours per day**.



Why sleep deprivation?



Twenge et al., 2019 Sleep Med

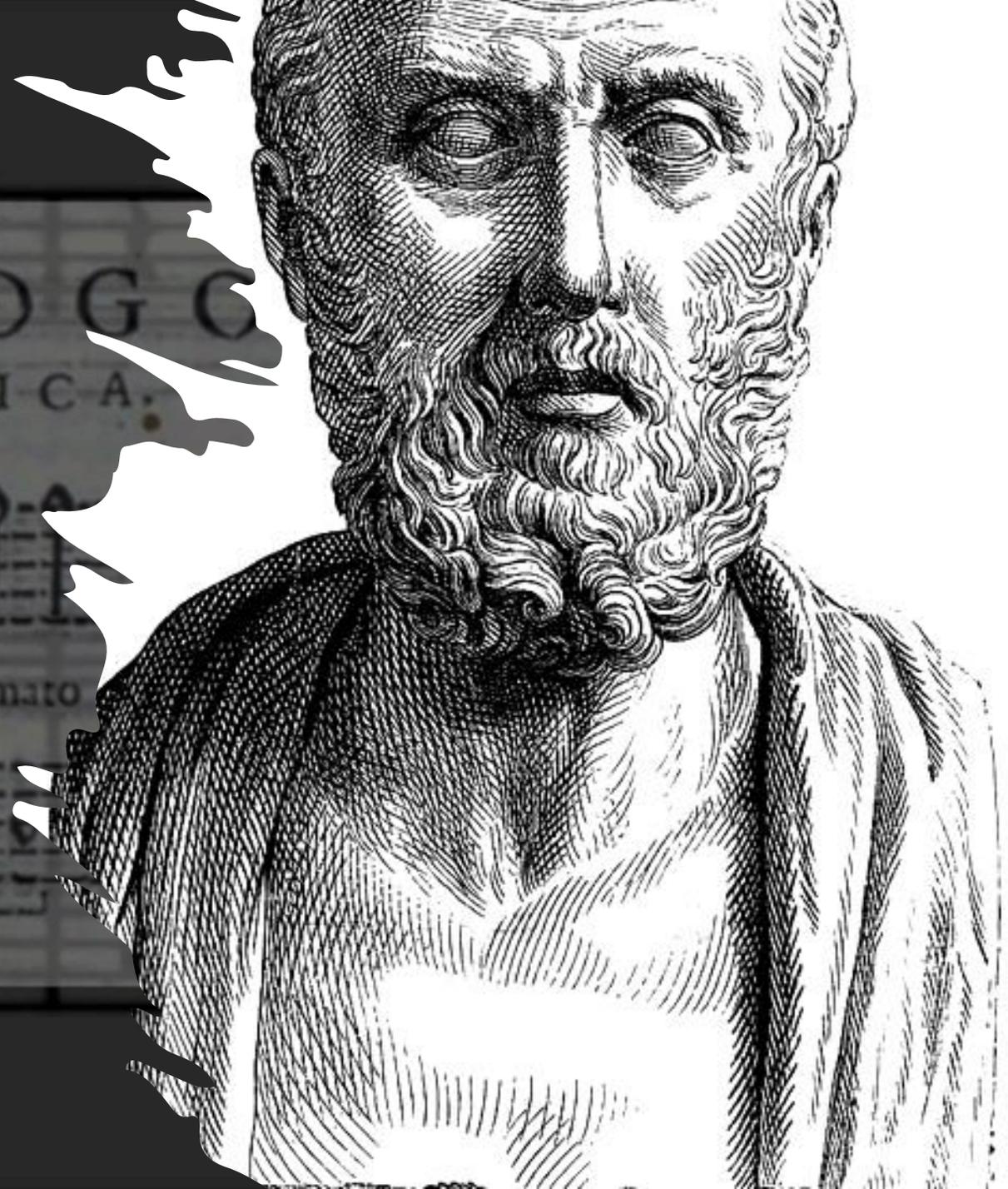


Portable devices > **stationary devices**

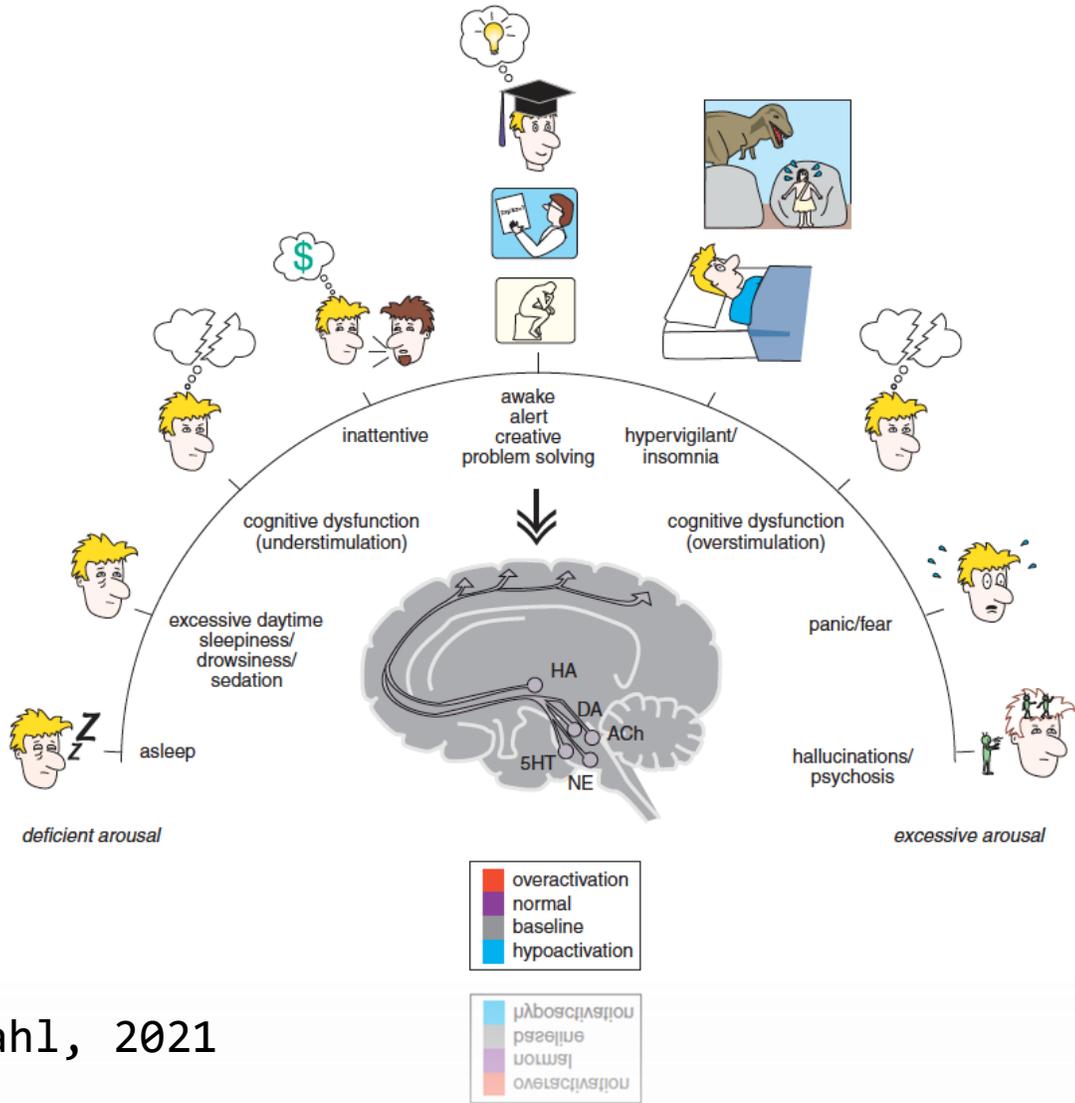
*«Εἴτε ὁ ὕπνος εἴτε ἡ ἀϋπνία, πέραν τοῦ
μέτρου, νόσος ἐστίν.»*

*«Sleep and wakefulness, both of them,
when immoderate constitute disease»*

Hippocrates (Aphorism 400 BC)



Arousal Spectrum of Sleep and Wakefulness



AROUSAL SPECTRUM BETWEEN SLEEP & WAKEFULNESS

Insomnia e **sleepiness** are not 2 separate disorders but a **continuum** of a single spectrum of deficient or excessive excitation

Hyperactivation

Normal

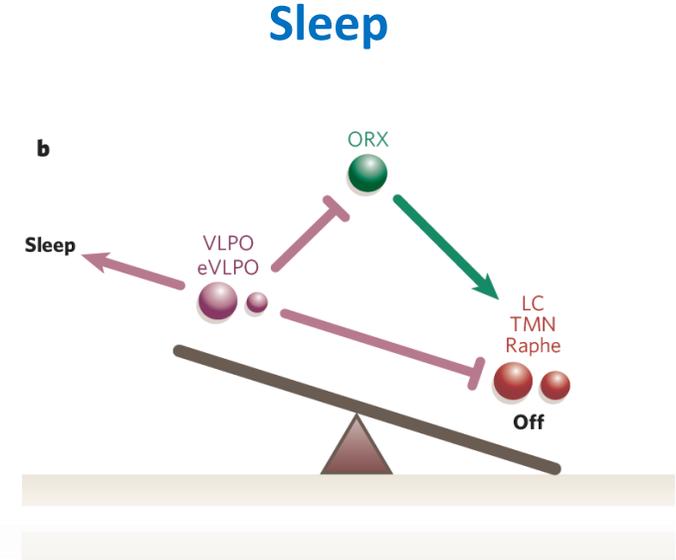
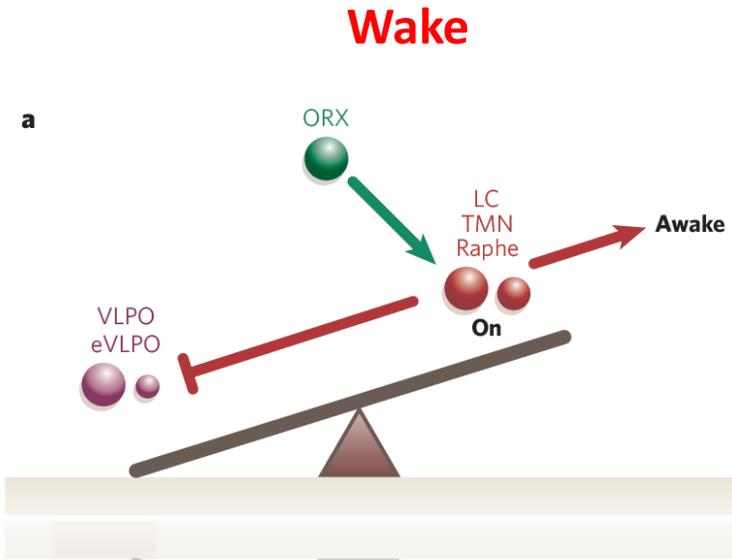
Basal

Hypoactivation

Stahl, 2021



Flip-flop switch model



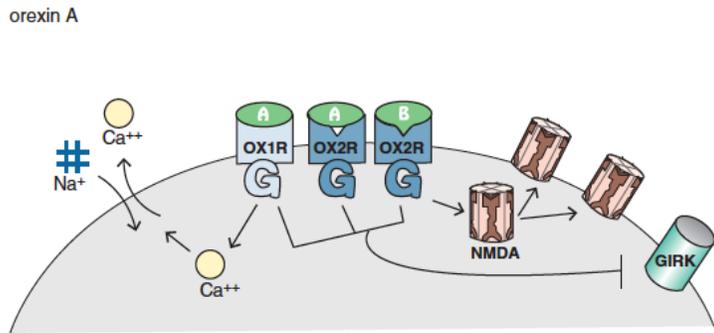
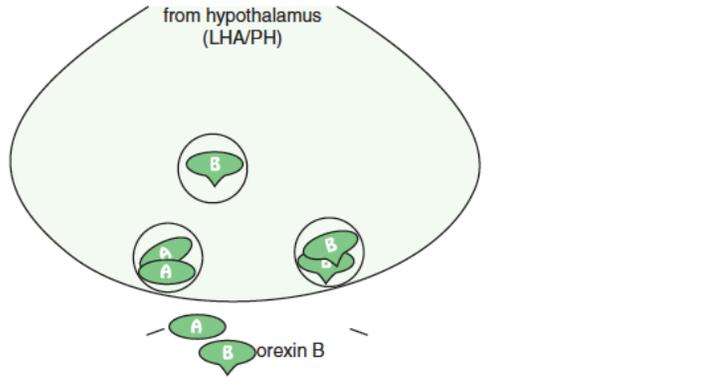
LAT HYP → ORX

{
 TMN → HIS
 DRN → 5HT
 VTA → DA
 LC → NA

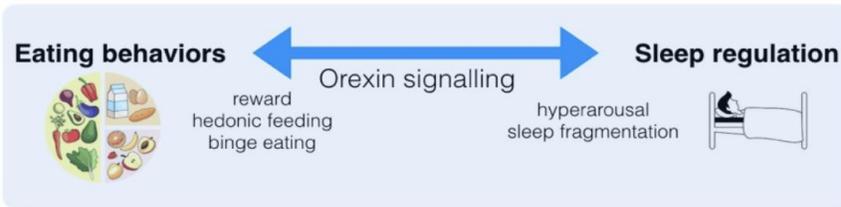
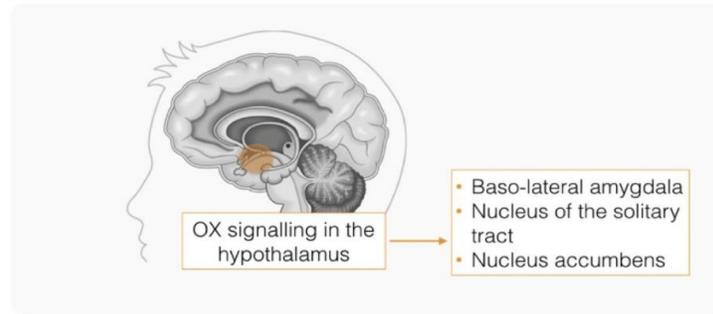
VLPO → GABA, Adenosine, PGD2

Saper, 2005 Nature

Ruolo dell'orexina



Stahl, 2021



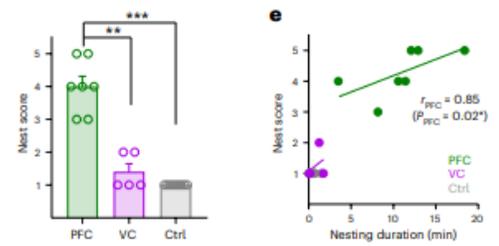
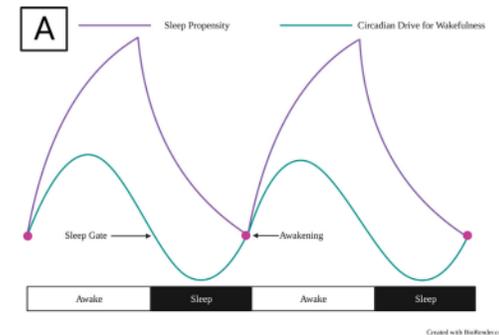
Mutti et al., 2023



A role for the cortex in sleep-wake regulation

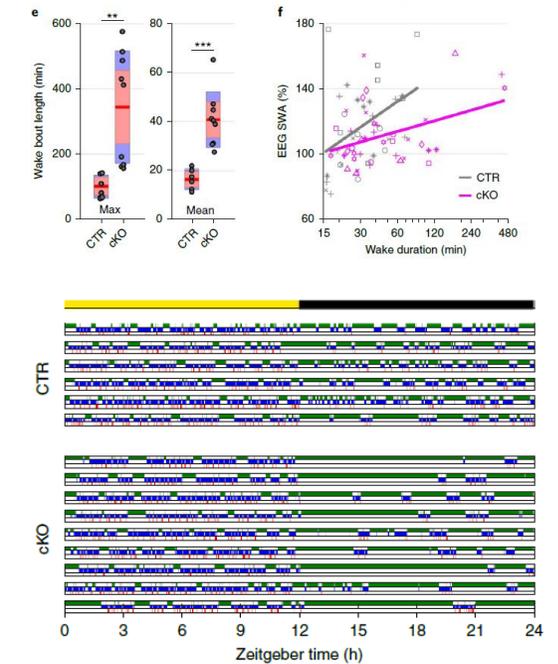
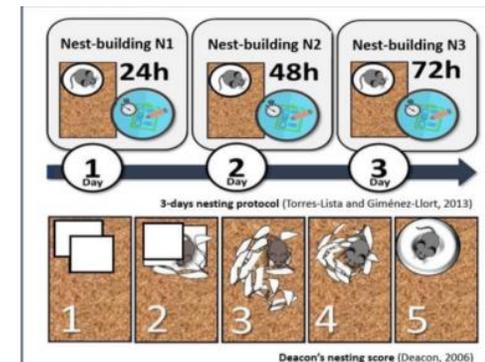
Lukas B. Krone^{1,2}, Tomoko Yamagata^{2,3}, Cristina Blanco-Duque^{1,2,4}, Mathilde C. C. Guillaumin^{2,3,5}, Martin C. Kahn^{1,2,4}, Vincent van der Vinne^{1,2,6}, Laura E. McKillop^{1,2}, Shu K. E. Tam^{2,3}, Stuart N. Peirson^{2,3}, Colin J. Akerman⁷, Anna Hoerder-Suabedissen¹, Zoltán Molnár¹ and Vladyslav V. Vyazovskiy^{1,2}

- Traditionally, the cerebral cortex is recognized as the primary generator of slow waves characteristic of deep sleep, but new research indicates its direct contribution to the **homeostatic regulation of sleep**
- Distinct neuronal populations within the **prefrontal cortex** have been identified as playing a crucial role in **Sleep preparation and initiation (S)**
- These neurons **become active before falling asleep**, facilitating the transition from wakefulness to sleep.
- Regulation of the amount and characteristic **features of REM** (Hong et al. 2023): Through descending projections to the hypothalamus, these cortical areas **actively influence the REM sleep phase**



Tollen et al., Nat Neurosc. 2023

Increase of «nesting» in mouse model with optogenetic activation of PFC



Increase of «wake» in cKO (PFC KO) mouse model

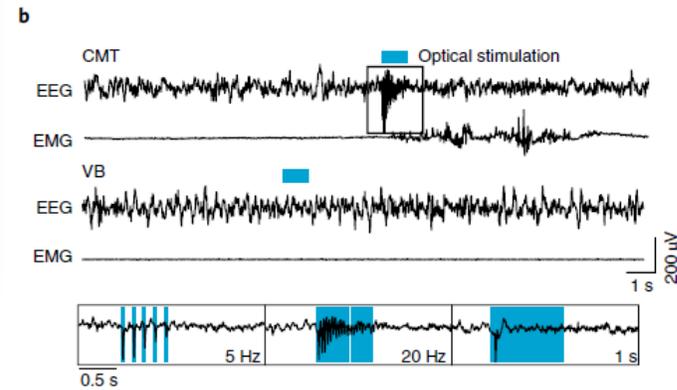
«Nesting»

2018

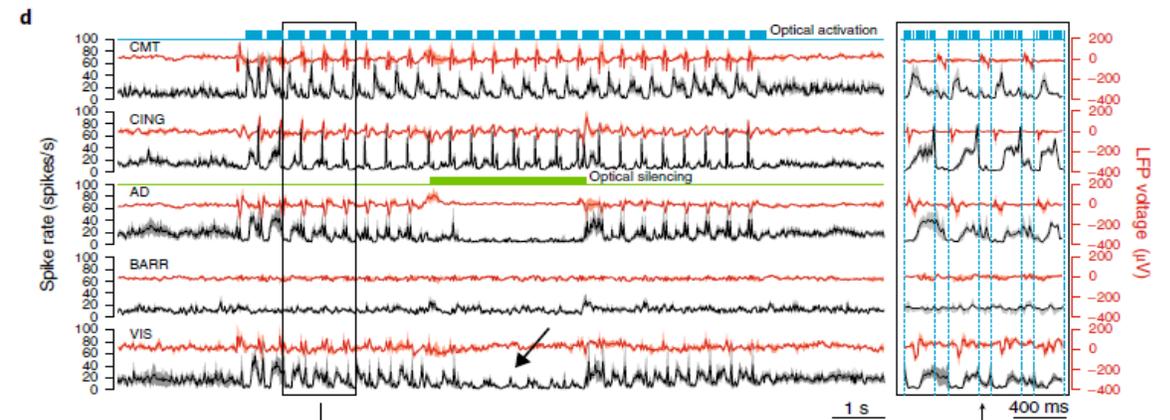
Thalamic dual control of sleep and wakefulness

Thomas C. Gent¹, Mojtaba Bandarabadi¹, Carolina Gutierrez Herrera¹ and Antoine R. Adamantidis^{1,2*}

- The thalamus, particularly the thalamic reticular nucleus, has long been known for its involvement in generating sleep spindles (Steriade et al. 1985; Halassa et al. 2011).
- Recently a **dual role in sleep regulation to the centromedial thalamus**
- **Continuous firing** of its neurons induces a transition to wakefulness
- **Burst firing** enhances the brain-wide synchrony of cortical slow waves during sleep through projections to the anterodorsal thalamus and cingulate cortex
 - This suggests a mechanism by which the thalamus can actively promote and intensify deep sleep



Continuous firing: arousal (CMT centromedial thalamus)



Burst firing: arousal (CMT centromedial thalamus): increase of «UP» state organizes cortical slow waves during deep sleep, rather than inducing arousal.

This indicates the CMT actively generates and coordinates deep sleep states, distinct from its arousal-promoting function

One brain, one mind, one health, one planet—a call from Switzerland for a systemic approach in brain health research, policy and practice

www.thelancet.com Vol 50 March, 2025

Indrit Bëgue,^{a,g,*} Antoine Flahault,^{c,d} Isabelle Bolon,^c Rafael Ruiz de Castañeda,^c Ana Maria Vicedo-Cabrera,^{e,f} and Claudio L. A. Bassetti^b

The need to promote sleep health in public health agendas across the globe

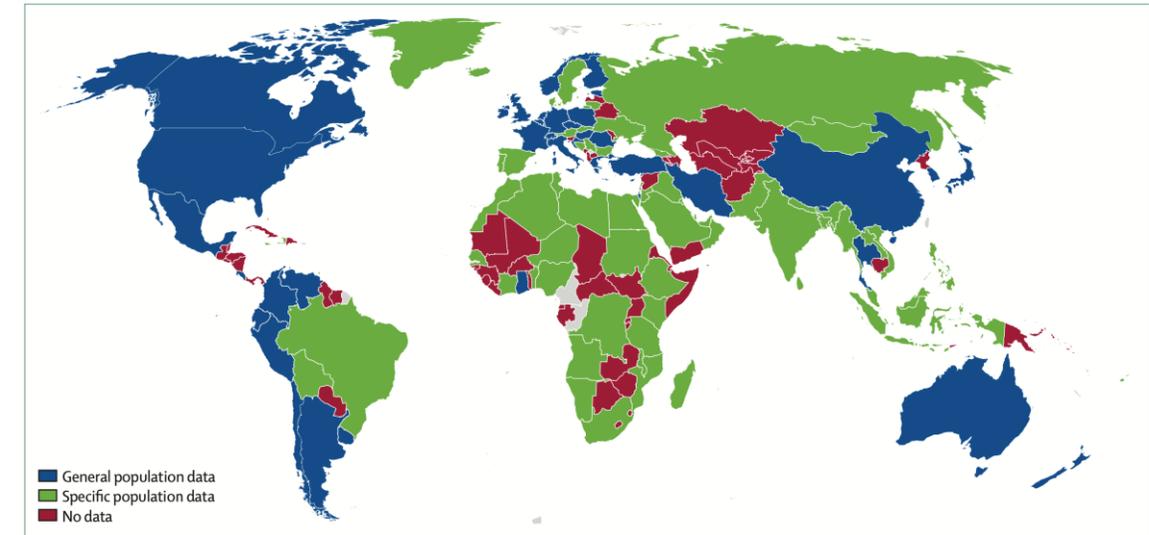
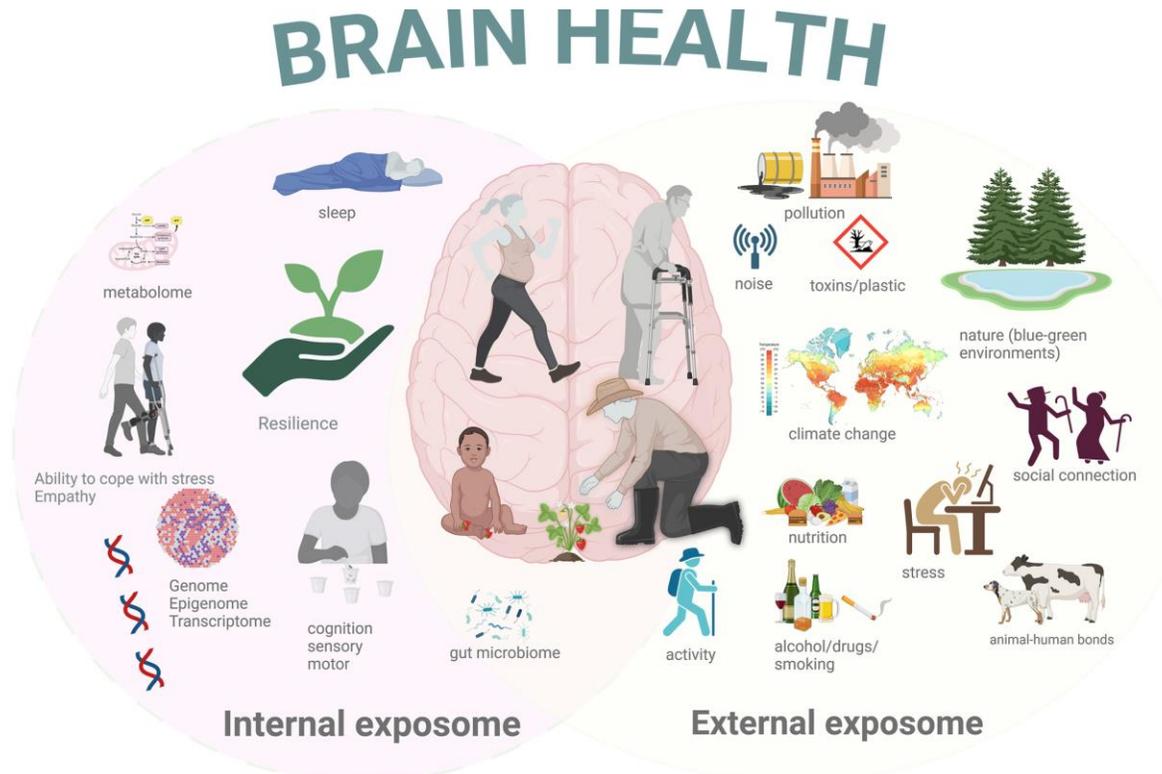


Diane C Lim*, Arezu Najafi*, Lamia Affifi, Claudio LA Bassetti, Daniel J Buysse, Fang Han, Birgit Högl, Yohannes Adama Melaku, Charles M Morin, Allan I Pack, Dalva Poyares, Virend K Somers, Peter R Eastwood†, Phyllis C Zee†, Chandra L Jackson†, on behalf of the World Sleep Society Global Sleep Health Taskforce

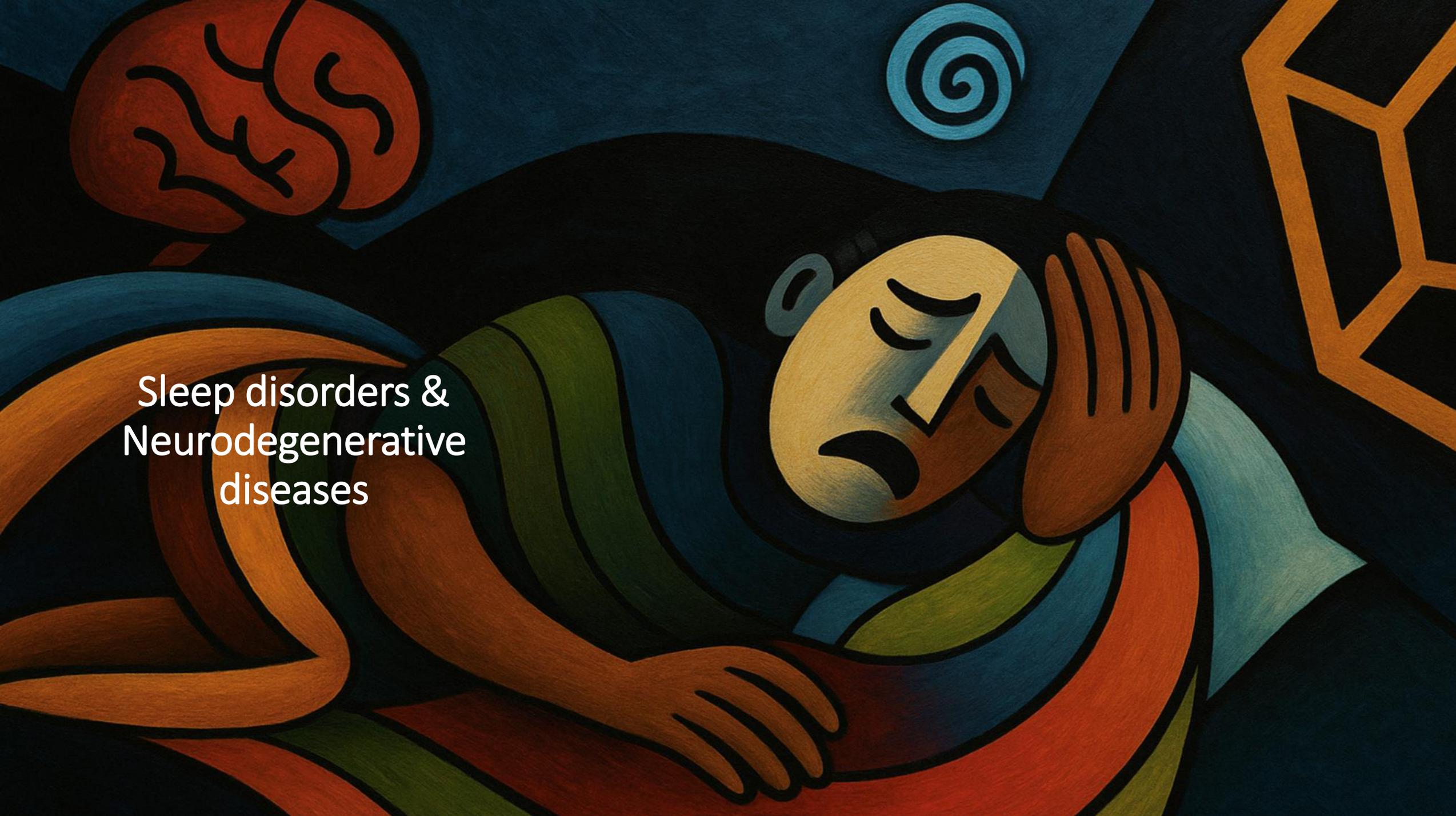


Healthy sleep is essential for physical and mental health, and social wellbeing; however, across the globe, and particularly in developing countries, national public health agendas rarely consider sleep health. Sleep should be

Lancet Public Health 2023; 8: e820-26



«...while conditions such as sleep disorders are both comorbid with psychiatric disorders and **independent risk factors for stroke and dementia**» ... «neurological disorders the main cause of **disability** and second cause of **mortality**»

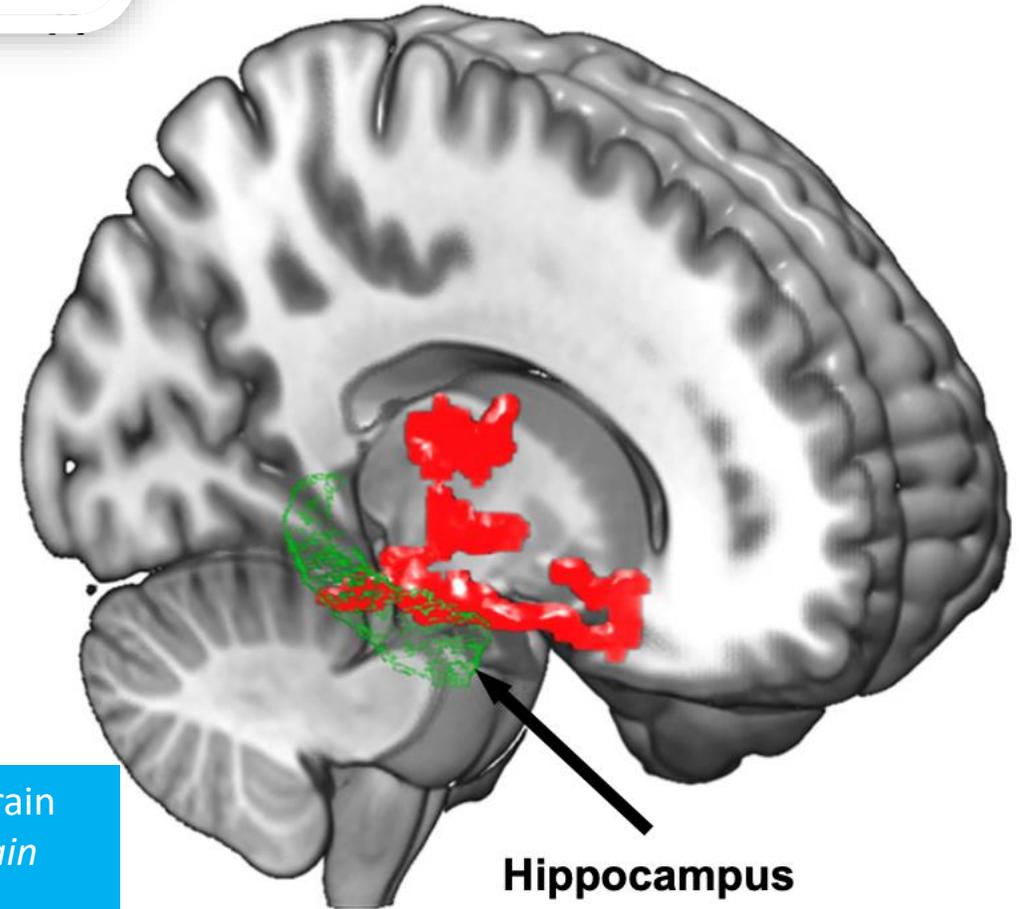
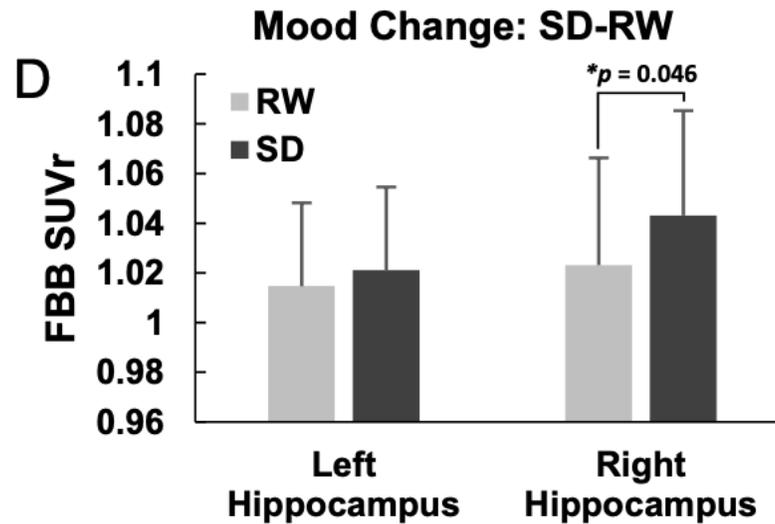


Sleep disorders &
Neurodegenerative
diseases

β -Amyloid accumulation in the human brain after one night of sleep deprivation

2018 PNAS

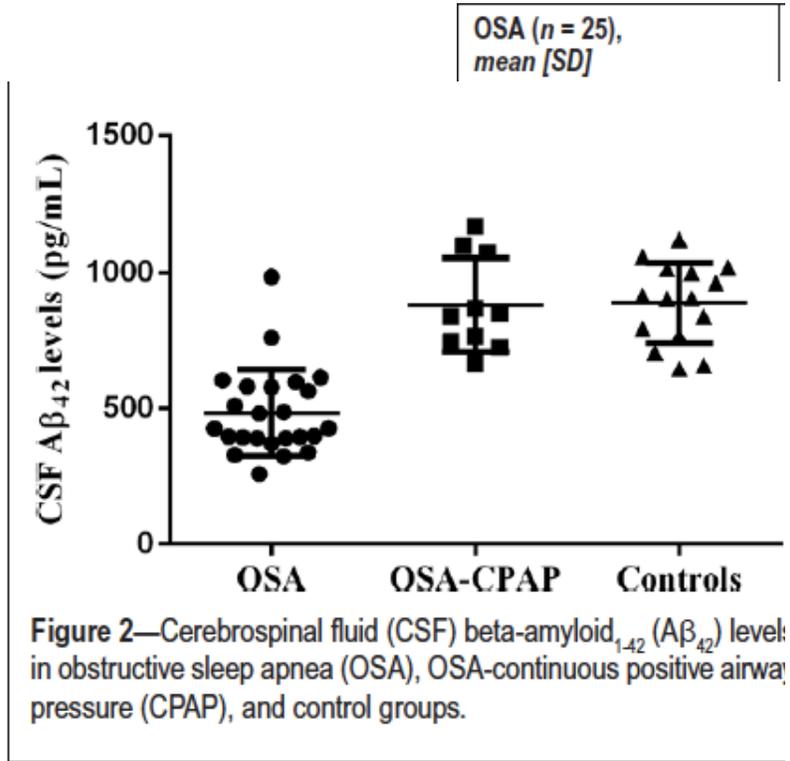
Ehsan Shokri-Kojori^{a,1}, Gene-Jack Wang^{a,1}, Corinde E. Wiers^a, Sukru B. Demiral^a, Min Guo^a, Sung Won Kim^a, Elsa Lindgren^a, Veronica Ramirez^a, Amna Zehra^a, Clara Freeman^a, Gregg Miller^a, Peter Manza^a, Tansha Srivastava^a, Susan De Santi^b, Dardo Tomasi^a, Helene Benveniste^c, and Nora D. Volkow^{a,1}



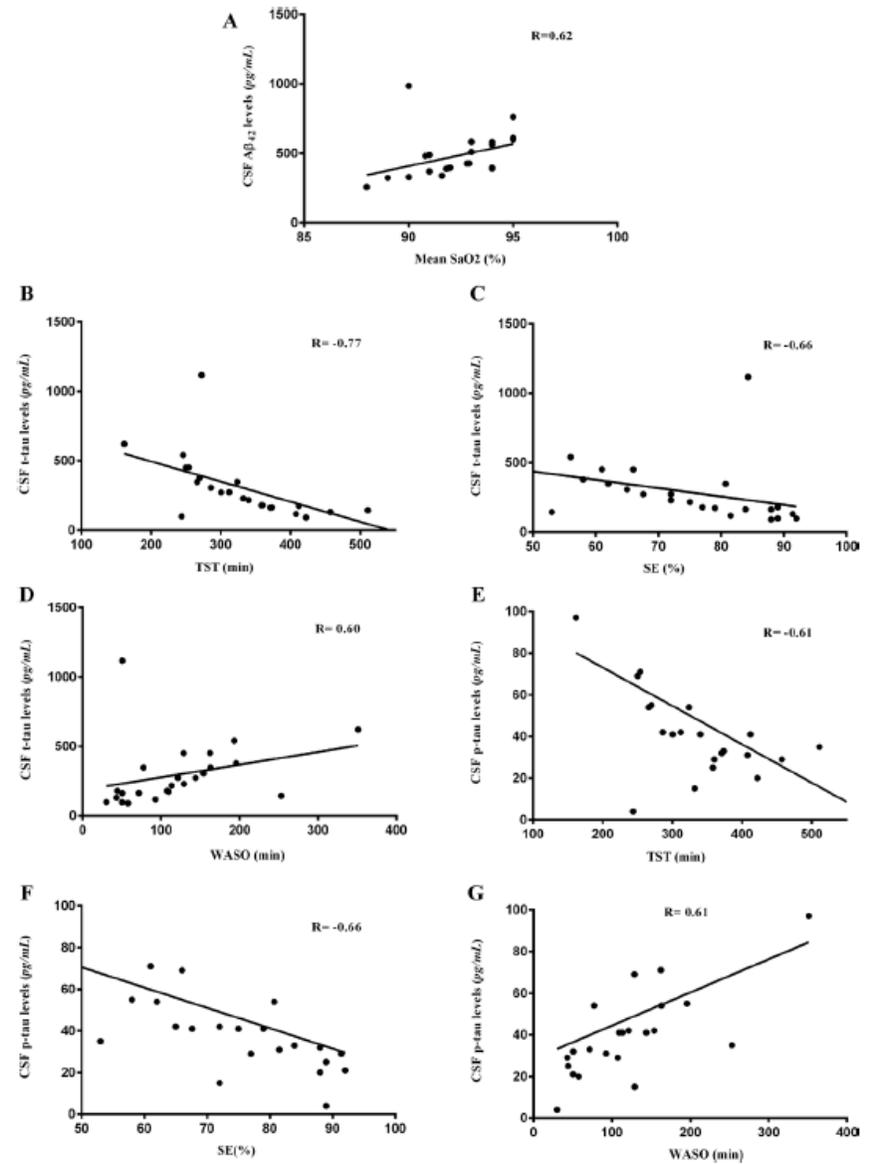
negative effect of sleep deprivation on β -amyloid burden in the human brain
«Our results highlight the relevance of good sleep hygiene for proper brain function and as a potential target for prevention of AD»
... why asymmetric? And position?

Obstructive Sleep Apnea is Associated with Higher Levels of Alzheimer's Disease Biomarkers in Cerebrospinal Fluid

Claudio Liguori, MD¹; Nicola Biagio Mercuri, MD^{1,2,3}; Francesca Izzi, PhD¹; Giuseppe Sancesario, MD³; Fabio Placidi, PhD¹



Better cognitive profile and sleep macrostructure in OSAS with CPAP



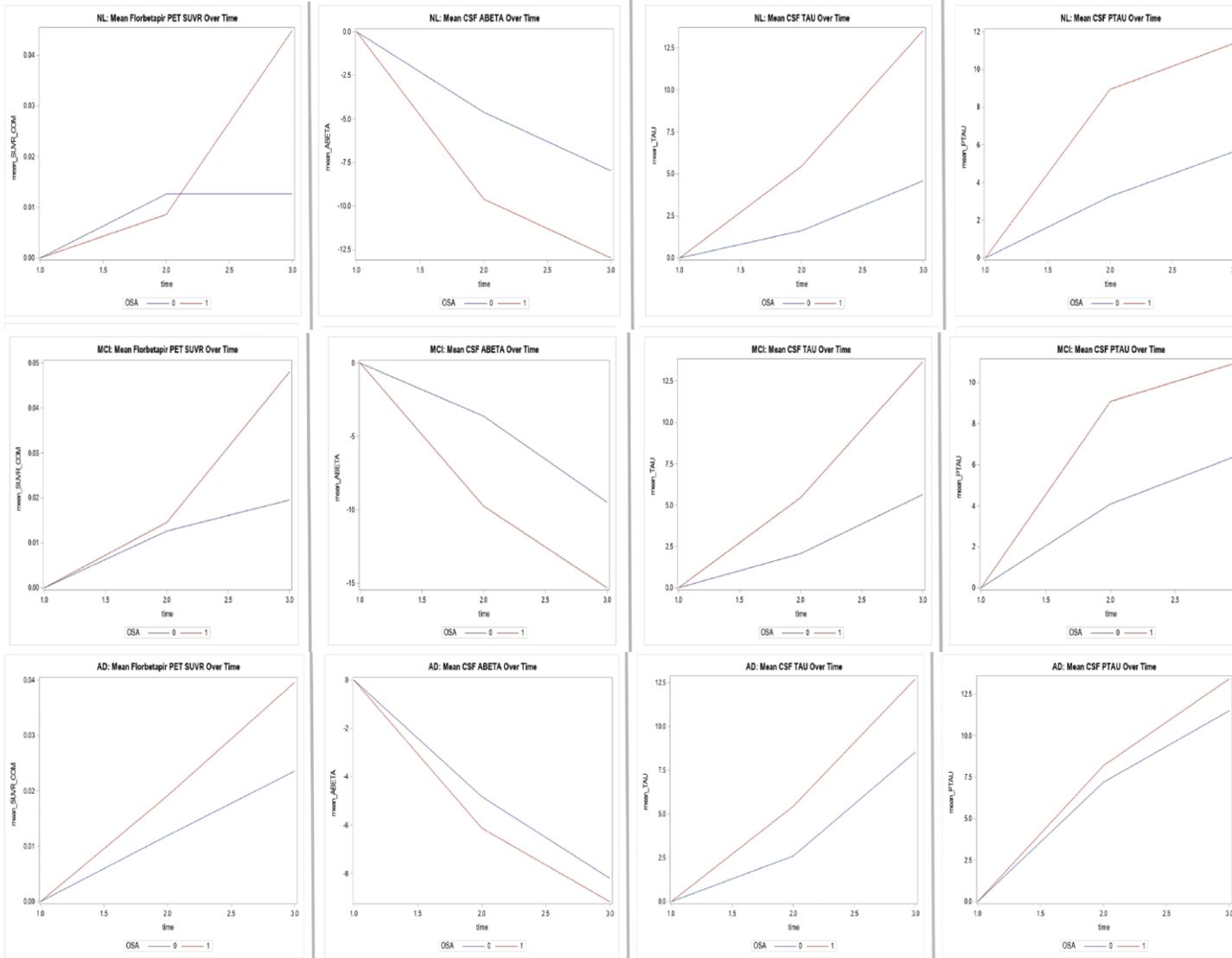
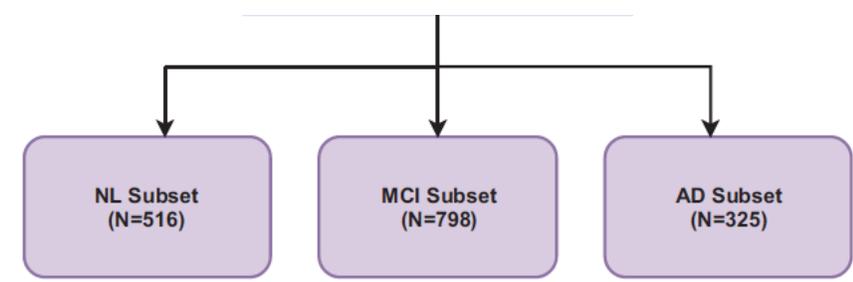
Obstructive sleep apnea and longitudinal Alzheimer's disease biomarker changes

PET Florbetapir

CSF beta

CSF tau

CSF pTau



Cognitively Normal: faster annual change in OSA+

OSA appears to accelerate increases in amyloid deposition, CSF T-tau and P-tau levels over time, both in NL and MCI individuals.

MCI: faster annual change in OSA+

Sleep fragmentation, intermittent hypoxia, and intrathoracic pressure swings from OSA are likely candidate mechanisms.

AD: no change in OSA+

Thus, clinical interventions aimed at OSA, in cognitive normal and MCI patients, could possibly mitigate or slow the progression of cognitive impairment to AD.

...BACK to the future...

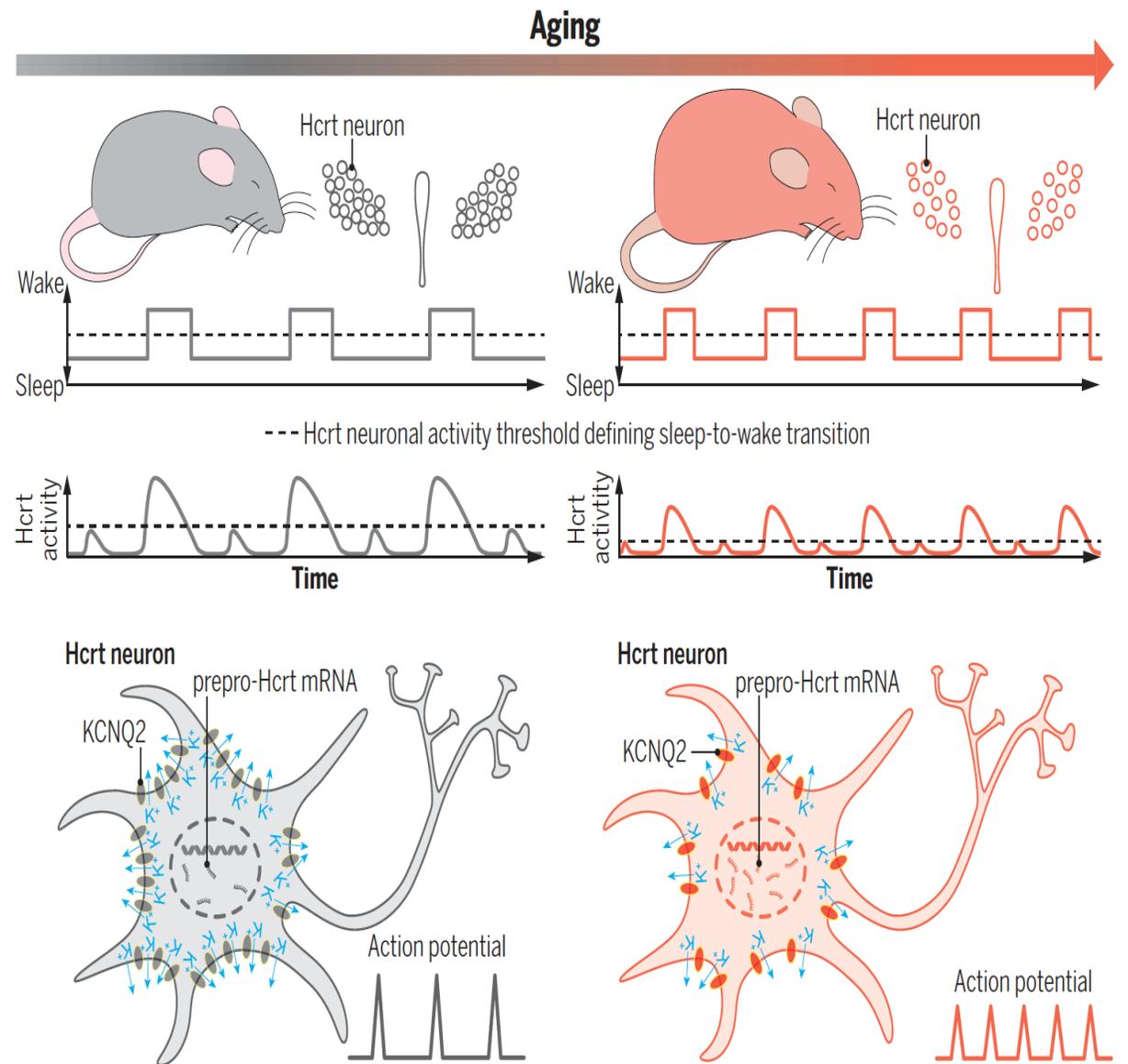


Hyperexcitable arousal circuits drive sleep instability during aging

25/02/2022

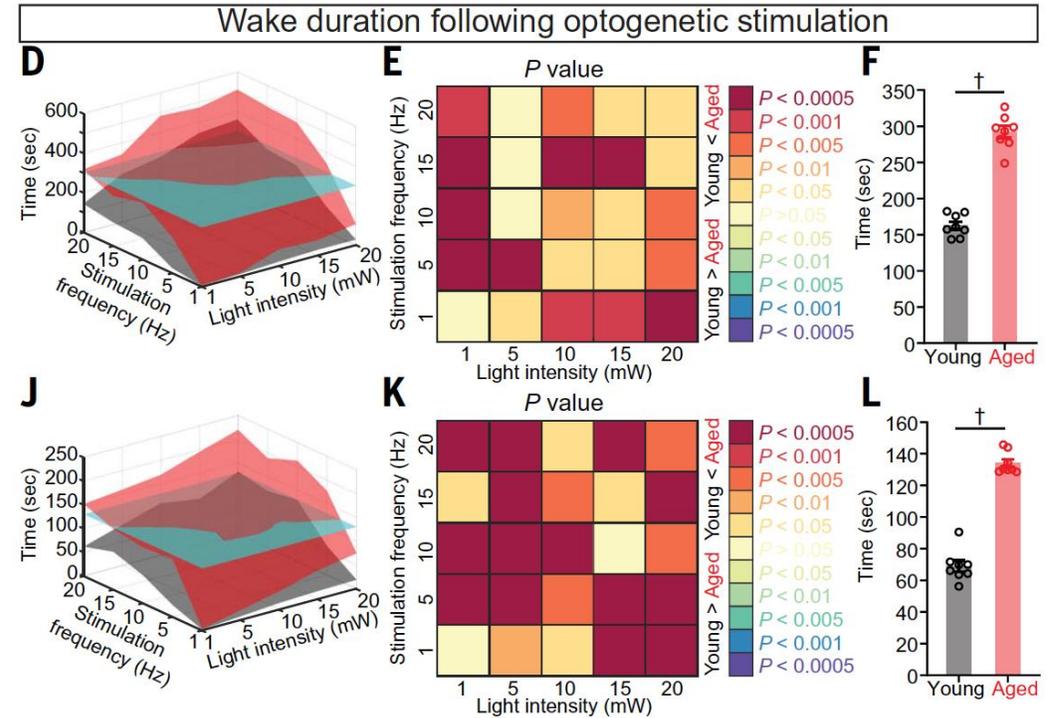
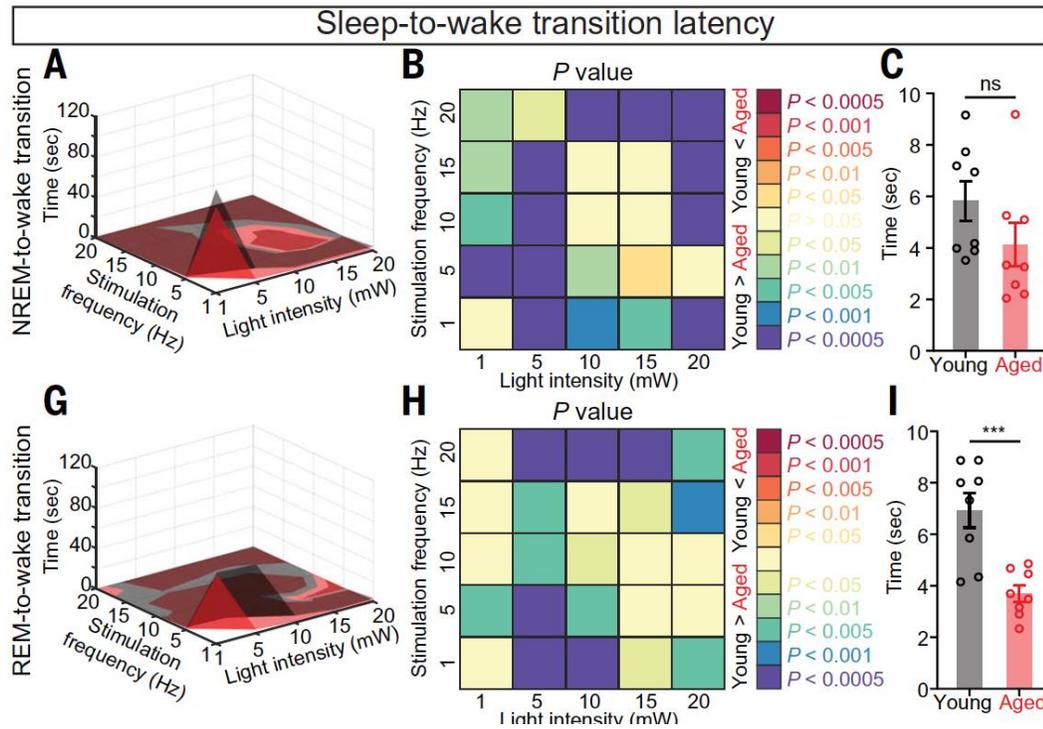
Shi-Bin Li^{1,2†}, Valentina Martinez Damonte^{1,2†}, Chong Chen^{3,4}, Gordon X. Wang¹, Justus M. Keeschull^{5†}, Hiroshi Yamaguchi^{1,2§}, Wen-Jie Bian^{1,2}, Carolin Purmann^{1,6}, Reenal Pattni^{1,6}, Alexander Eckehart Urban^{1,6}, Philippe Murrain^{1,7}, Julie A. Kauer^{1,2}, Grégory Scherrer^{3,4}, Luis de Lecea^{1,2*}

- age-dependent decreased hypocretin neuron density
- calcium peaks in hypocretin neurons associated with wakefulness
- During the inactive phase («*sleep*»), calcium transients were **more frequent and lower in amplitude in old** versus young associated with increased wakefulness



Hyperexcitable arousal circuits drive sleep instability during aging

Shi-Bin Li[†], Valentina Martinez Damonte[†], Chong Chen, Gordon X. Wang, Justus M. Kebschull, Hiroshi Yamaguchi, Wen-Jie Bian, Carolin Purmann, Reenal Pattni, Alexander Eckehart Urban, Philippe Murrain, Julie A. Kauer, Grégory Scherrer, Luis de Lecea^{*}



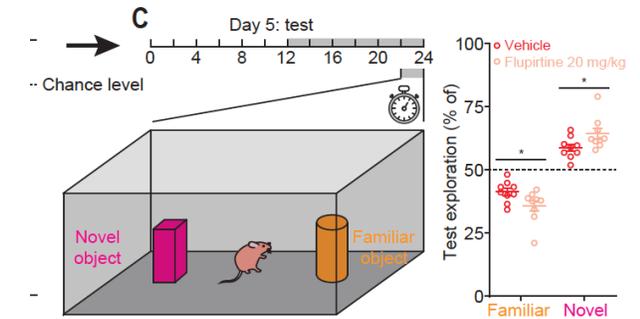
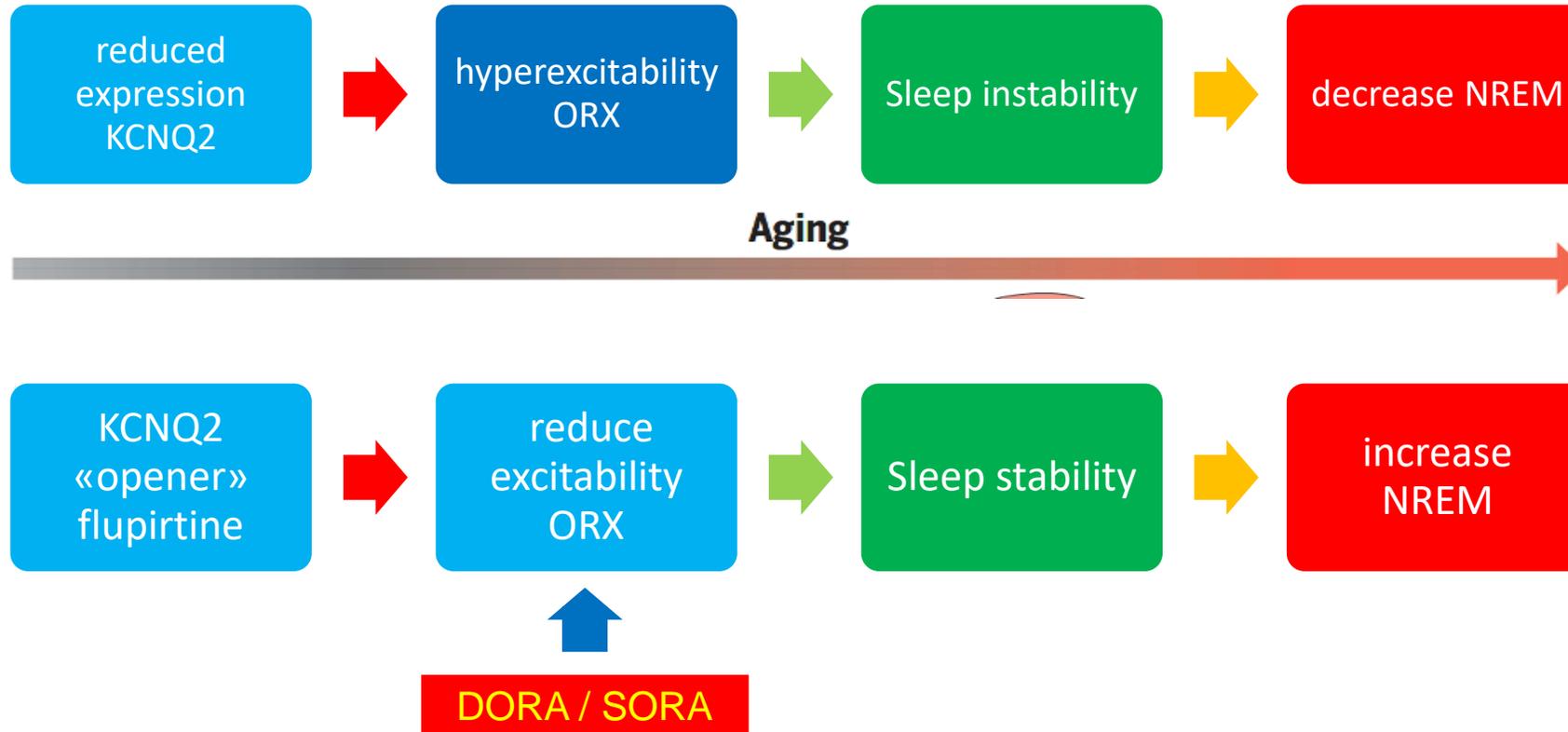
lower threshold to arousal in aged hypocretin neurons

Increased wakefulness by optogenetic stimulation of orx neurons



Hyperexcitable arousal circuits drive sleep instability during aging

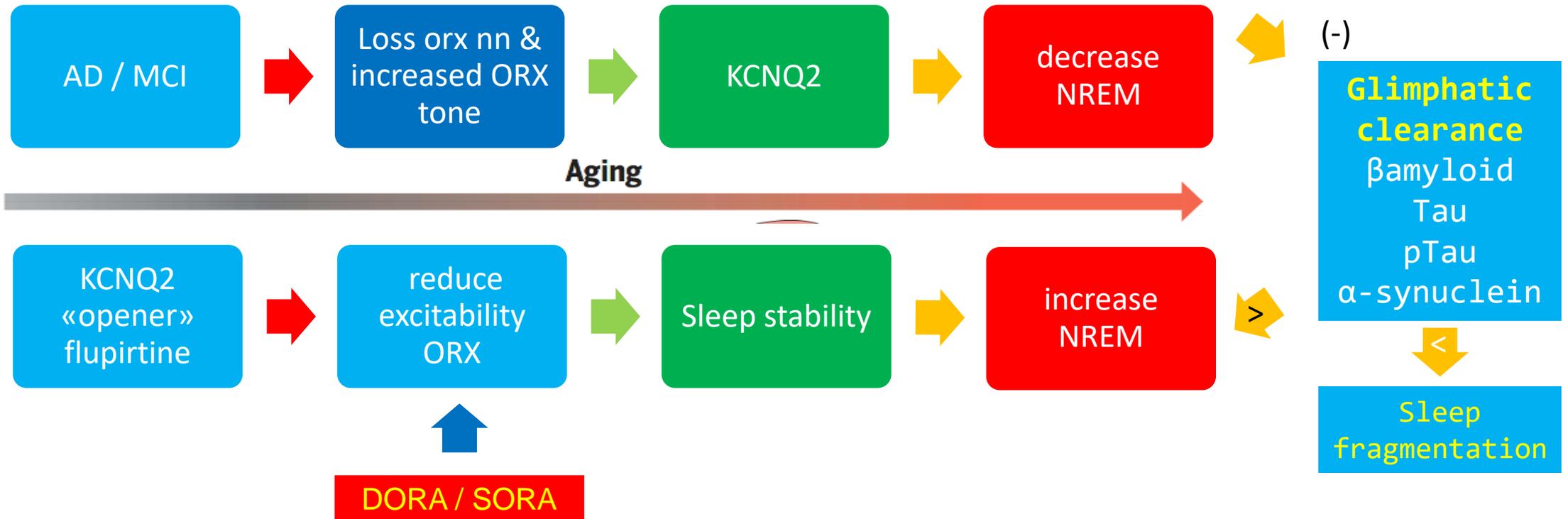
Shi-Bin Li[†], Valentina Martinez Damonte[†], Chong Chen, Gordon X. Wang, Justus M. Kebschull, Hiroshi Yamaguchi, Wen-Jie Bian, Carolin Purmann, Reenal Pattni, Alexander Eckehart Urban, Philippe Murrain, Julie A. Kauer, Grégory Scherrer, Luis de Lecea*



Cognitive improvement

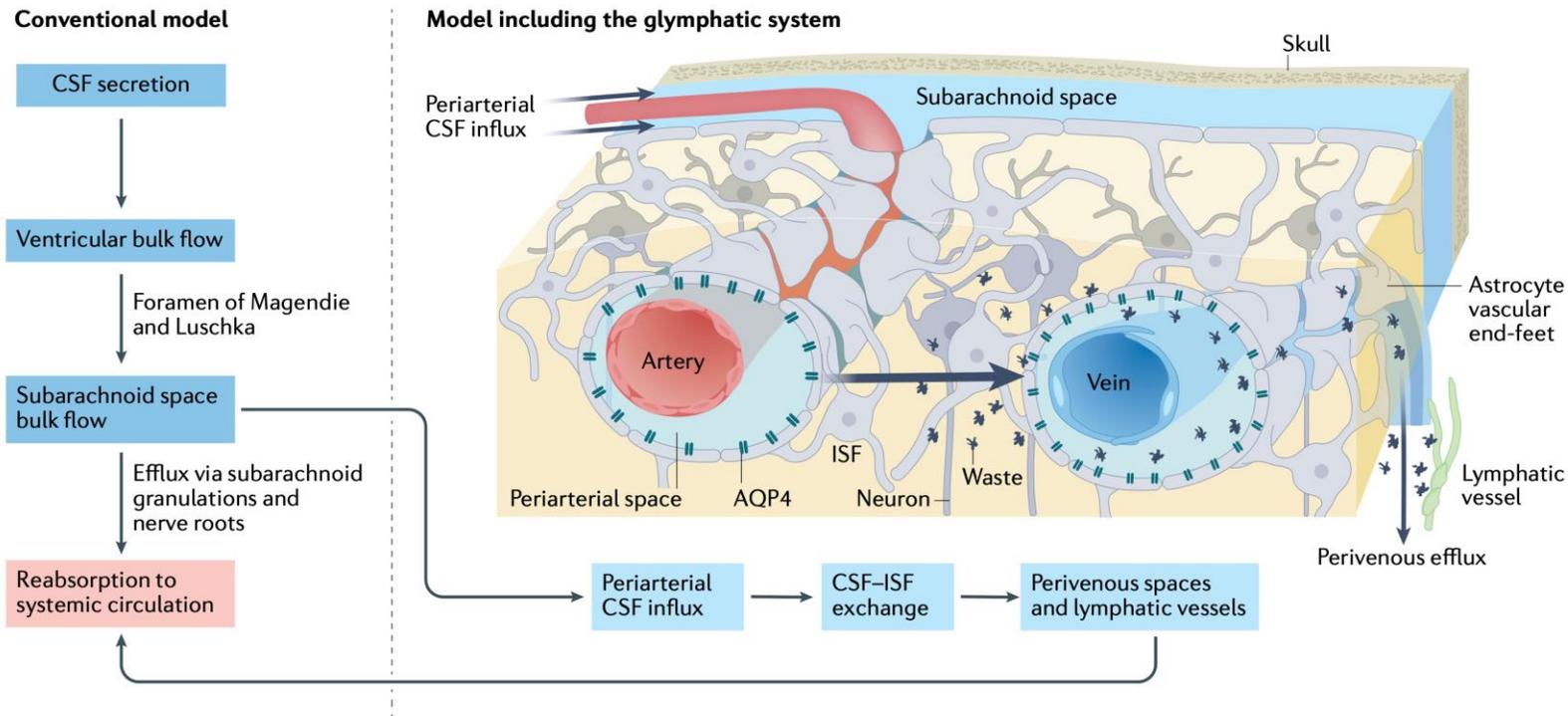
Hyperexcitable arousal circuits drive sleep instability during aging

Shi-Bin Li[†], Valentina Martinez Damonte[†], Chong Chen, Gordon X. Wang, Justus M. Kebschull, Hiroshi Yamaguchi, Wen-Jie Bian, Carolin Purmann, Reenal Pattni, Alexander Eckehart Urban, Philippe Murrain, Julie A. Kauer, Grégory Scherrer, Luis de Lecea*



Glymphatic system: overview

Lohela et al., 2022 Nat Rev



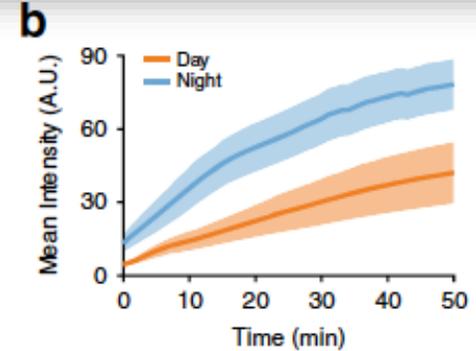
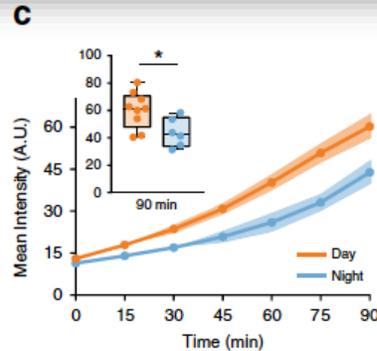
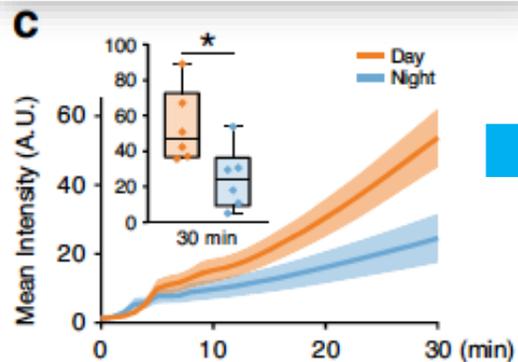
Dysfunction of the glymphatic system has been linked to various neurological disorders.

A vital brain cleaning system that utilizes **CSF to remove waste products from brain tissue**. It's a relatively new area of research with significant implications for understanding and treating neurological diseases.

Circadian control of brain glymphatic and lymphatic fluid flow

Lauren M. Hablitz ¹✉, Virginia Plá ¹, Michael Giannetto¹, Hanna S. Vinitsky ¹, Frederik Filip Stæger², Tanner Metcalfe¹, Rebecca Nguyen¹, Abdellatif Benrais¹ & Maiken Nedergaard^{1,2}✉

The glymphatic system is a network of perivascular spaces that promotes movement of cerebrospinal fluid (CSF) into the brain and clearance of metabolic waste. This fluid transport system is supported by the water channel aquaporin-4 (AQP4) localized to vascular endfeet of astrocytes. The glymphatic system is more effective during sleep, but whether sleep timing promotes glymphatic function remains unknown.



Glymphic Fluid Flow
> mid-day (sleep)

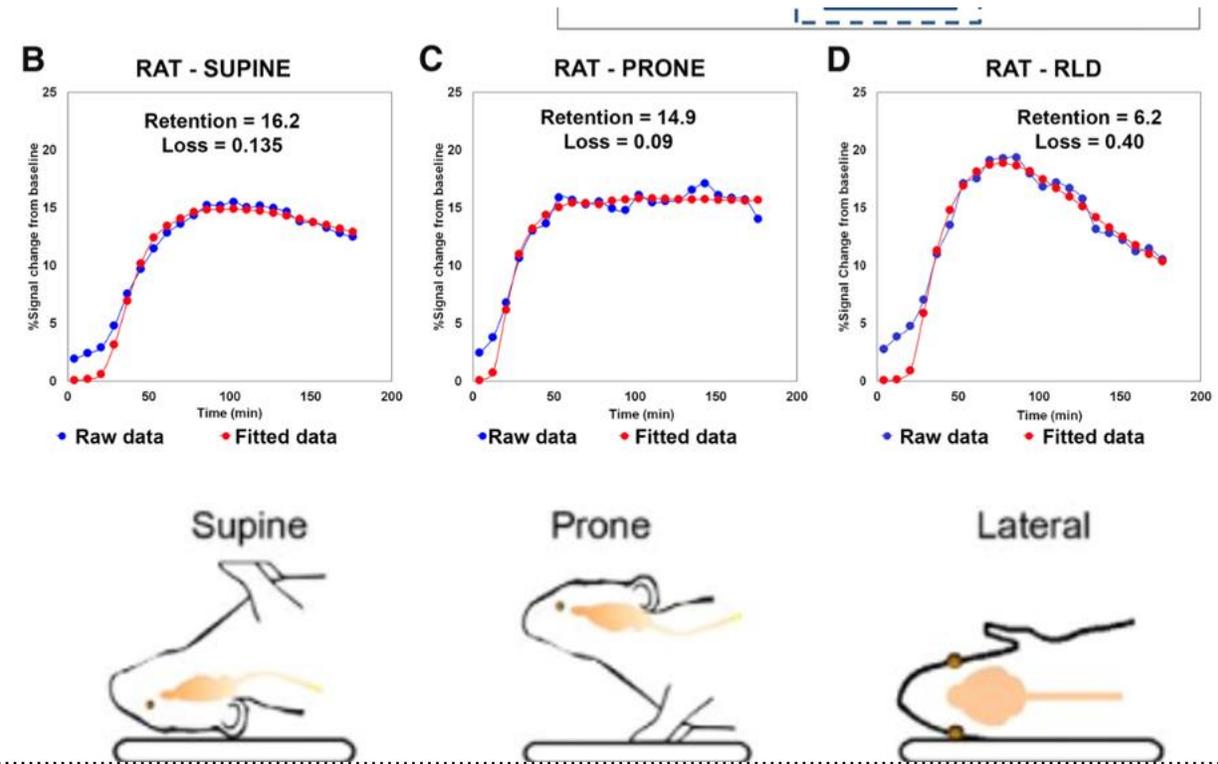
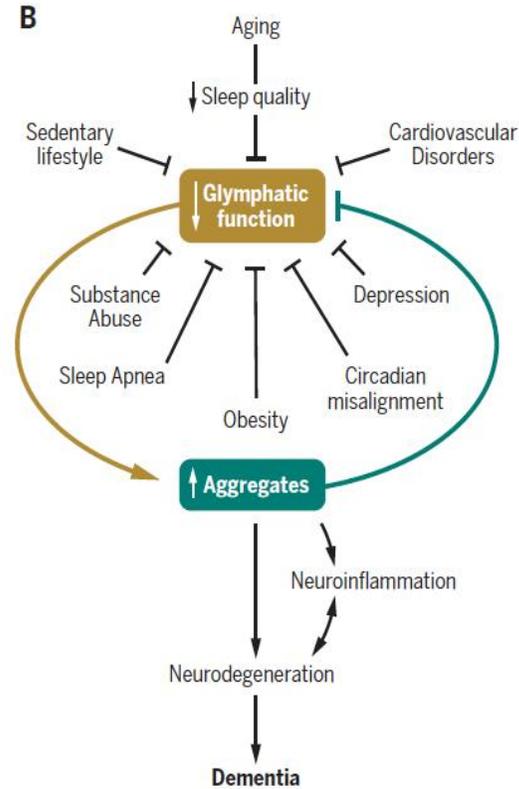
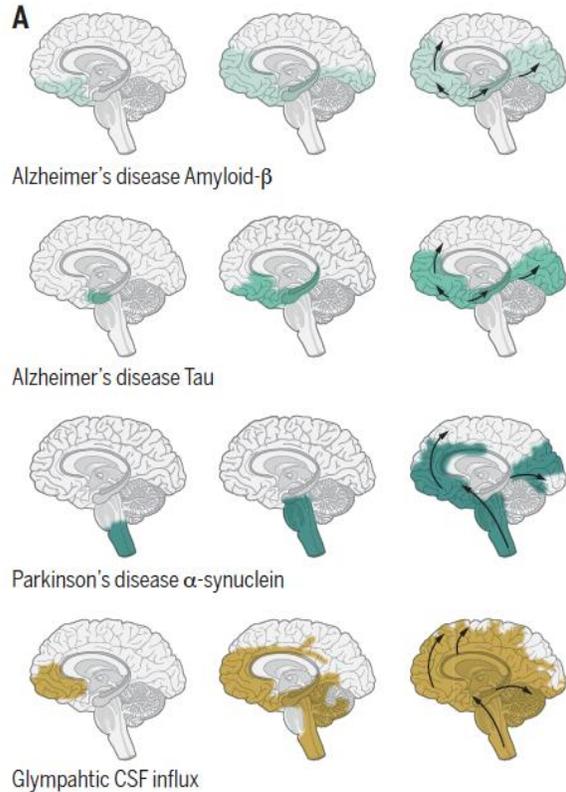
Interstitial fluid clearance > mid-day
(sleep)

Lymph node drainage from
cisterna magna > during night

Glymphatic failure as a final common pathway to dementia

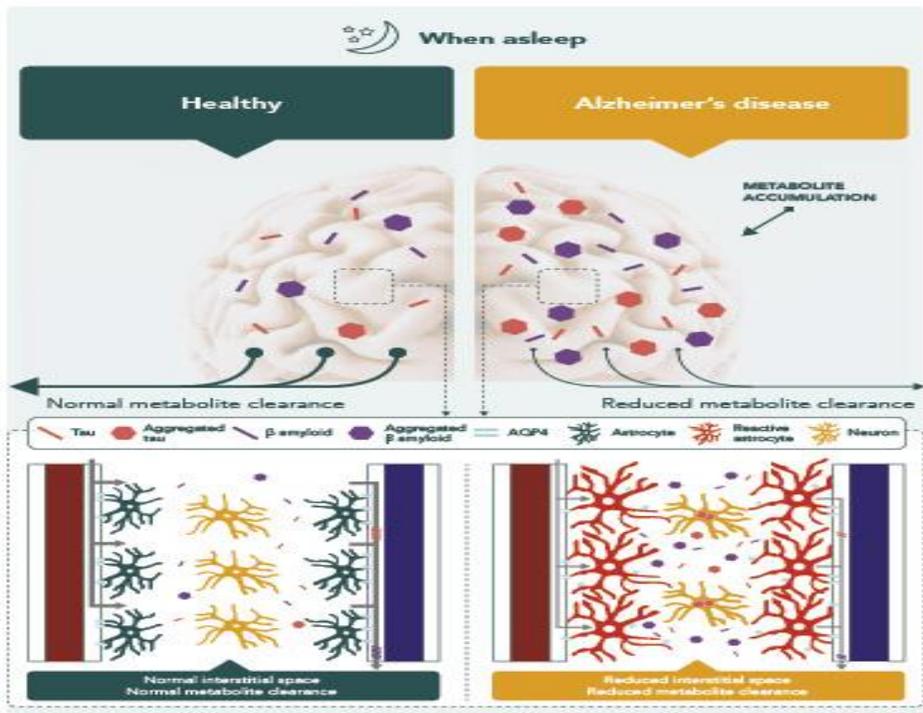
Science **370**, 50–56 (2020)

Maiken Nedergaard^{1,2*} and Steven A. Goldman^{1,2*}

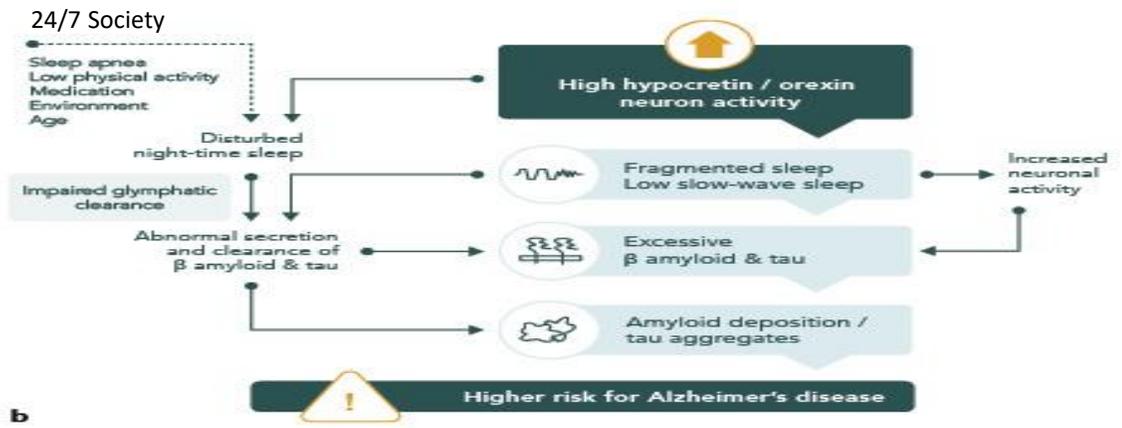


The analysis showed that glymphatic transport was **most efficient in the lateral position compared with the supine or prone positions**. In the **prone position**, in which the rat's head was in the most upright position (**mimicking awake state**), transport was characterized by “**retention**” of the tracer, **slower clearance**, and **more CSF efflux** along larger caliber cervical vessels.

Lee et al., 2015 JNS



*"...obviously **mice are not people**, just as **apples are not planets**. Nonetheless, because **apples & planets** both have mass, falling apples allowed Newton to elucidate the forces underlying planetary movements..."*
Palop, 2009



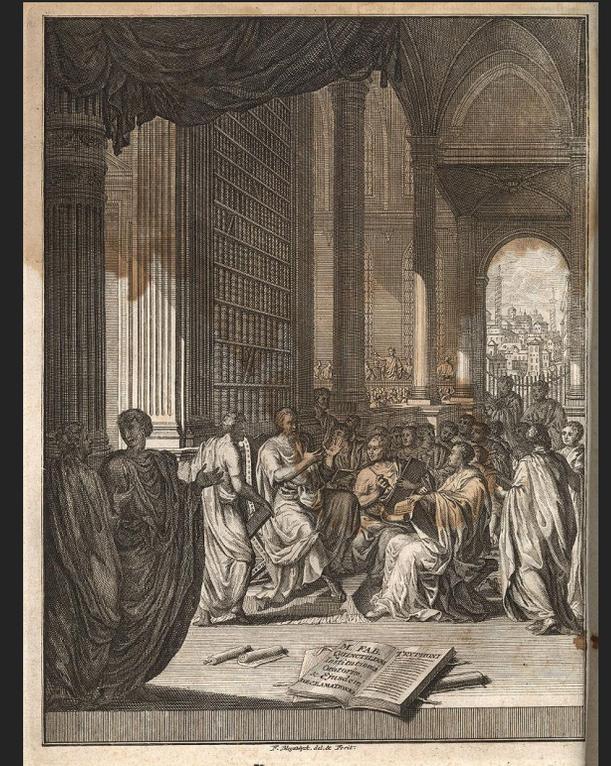
Prequel...



- «...quae statim referri non poterant, contexuntur postera die, confirmatque memoriam idem illud tempus quod esse in causa solet oblivionis...»

- «Ciò che non poteva essere ripetuto alla prima, è facilmente messo insieme il giorno seguente; e il tempo che si ritiene in genere provochi dimenticanza (ovvero **il sonno**), si trova a rafforzare la memoria»

- Quintilianus, Institutio Oratoria XI, 2:43



MINOR STUDIES FROM THE PSYCHOLOGICAL LABORATORY
OF CORNELL UNIVERSITY

Communicated by E. B. TITCHENER

LXXII. OBLIVISCENCE DURING SLEEP AND WAKING

By JOHN G. JENKINS and KARL M. DALLENBACH 1924

Primi a dimostrare scientificamente che **dormire impedirebbe la normale curva di decadimento della memoria** che si sviluppa attraverso il tempo trascorso sveglio

Il richiamo del materiale è migliore quando il **periodo di ritenzione viene trascorso in sonno** rispetto alla veglia ("**SLEEP EFFECT**")

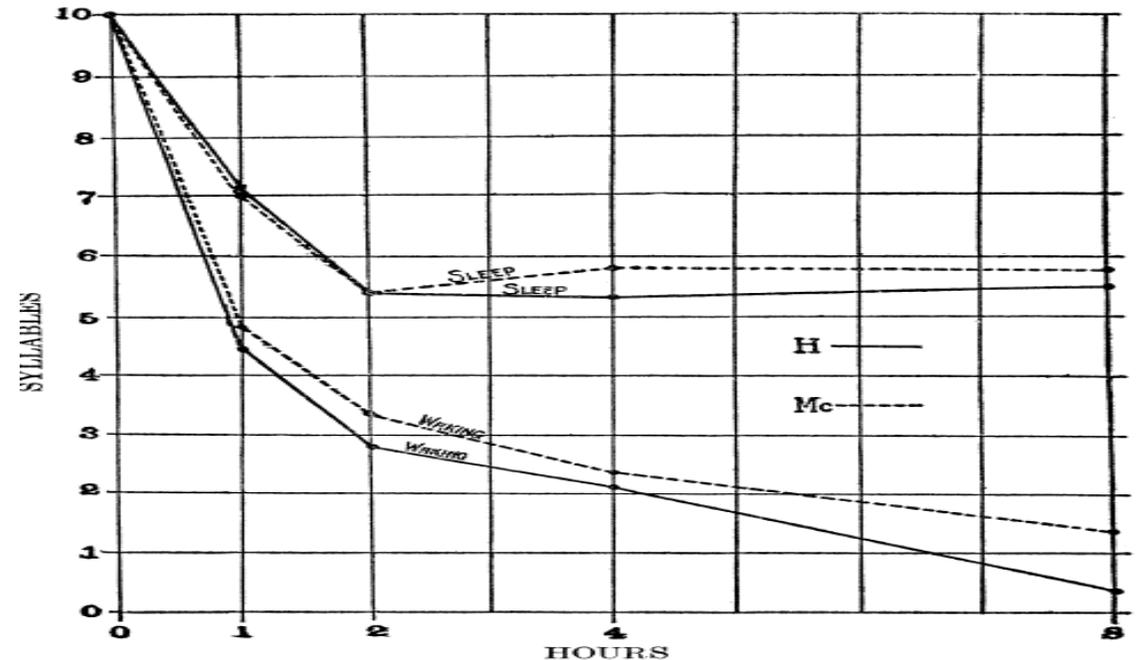


FIG. I. Average Number of Syllables Reproduced by each O after the Various Time-Intervals of Sleep and Waking



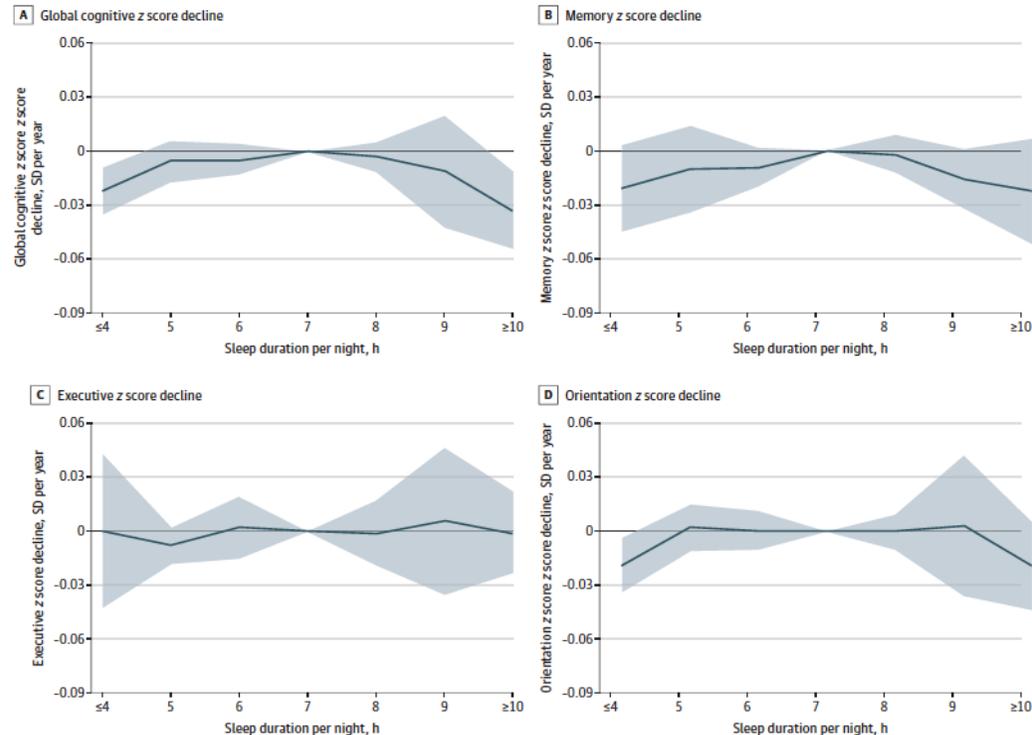
One century later...

Original Investigation | Geriatrics

September 21, 2020

Association Between Sleep Duration and Cognitive Decline

YanJun Ma, BA; Lirong Liang, MD; Fanfan Zheng, PhD; Le Shi, MD; Baoliang Zhong, MD; Wuxiang Xie, PhD



Baseline & Decline

Conclusions

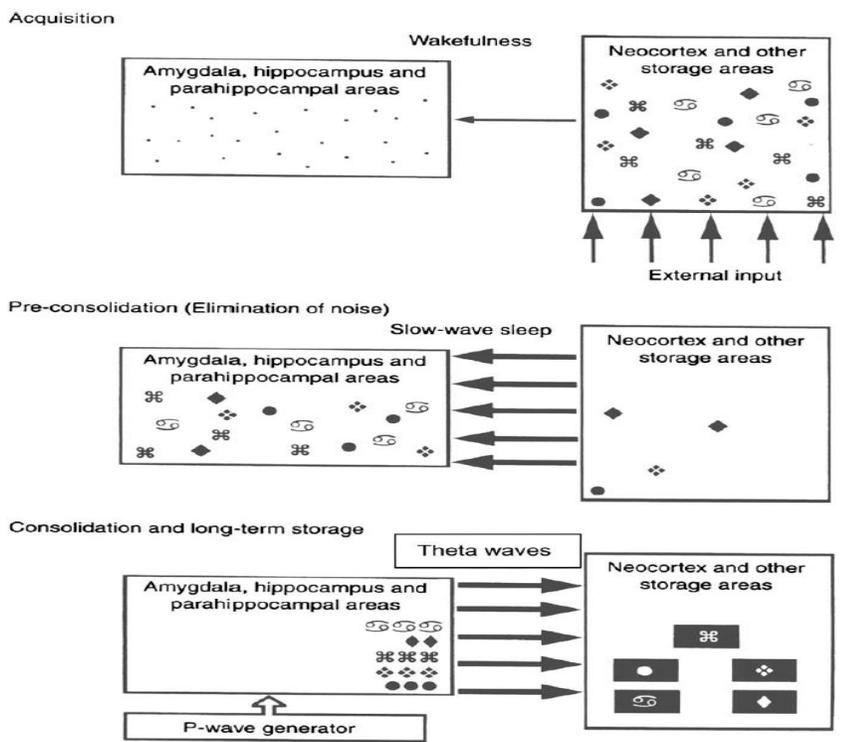
A statistically significant inverted U-shaped association was observed between sleep duration and cognitive function, as well as subsequent decline. Extreme sleep duration (ie, ≤ 4 or ≥ 10 hours per night) was associated not only with lower cognitive function at baseline but also with faster cognitive decline during the follow-up assessments. The inverted U-shaped association indicates that cognitive function should be monitored in middle-aged and older individuals with insufficient or excessive sleep duration. Future mechanism studies and intervention studies examining the association between sleep duration and cognitive decline are needed.

Ma non sappiamo le cause della sleep duration...

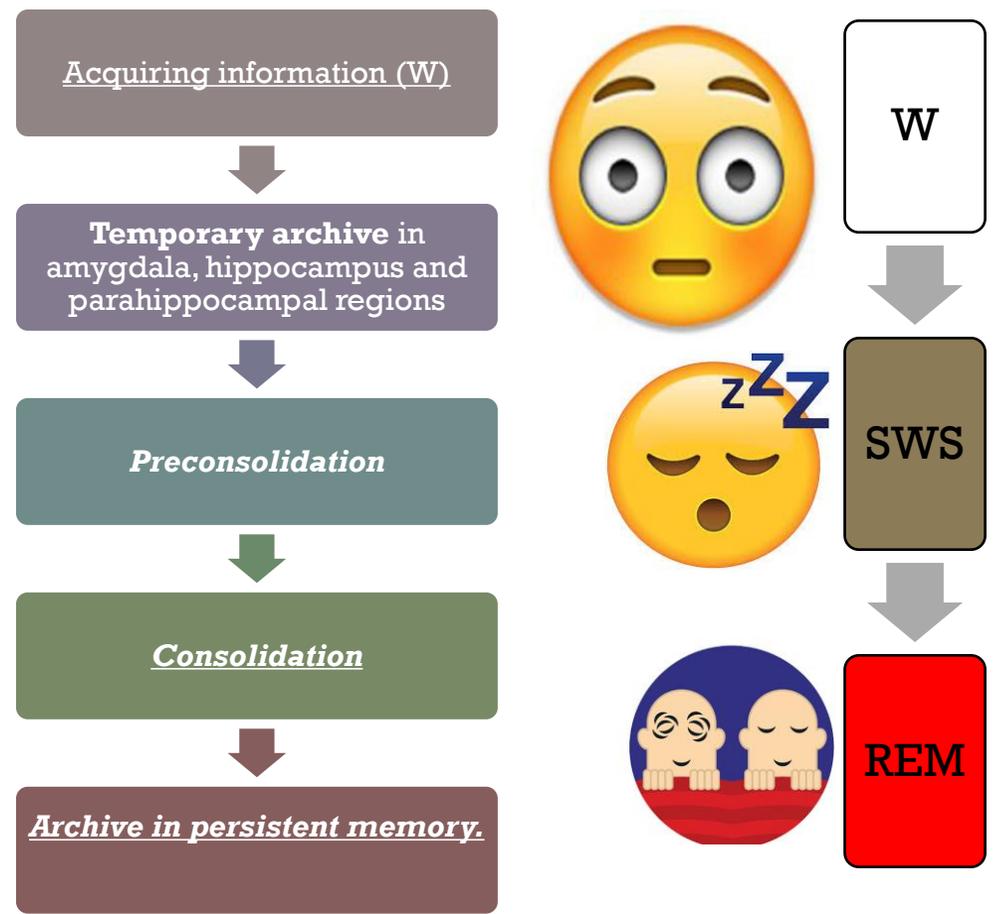


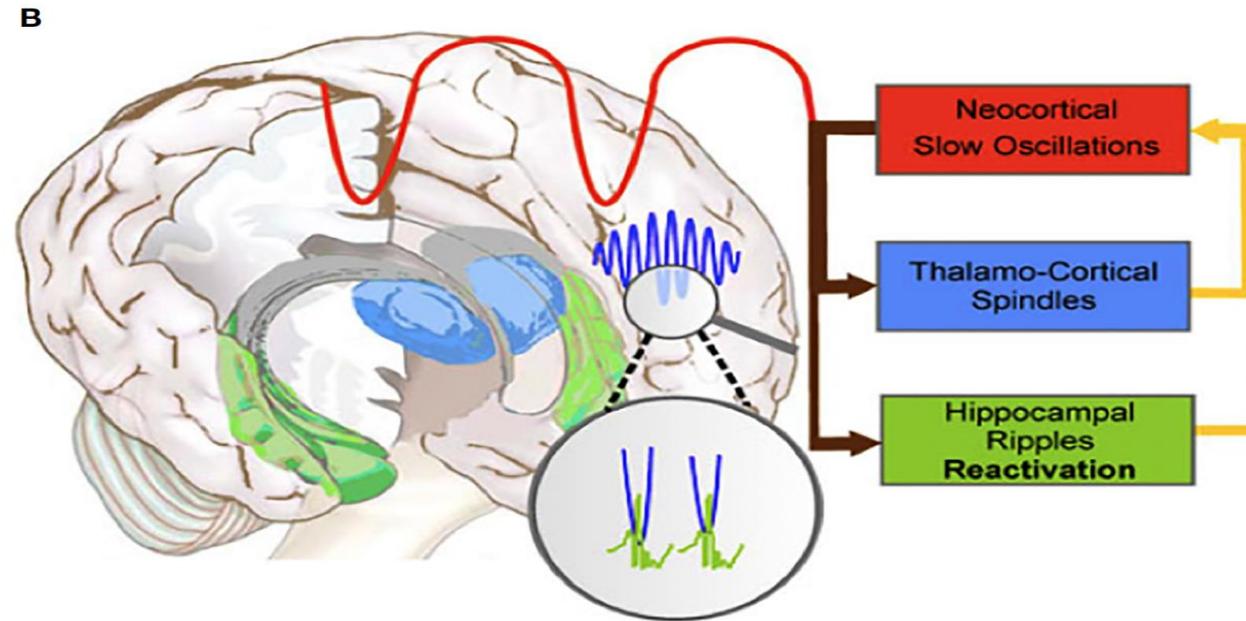
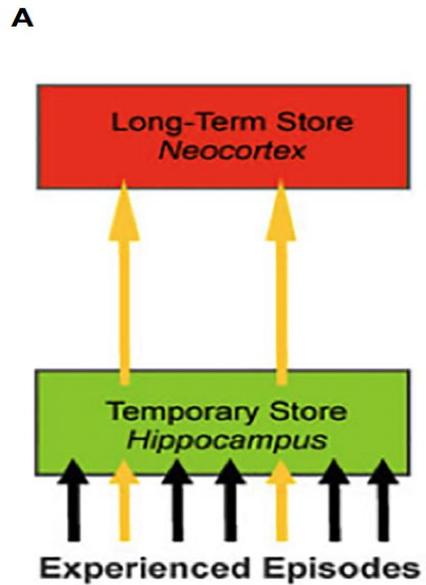


SLEEP-DEPENDENT MEMORY CONSOLIDATION MODEL AND LONG-TERM ACQUISITION



Graven, 2006





During NREM sleep, memories temporarily stored in the hippocampus are transferred to the long-term store in the neocortex.

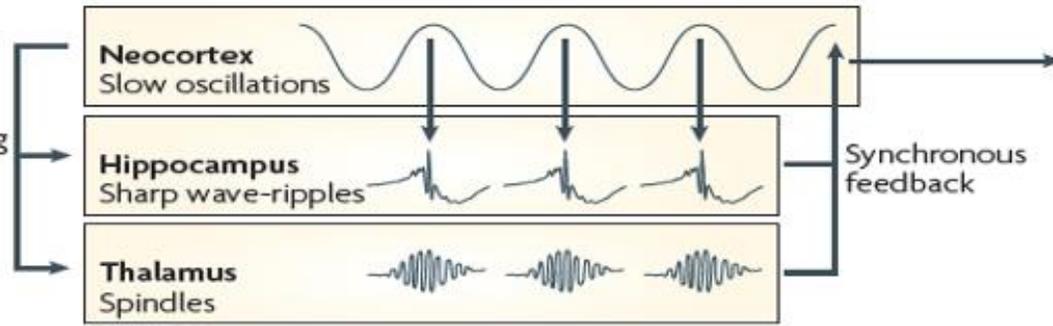
The dialogue involves the interaction between the cortical **slow oscillations**, thalamic **sleep spindles** and hippocampal **ripples** to create spindle-ripple events



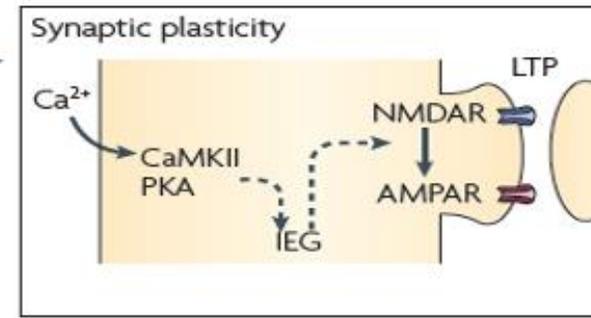


Synchronizing feed-forward effect

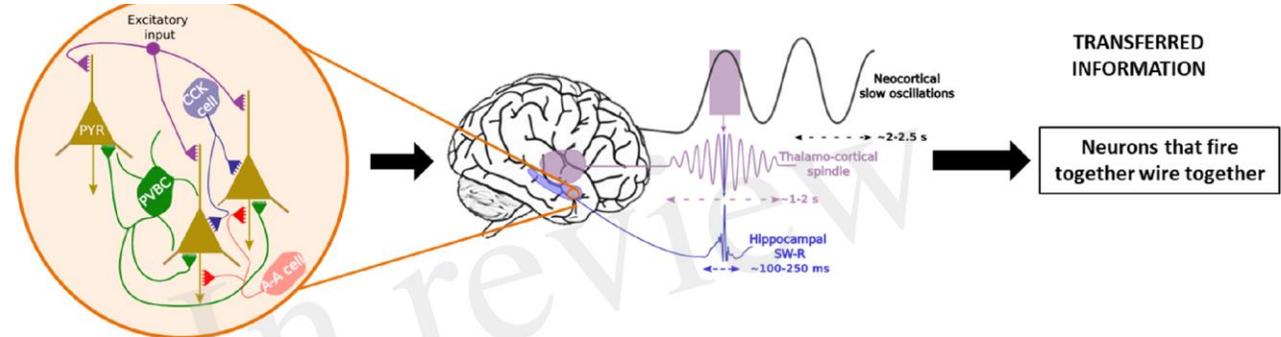
SWS



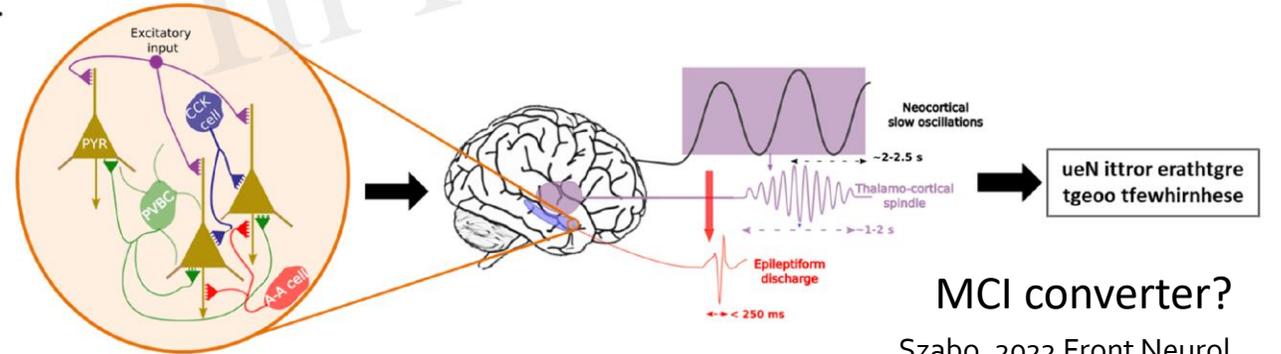
REM persistent synaptic plastic changes (REM)



Diekelman, 2010, Nature Rev Neurosci



B.



SLOW OSCILLATIONS & COUPLING

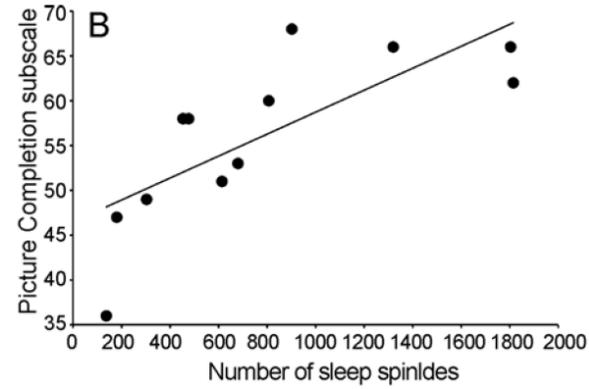
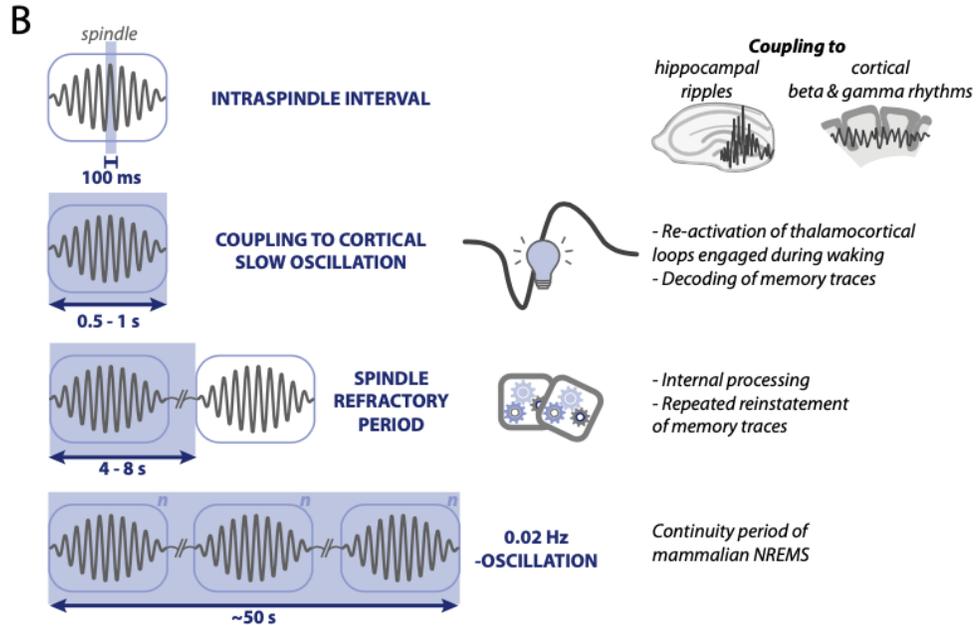
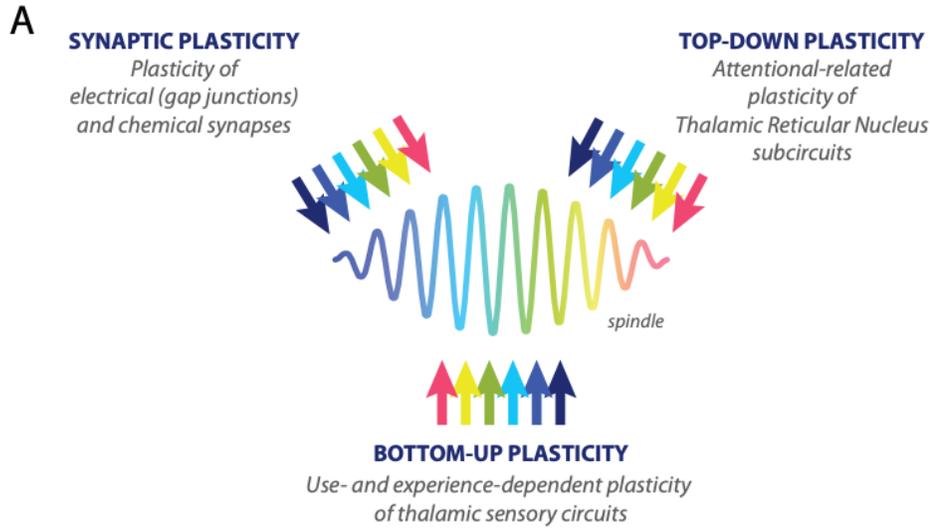
Paroxysmal epileptic activity? LOEU? OSAS? Sleep restriction?

MCI converter?

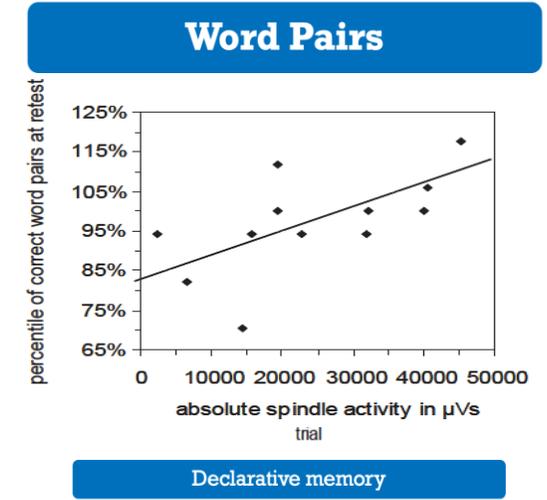
Szabo, 2022 Front Neurol



Stage 2 spindle density (#/min)



N Spindle & IQ



linked to intellectual ability and memory consolidation

Fogel et al., 2011 Neurosc & Behav
Genzel., 2009 Sleep



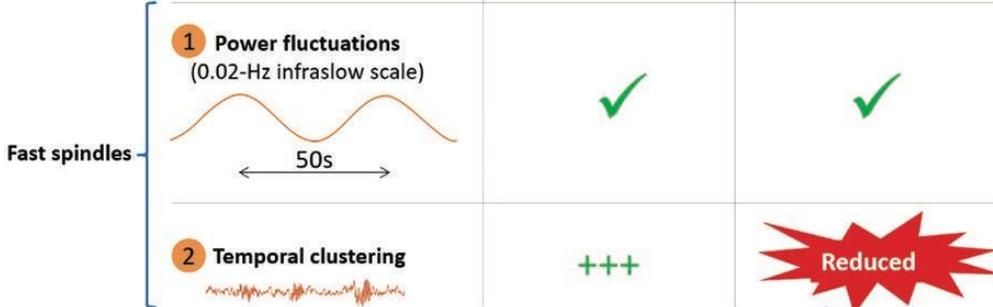
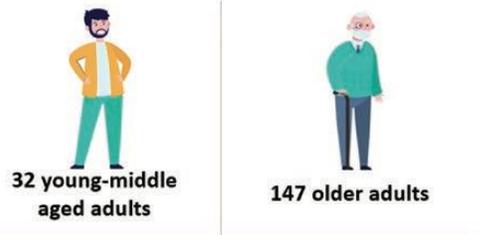
Original Article

Age-related changes in fast spindle clustering during non-rapid eye movement sleep and their relevance for memory consolidation

Pierre Champetier^{1,2}, Claire André^{1,2}, Frederik D. Weber^{1,2}, Stéphane Rehel^{1,2}, Valentin Ourry^{1,2}, Alice Laniepe^{1,2}, Antoine Lutz^{1,2}, Françoise Bertran^{1,2}, Nicolas Cabé¹, Anne-Lise Pitel¹, Géraldine Poinsin¹, Vincent de la Sayette^{1,2}, Denis Vivien^{1,2}, Gaël Chételat¹, and Géraldine Rauchs^{1,2}, on behalf of the Medit-Ageing Research Group

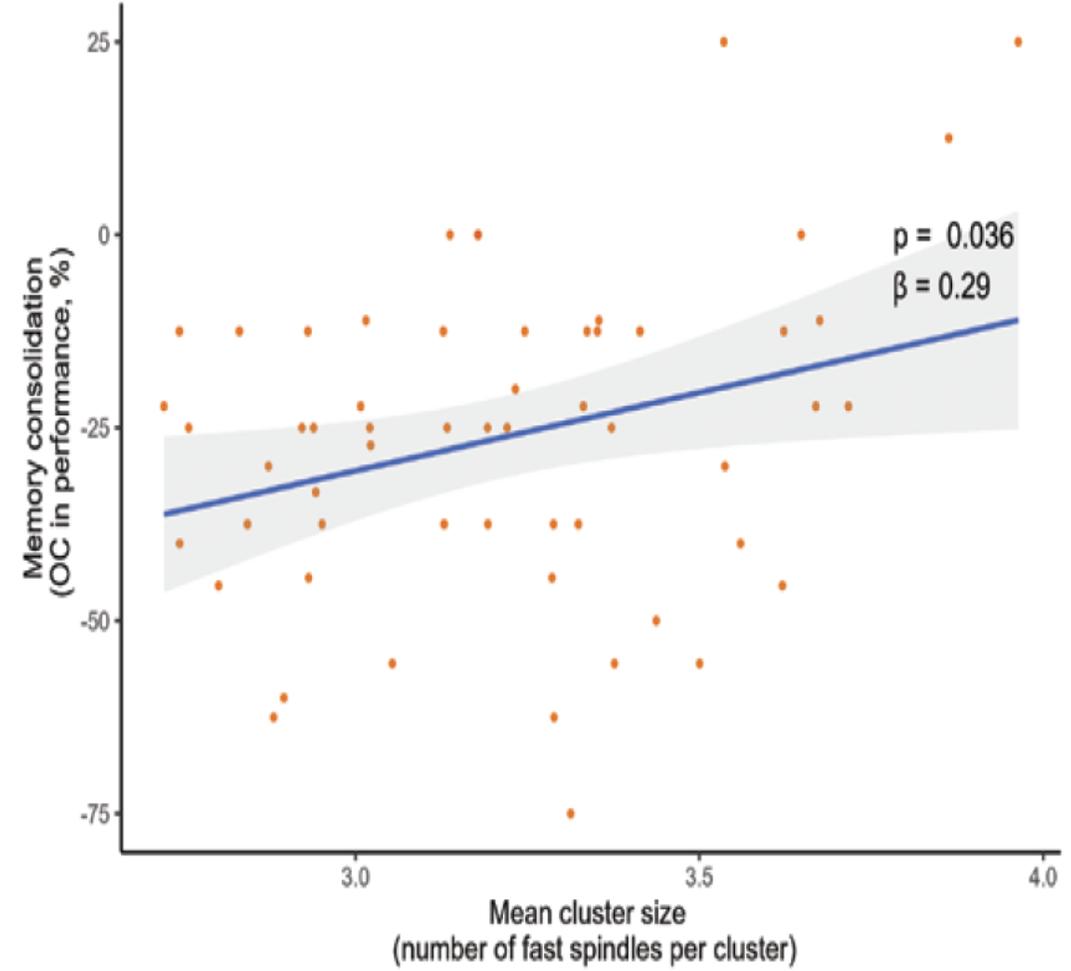
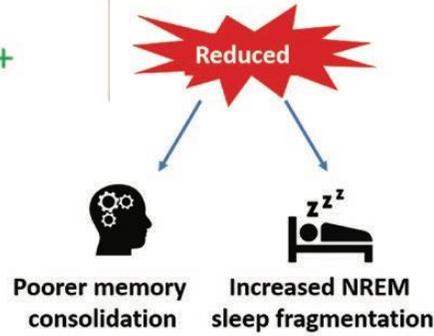
! & AGEING

Study question:
 Does age impact fast spindle temporal dynamics?



Main findings:

- Age reduces fast spindle clustering.
- These changes are associated with poorer memory consolidation and increased NREM sleep fragmentation.



Images: Freepik (pch.vector), Noun Project (ImageCatalog, Jayson Lim, Yannik Wölfl and Adrien Coquet)



Biological Clock



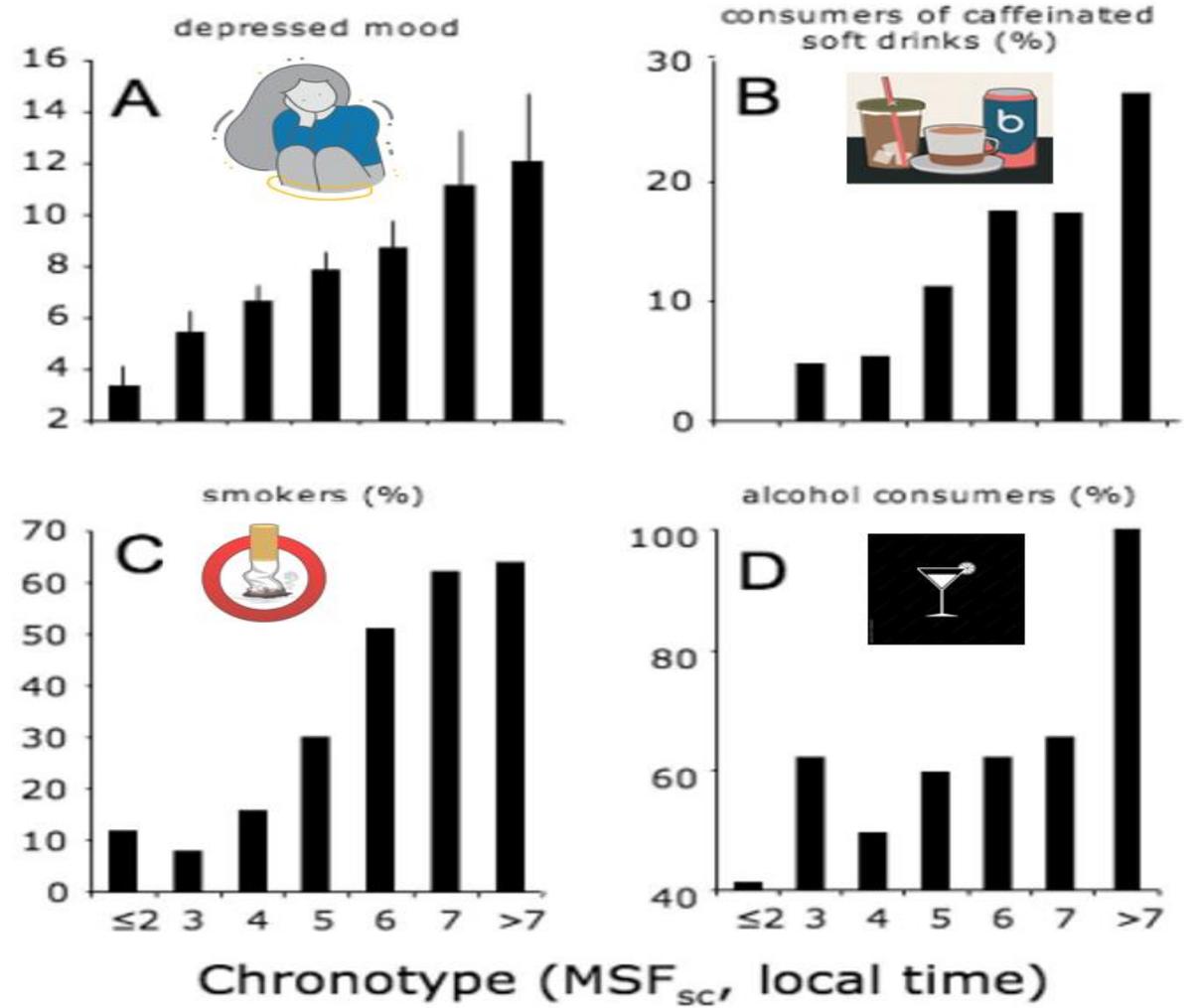
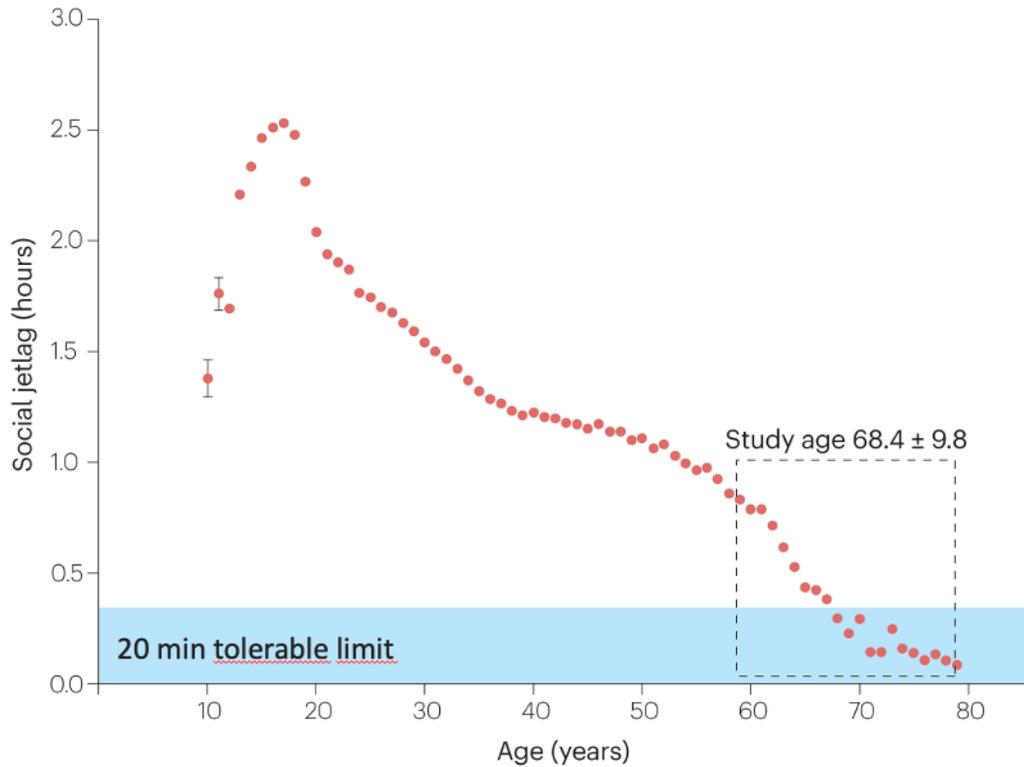
Social clock



Sun clock



Social Jetlag



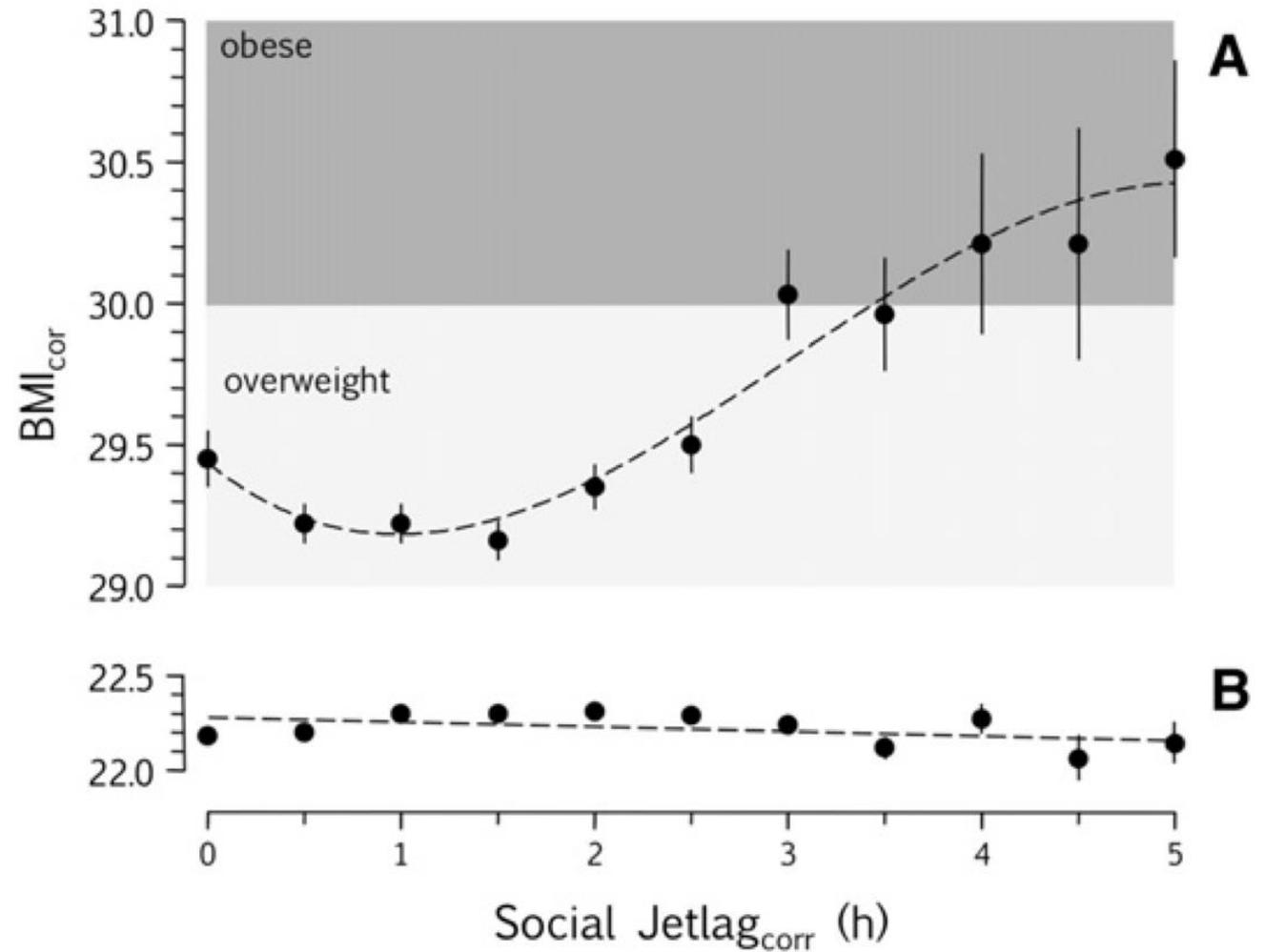
'Social jetlag' difference between local clock and circadian clock

Obesity & SJL

- Circadian misalignment & shift work (more data)
- Smaller degree in
 - SJL
 - JL
 - DST

For every hour of shift **O.R. 1.3**
metabolic syndrome

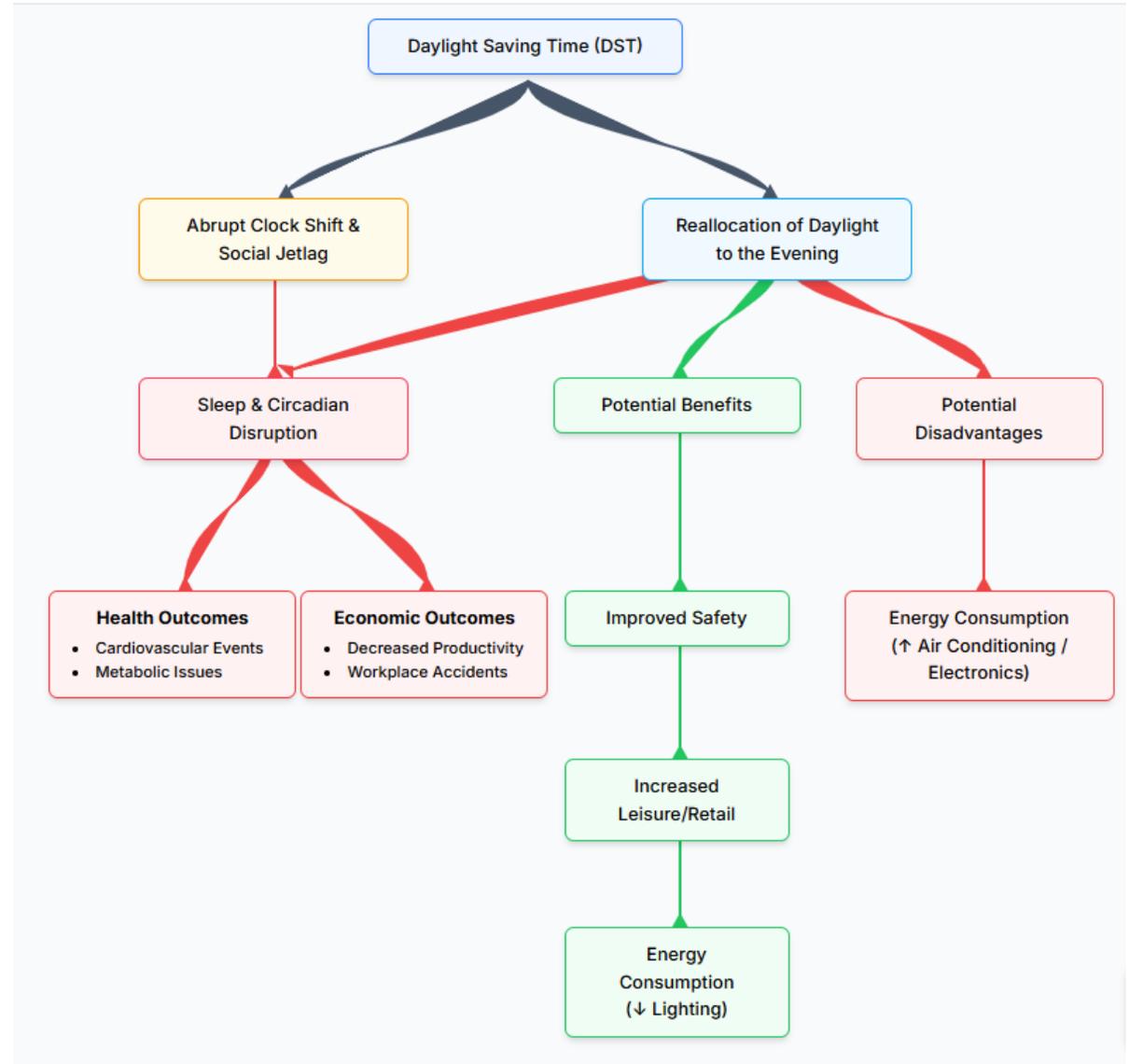
Social Jetlag score positive correlation
with obesity



Roenneberg 2012, Curr Biol

- **Ideal standard time** zones have solar time align with the time zone meridian at noon with the entire time zone within 30 min of solar time.
- **“Gerrymandered” ST** zones caused the western edge of most time zone to be delayed by more than 30 min from solar time and in places over an hour (for political and economic interests)
- **“Gerrymandered” DST zone** delays clock time by 1 h, resulting in a 1 h delay at the time zone median and around 2 h delay from solar time on the western edge

DST affects **a quarter of the world's population**.
EU Commission (autumn 2018) decided that biannual clock change in Europe **would**

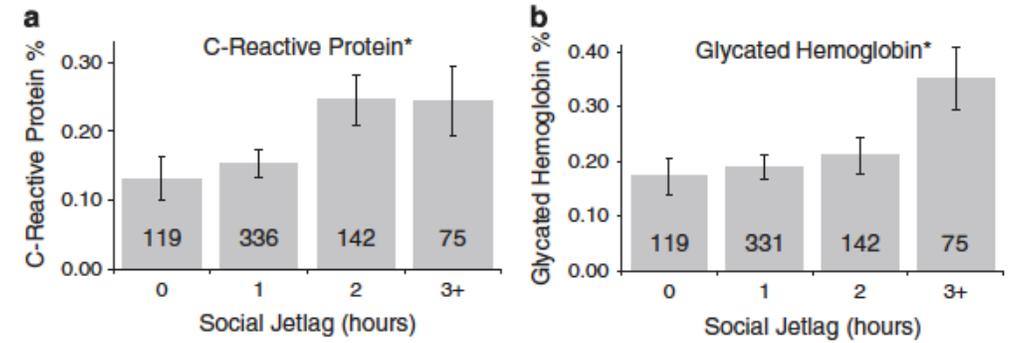
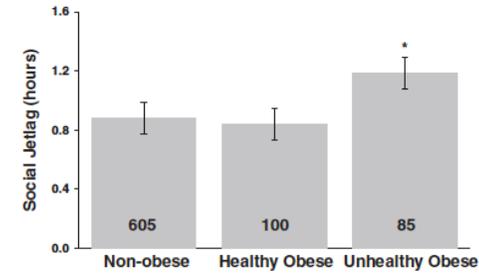
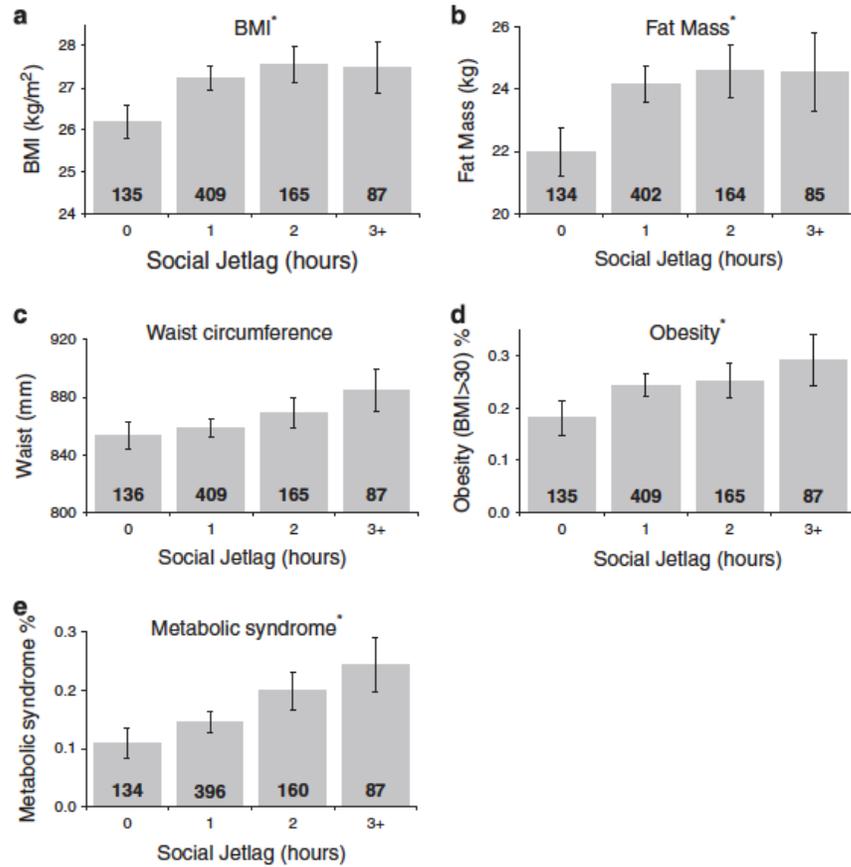


Romigi et al., 2025 submitted

DST transitions impact sleep by disrupting sleep duration, quality, and efficiency

Social jetlag, obesity and metabolic disorder: investigation in a cohort study

MJ Parsons¹, TE Moffitt^{2,3,4,5}, AM Gregory⁶, S Goldman-Mellor^{2,3,4,7}, PM Nolan¹, R Poulton⁸ and A Caspi^{2,3,4,5}



«**‘living against our internal clock’** may contribute to metabolic dysfunction and its consequences»

The role of insufficient sleep and circadian misalignment in obesity

Social Jetlag and Obesity

ORIGINAL ARTICLE

Social jetlag, obesity and metabolic disorder: investigation in a cohort study

Is time of eating associated with BMI and obesity? A population-based study

Social jet lag and (changes in) glycemic and metabolic control in people with type 2 diabetes

Circadian rhythms

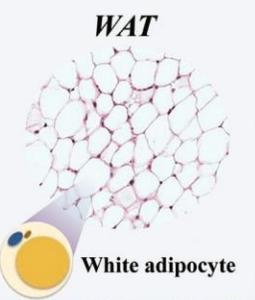
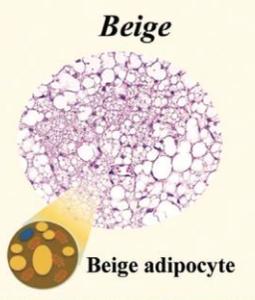
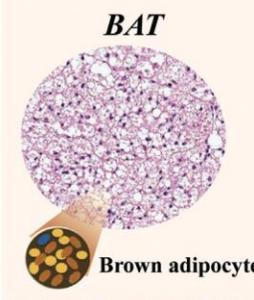
<https://doi.org/10.1038/s41574-023-00851-2>

How can social jetlag affect health?



Courtesy by ChatGPT 4

Melatonin & adiposity

	WAT	Beige	BAT
			
	White adipocyte	Beige adipocyte	Brown adipocyte
Location	Subcutaneous Visceral Intramuscular	Subcutaneous Intramuscular Other location	Interscapular Axillary Cervical Paravertebral
Characters	Store energy Single large fat droplet Few mitochondria UCP1-nearly undetectable	Dissipate energy Develop in WAT High mitochondria High UCP1 and PGC1 α	Dissipate energy Multiple small lipid droplets High mitochondria High UCP1 and PGC1 α
Markers	<i>Tcf21</i> <i>Hoxc9</i> ...	<i>Tbx1</i> <i>Tnfrsf9/Cd137</i> <i>Tmem26</i> ...	<i>Zic1</i> <i>Lhx8</i> <i>Epst1l</i> ...

Xu et al., 2019

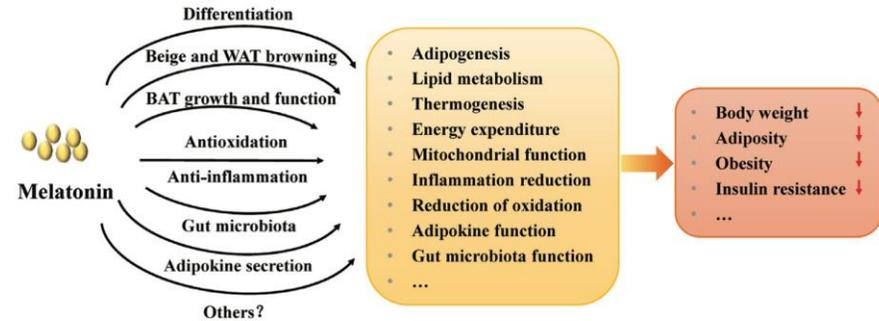


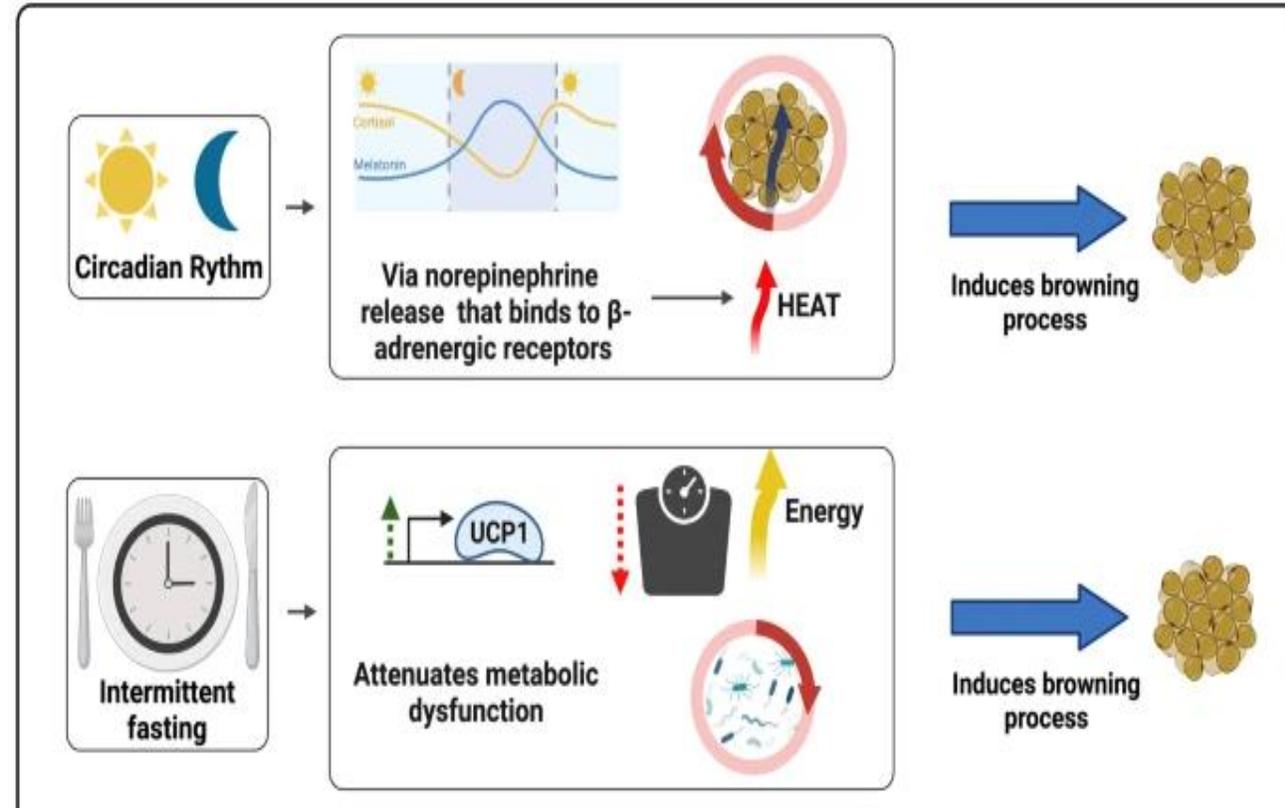
FIGURE 6 The regulatory mechanisms of melatonin on adiposity and body weight. Melatonin regulates body weight and adiposity in different ways, such as affecting adipogenic differentiation and adipogenesis, inducing beige adipocyte formation and WAT browning, promoting BAT growth and increasing BAT function, reprogramming gut microbiota, improving antioxidant and anti-inflammatory capacity, and restoring adipokine secretion and metabolism. BAT, brown adipose tissue; WAT, white adipose tissue.

Influenza bidirezionale sulla **melatonina** attraverso la proteina disaccoppiante 1 (**UCP1**), espressa nelle membrane degli adipociti.

*La **melatonina** stimola la conversione degli adipociti in grasso bruno e la produzione di **UCP1**. A sua volta, l'**mRNA di UCP1** stimola l'espressione della **melatonina**, stabilizzando e rafforzando il ritmo circadiano e il sonno.*

Impatto ritmi circadiani e dieta su “BAT”

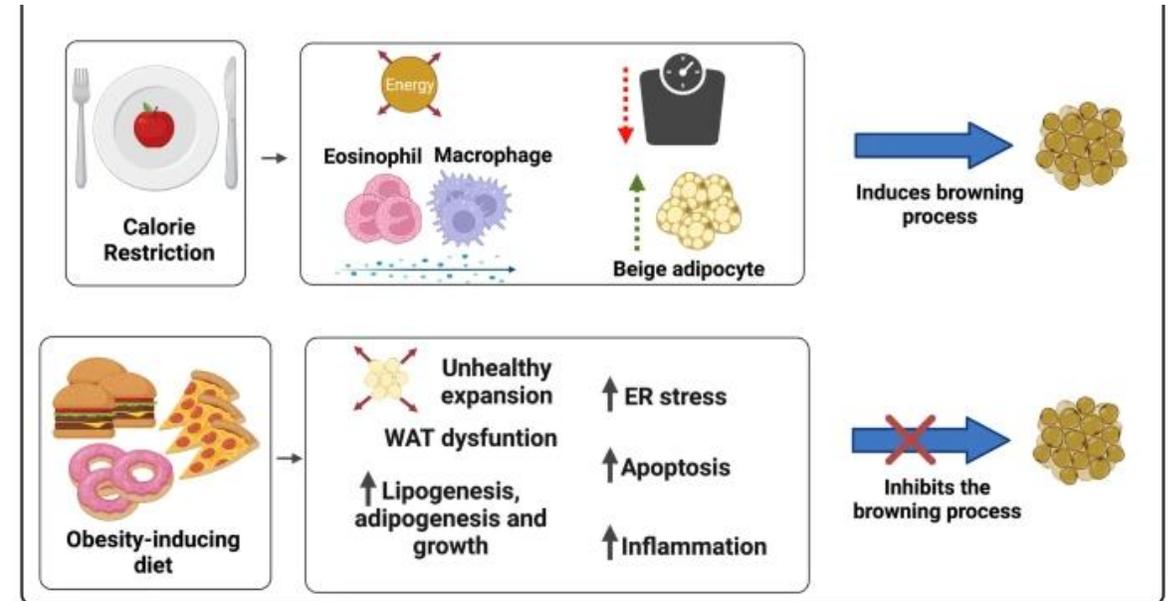
- **Ritmo circadiano**: Il rilascio di MT è mediata dal rilascio di NE, che si lega ai recettori β -adrenergici.
- Il **digiuno intermittente (IF)** induce una maggiore tolleranza glicemica, < WAT e dell'infiammazione del tessuto adiposo, oltre a **un aumento dell'espressione di geni termogenici (es. UCP1)** e al **reclutamento di adipociti beige**.



Modificata da Machado-Azevedo et al 2022 Nutrition

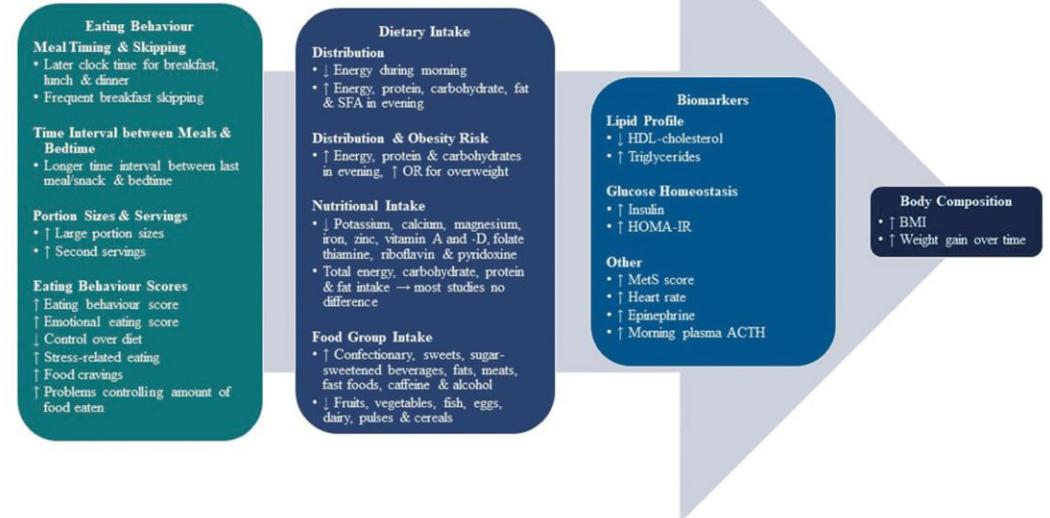
Impatto ritmi circadiani e dieta su “BAT”

- Anche la **restrizione calorica** è associata alla perdita di peso e favorisce un maggiore reclutamento di adipociti beige grazie al coinvolgimento dei macrofagi M2 e all'infiltrazione di eosinofili nel WAT.
- **Diete che inducono obesità** sono correlate a un'espansione anomala e disfunzionale del WAT e alla sua disregolazione. L'espansione anomala del WAT (stress del RE, apoptosi degli adipociti e un aumento dell'infiammazione attraverso l'attivazione del fattore di trascrizione **NF-κB** e la secrezione di citochine pro-infiammatorie).

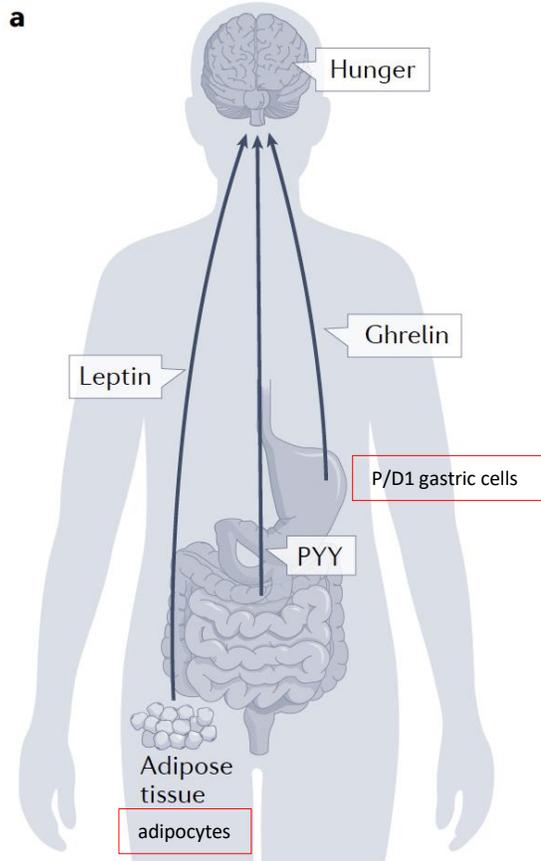


Cronotipo e alimentazione

Der Merwe et al., 2022 Adv Nutr



Meta-analisi il cronotipo mattiniero ha un comportamento alimentare più sano rispetto al cronotipo serale, il quale tende a consumare più grassi e carboidrati. Nessun dato oggettivo in letteratura (attigrafia o PSG)



Grelina

Il digiuno non induce un aumento, quindi è più importante **la diminuzione dopo i pasti** che l'aumento prima

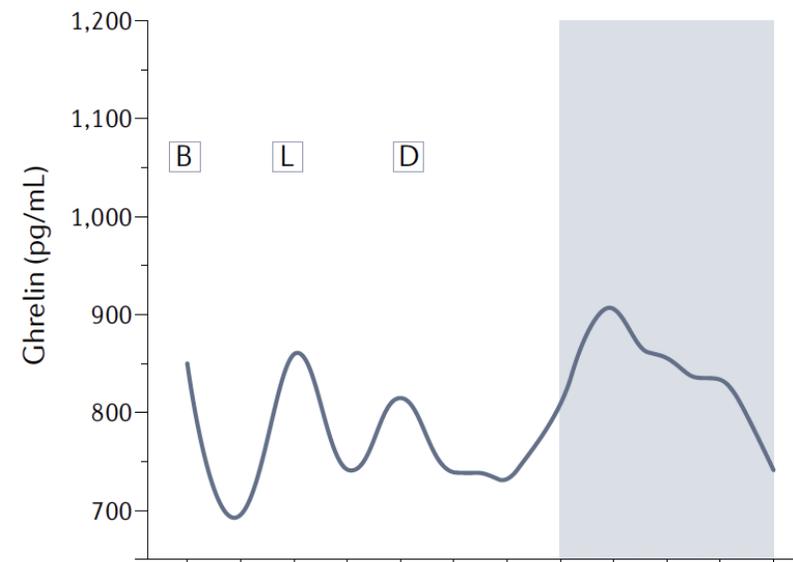


Leptina

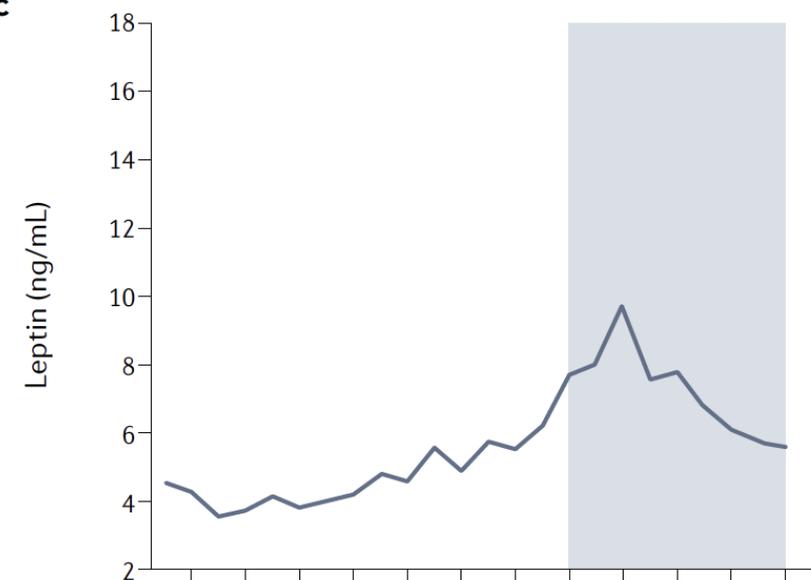
è prodotto dagli adipociti, questo **ormone diminuisce l'appetito**. I livelli sono correlati all'adiposità e sono considerati rappresentativi dell'accumulo di energia.

Sono adeguato con dieta controllata

a per il bilancio energetico al basale

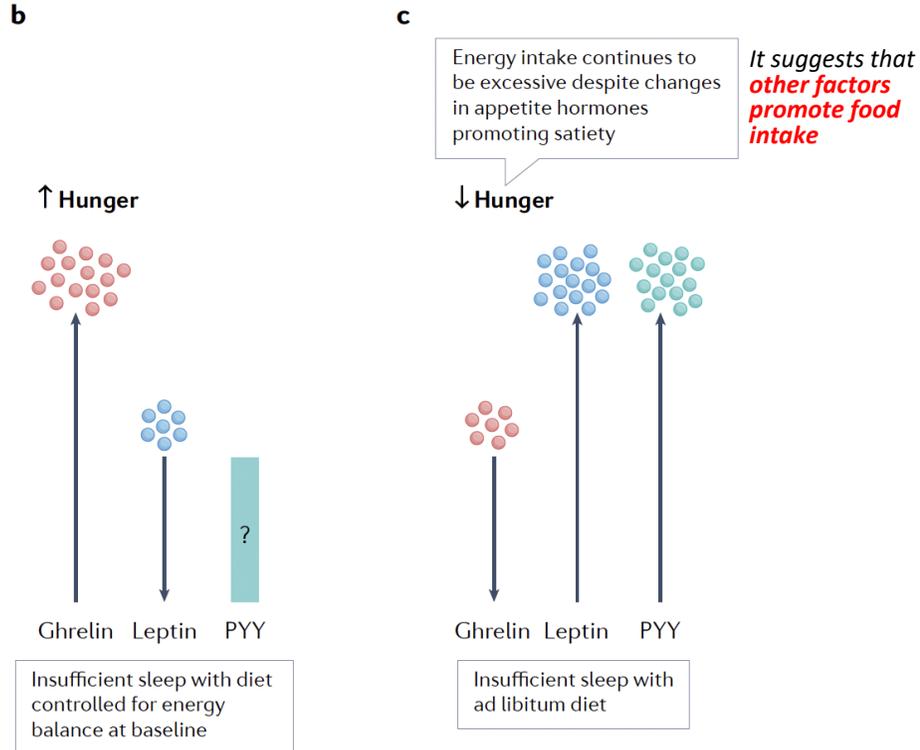


c



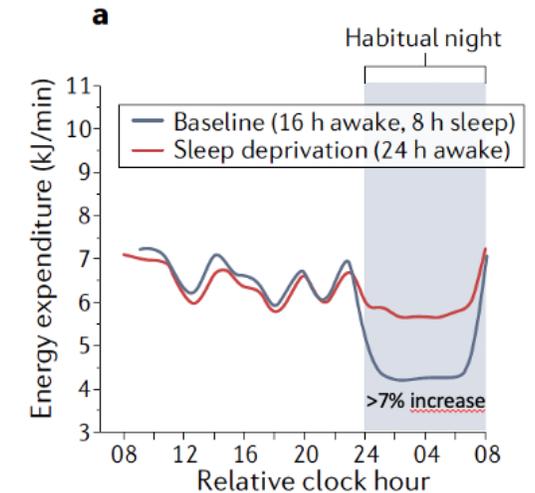
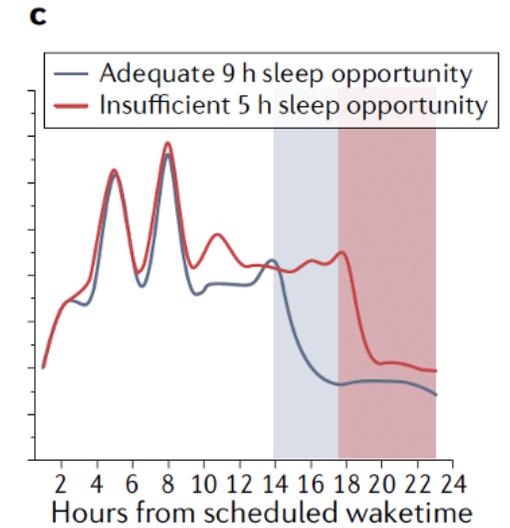
Energy Expenditure Energy Intake

Insufficient sleep increase energy expenditure **4-5%/24h** (**>100 Kcal**) **regardless energy intake** in maintained at level of adequate sleep or ad libitum energy intake



Insufficient sleep

Sleep deprivation



Insufficient sleep

Controlled energy intake: increased energy expenditure and negative energy balance occurs

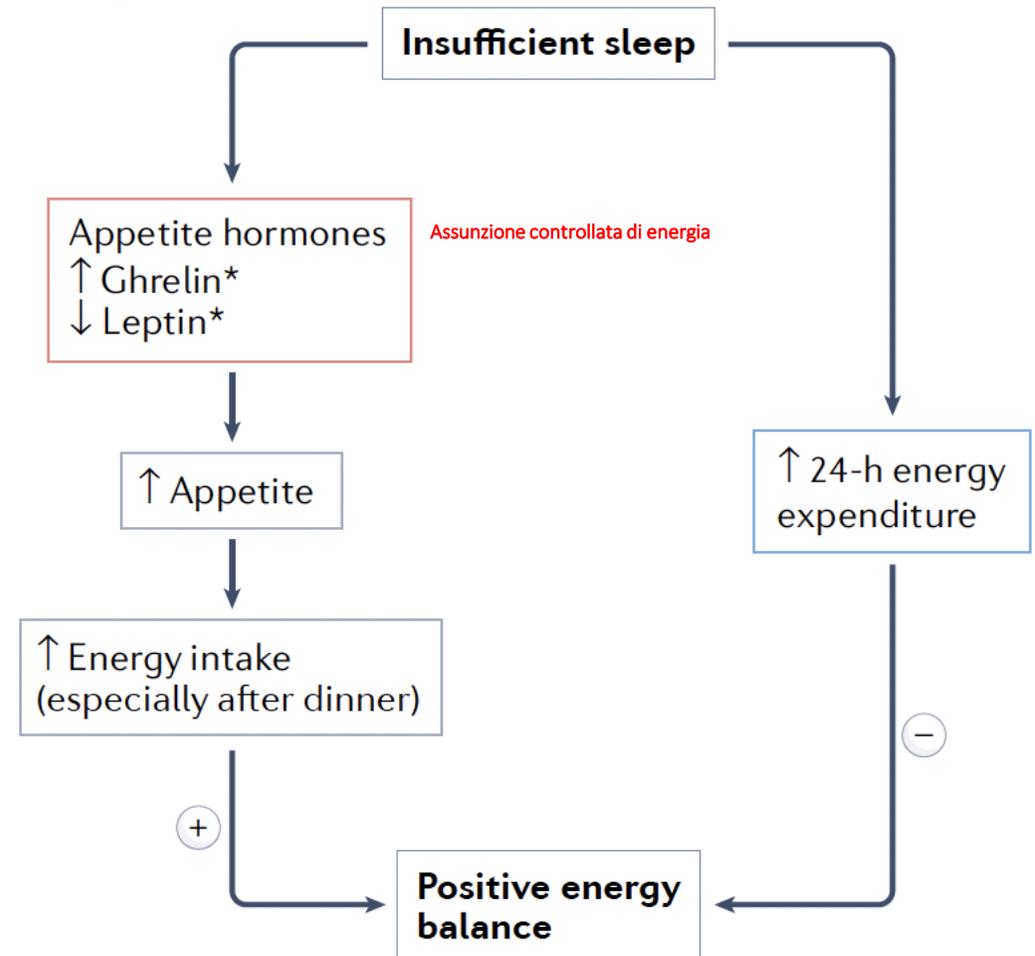
Uncontrolled energy intake: LEAN +253 Kcal/day OBESE +385 Kcal/day vs recommended sleep duration

Increase of energy intake even with changes in appetite hormones to reduce hunger (<ghrelin & >leptin/PYY)...

Why?... activation of Hypothalamus, Thalamus, N. Accumbens; Putamen; Insula; Prefrontal cortex → high carbohydrate/fat food alcohol, addiction...

Endocannabinoid system activation

"Hedonic eating"



*When energy intake controlled; opposite effects when energy intake ad libitum

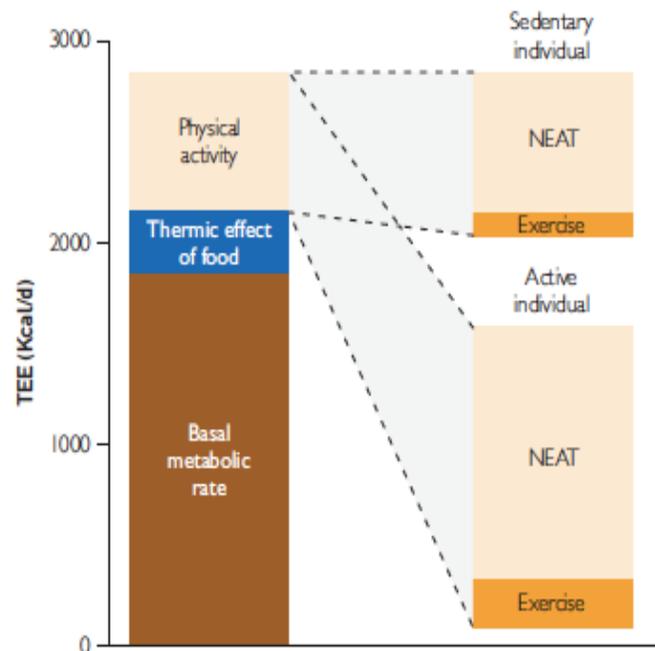
Nonexercise Activity Thermogenesis in Obesity Management



Pedro A. Villablanca, MD, MSc; Jorge R. Alegria, MD; Farouk Mookadam, MBChB, MSc; David R. Holmes Jr, MD; R. Scott Wright, MD; and James A. Levine, MD, PhD

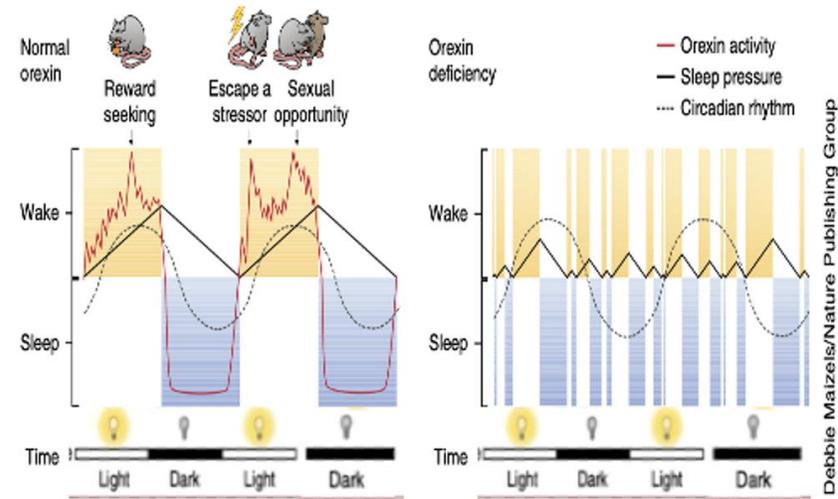
NonExercise Activity Thermogenesis (NEAT)

“... NEAT includes a series of continuous and vital movements that do not involve moderate-to-vigorous-intensity exercise. These additive activities account for significant thermogenesis and energy consumption...”



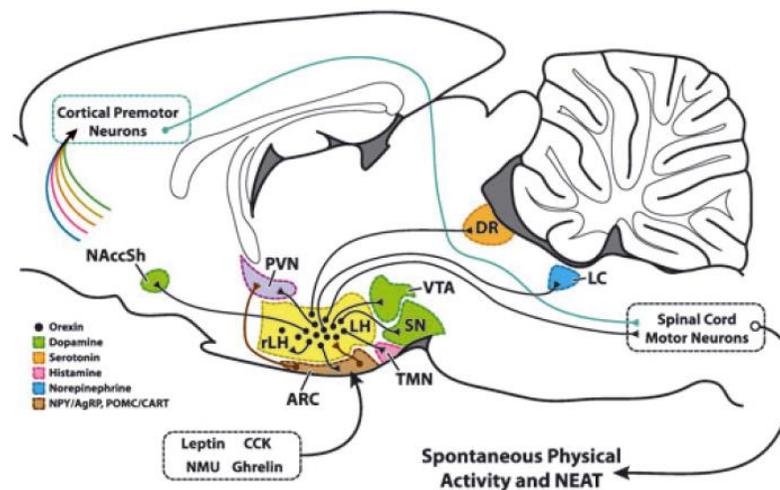
“Life is like riding a bicycle. To keep your balance, you must keep moving.”

Albert Einstein



Modified from Mahler 2014 Nature

Physical Activity Network



Koltz, 2012

Signals from all of these areas have the potential to influence cortical premotor neurons, and feedback from premotor neurons and **orexinergic projections** may interact to **drive SPA**.

SPA spontaneous physical activity

Circadian misalignment

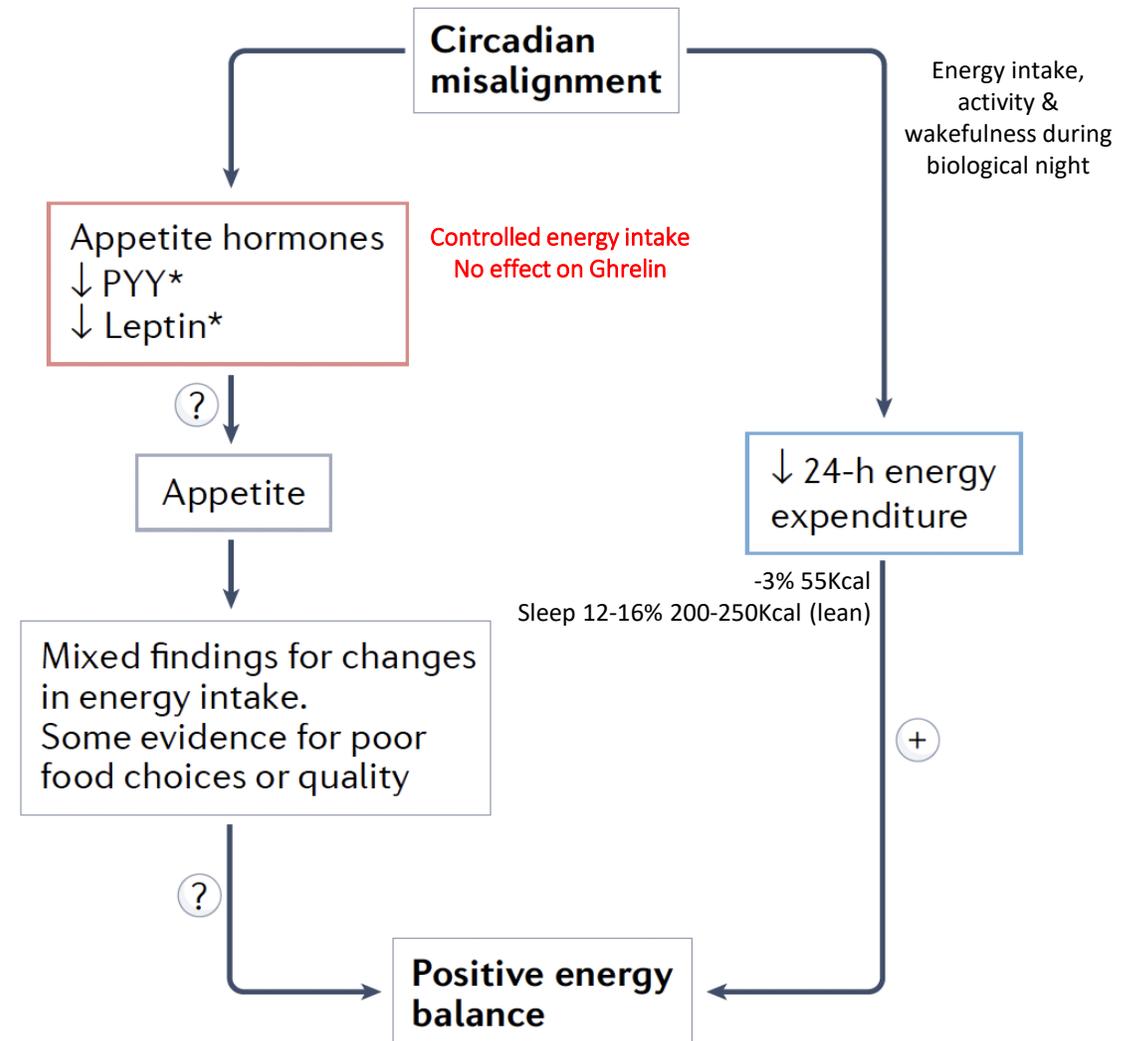
Unhealthy food choices (less vegetables and more sweets and saturated fats both in lean, overweight and obese «misaligned»)

Weight gain for less activity in lean m/w

The <24h expenditure even without a change in energy intake could result in weight gain

Animal Model: restricted food intake to the time of day typically reserved for sleep: **higher weight gain than when their food intake is restricted to the time of typical wakefulness.** Despite similar amounts of caloric intake and activity levels.

a calorie is not a calorie per se and that **the timing of calorie intake has importance for metabolic health**



*When energy intake controlled Modified by Chaput 2023 Nat Rev

Association between social jetlag food consumption and meal times in patients with obesity-related chronic diseases

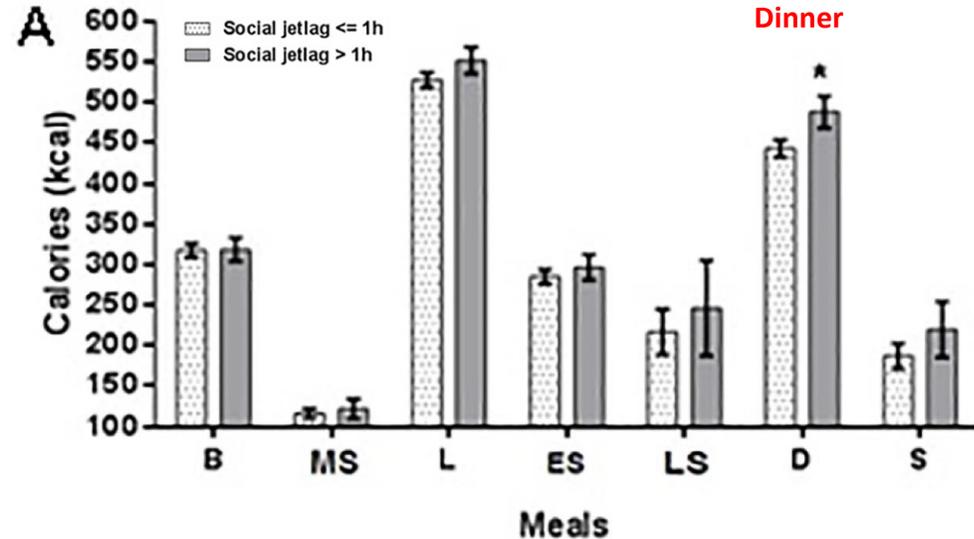
Maria Carliana Mota¹, Catarina Mendes Silva¹, Laura Cristina Tibiletti Balieiro¹, Bruna Fernandes Gonçalves¹, Walid Makin Fahmy², Cibele Aparecida Crispim^{1*}

¹ Faculty of Medicine of the Federal University of Uberlândia, Minas Gerais, Brazil, ² Hospital e Maternidade Municipal de Uberlândia, Department of Obstetrics, Uberlândia, Brazil

Higher ghrelin in social jetlag (lean)? Rusu et al., 2021

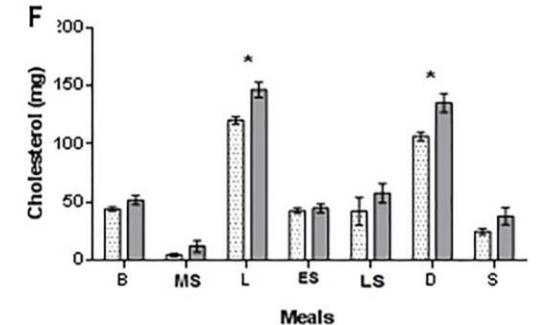
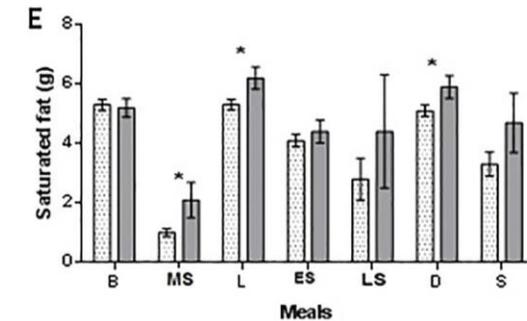
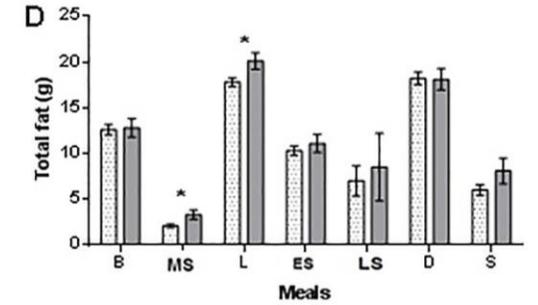
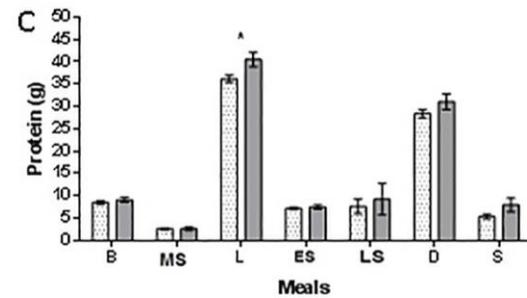
«...**social jetlag is associated with a poor diet and later meal times**, which should be avoided in individuals with obesity-related chronic diseases»

All (n = 792)	Social Jetlag ≤ 1h (n = 598)	Social Jetlag > 1h (n = 194)	
	Means ± SE	Means ± SE	p*
<i>Total Calories and nutrients</i>			
Calories (kcal/day)	1508.3 ± 20.2	1621.6 ± 38.1	<0.001



Odd ratio for inadequate food consumption according to presence (>1h)

Total fat (%EI)	>30% (EI)	1.3 (1.1–1.9)	0.03
Saturated fat (%EI)	>10% (EI)	1.2 (1.1–2.0)	0.02
Cholesterol (mg/day)	>300 mg/day	1.8 (1.3–2.6)	<0.001



Di chi è la colpa?



Alessandro Barbero A che ora si mangia Quodlibet 2017



Take home messages: call to action

Despite the clear evidence, the importance of sleep health remains under-recognized globally

Educate and Raise Awareness: The global view of sleep through education should be changed. This includes developing **sleep health educational programs** and **awareness campaigns**, integrating sleep health into **medical curricula**, and using resources like the National Institutes of Health's electronic bookshelf on sleep.

Standardize and Centralize Research Data: To create effective policies, comprehensive global sleep data is needed. **Increasing, standardizing, and centralizing data on sleep in every country.** This involves adding **sleep-related questions to existing population-based surveys** and assessing **multiple dimensions of sleep, from duration and quality to the presence of specific disorders.**

Implement Public Health Policies: Urgency for the **development and implementation of sleep health policies across various sectors.** For sleep to be prioritized, it must be recognized as a **health priority** by major bodies like the WHO, **to encourage countries to include it in their national health agendas.** All public health initiatives related to sleep must have **health equity as a central, cross-cutting theme**

Grazie

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