El son és integral a la vida

Dr. Antoni Esteve

Chairman i fundador d'AdSalutem

28 d'Octubre de 2021

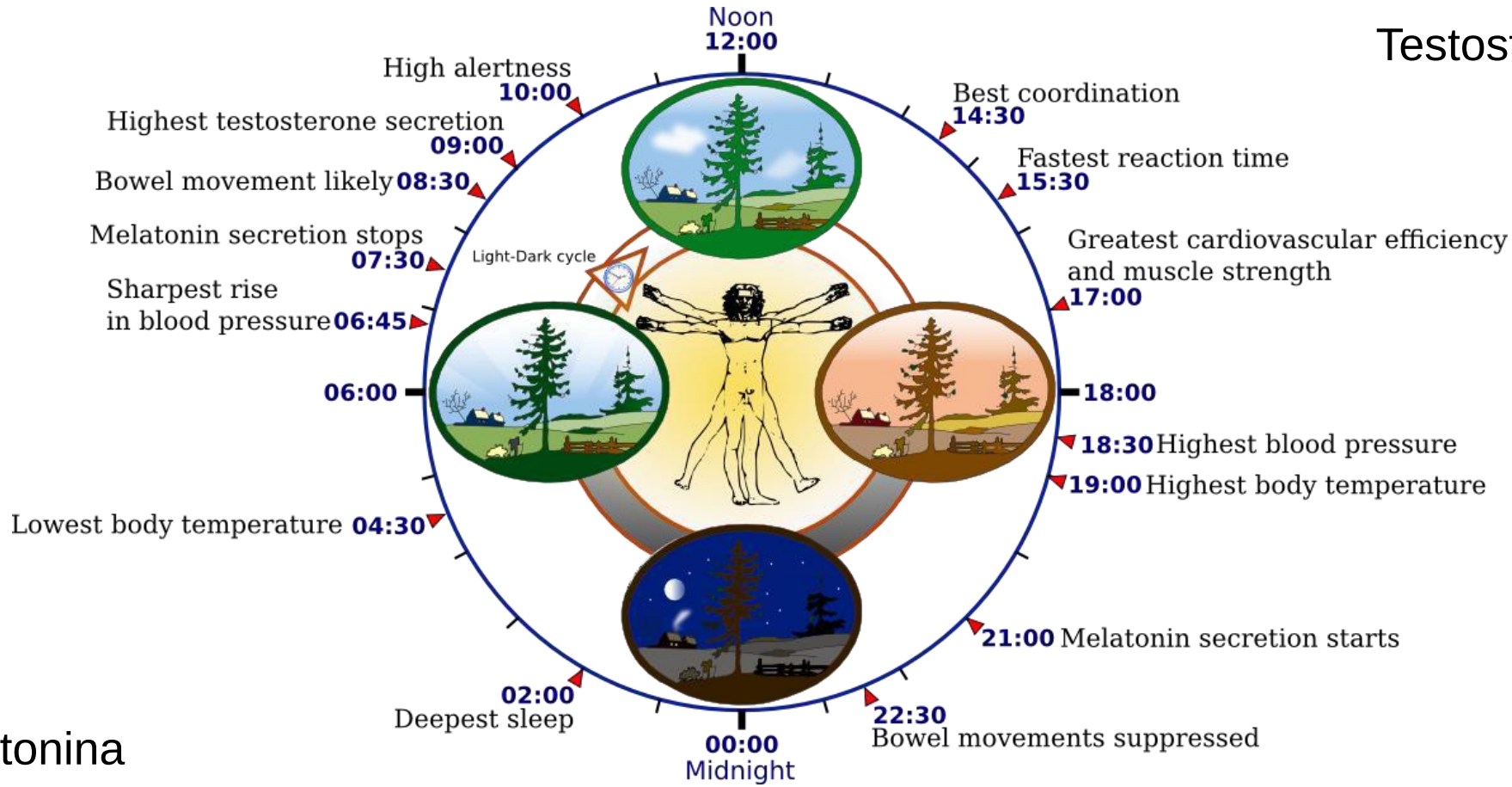
AdSalutem
Sleep Institute

"Tothom ha de saber que el son, o dormir bé és fonamental per a la salut i el benestar"

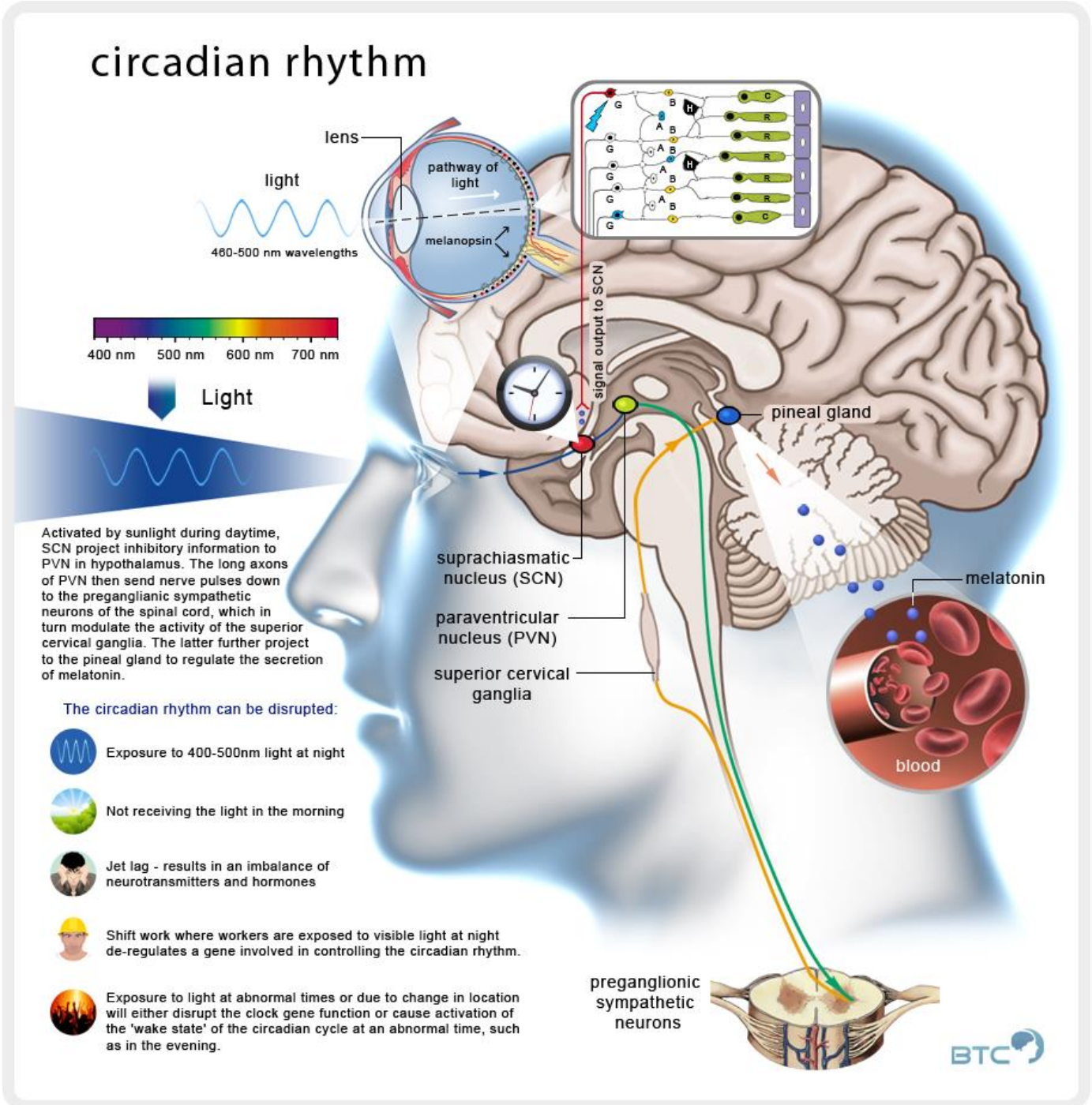
Dr. Antoni Esteve

El son i el ritme circadiari

Testosterona

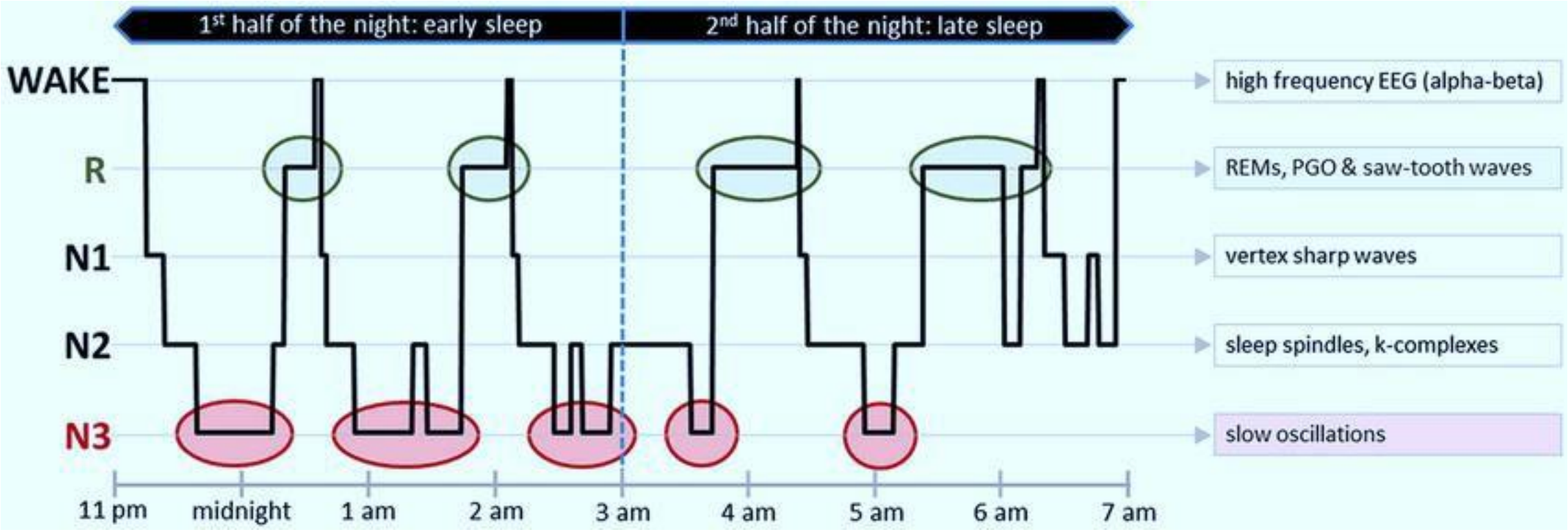


Melatonina

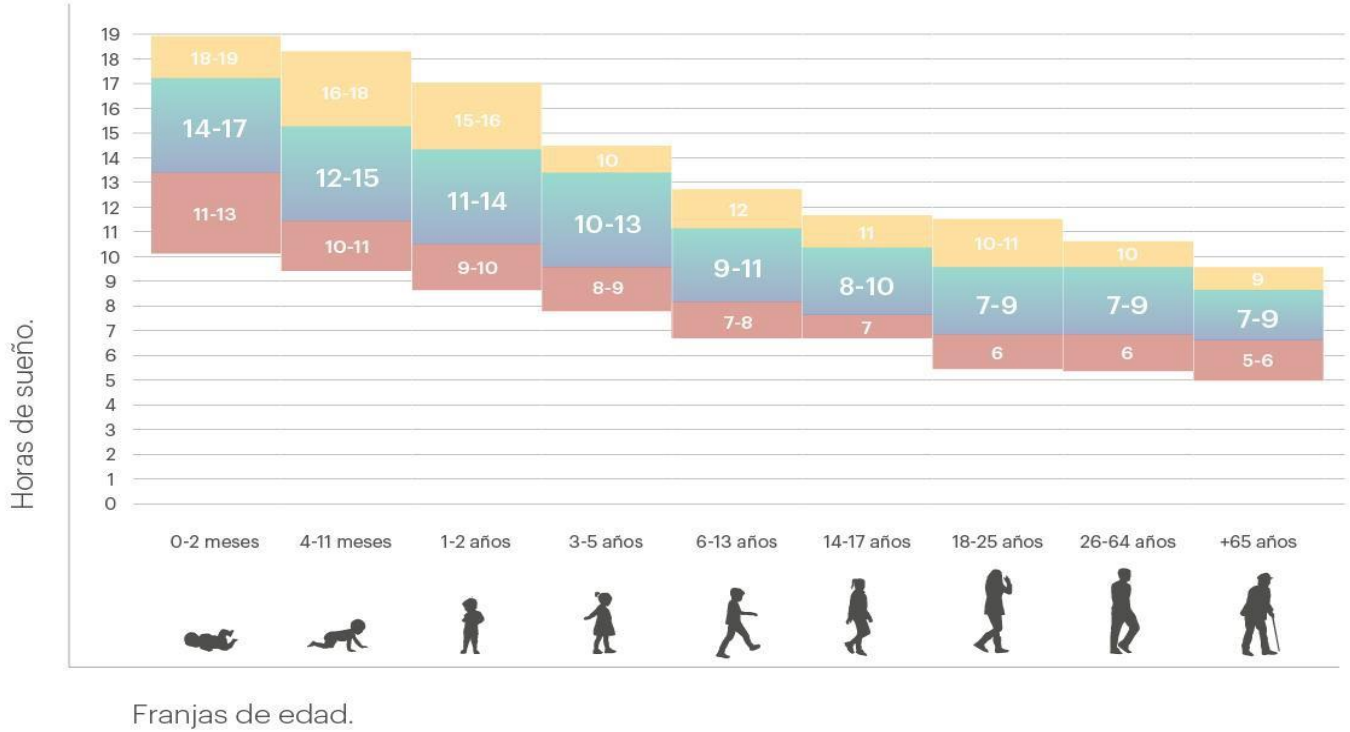

circadian rhythm
lens
light
pathway of light
melanopsin
460-500 nm wavelengths
400 nm
500 nm
600 nm
700 nm
Light
signal output to SCN
pineal gland
melatonin
blood
suprachiasmatic nucleus (SCN)
paraventricular nucleus (PVN)
superior cervical ganglia
preganglionic sympathetic neurons
Activated by sunlight during daytime, SCN project inhibitory information to PVN in hypothalamus. The long axons of PVN then send nerve pulses down to the preganglianic sympathetic neurons of the spinal cord, which in turn modulate the activity of the superior cervical ganglia. The latter further project to the pineal gland to regulate the secretion of melatonin.
The circadian rhythm can be disrupted:
Exposure to 400-500nm light at night
Not receiving the light in the morning
Jet lag - results in an imbalance of neurotransmitters and hormones
Shift work where workers are exposed to visible light at night de-regulates a gene involved in controlling the circadian rhythm.
Exposure to light at abnormal times or due to change in location will either disrupt the clock gene function or cause activation of the 'wake state' of the circadian cycle at an abnormal time, such as in the evening.
BTC

AdSalutem Sleep Institute

L'arquitectura del Son



Hores de son al llarg de la vida



Estas cifras reflejan tanto las horas nocturnas de sueño como las posibles siestas.

Recomendación Apropiado No recomendado

Adaptado de "The National Sleep Foundation". Sleep duration recommendation. Sleep health: The Official Journal of the National Sleep Foundation (2015)"

Proporcions de la població que dorm menys de 7 hores

	U.S.	UK	Germany	Japan	Canada
Less than 6 hours	18%	16%	9%	16%	6%
6 to 7 hours	27%	19%	21%	40%	20%

Notes: Sleep data based on data from the National Sleep Foundation (2013) representative survey. The proportions of people sleeping less than six and between six and seven hours have been calculated by using the weighted average among the proportions for workday and weekend sleep patterns.

Why sleep matters - the economic costs of insufficient sleep.

El son com a promotor de la cognició, l'equilibri emocional i la salut

Aprenentatge i memòria

Benestar emocional

Sistema immunitari

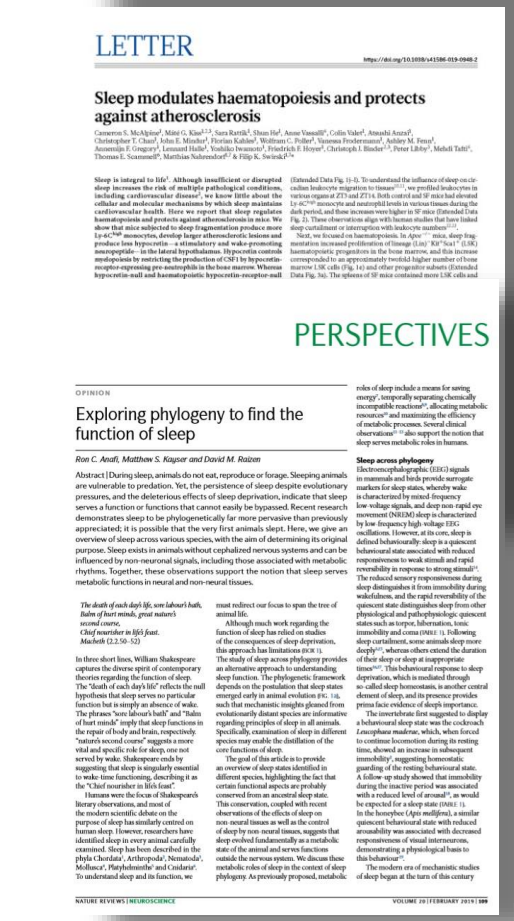
Neuroprotecció

Cardiometabolisme

Sleep is integral to life!

AdSalutem Sleep Institute

Evidències científiques, el son com a promotor de la salut


LETTER

https://doi.org/10.1038/s41586-019-0948-2

Sleep modulates haematopoiesis and protects against atherosclerosis

Cameron S. McAlpine[1], Máté G. Kiss[1,2,3], Sara Rattik[1], Shuo He[1], Anne Vassalli[4], Collin Valet[1], Atsushi Anzai[1], Christopher T. Chan[1], John E. Mindur[1], Florian Kahles[1], Wolfram C. Poller[1], Vanessa Frodermann[1], Ashley M. Fenn[1], Artemisia F. Gregory[1], Lennard Halle[1], Yoshiko Iwamoto[1], Friedrich F. Hoyer[5], Christoph L. Binder[1,3], Peter Libby[6], Mehdi Tafti[4], Thomas E. Scammell[4], Matthias Nahrendorf[1,7] & Filip K. Swirski[1,8]*

Sleep is integral to life[1]. Although insufficient or disrupted sleep increases the risk of multiple pathological conditions, including cardiovascular disease[2], we know little about the cellular and molecular mechanisms by which sleep maintains cardiovascular health. Here we report that sleep regulates haematopoiesis and protects against atherosclerosis in mice. We show that mice subjected to sleep fragmentation produce more Ly-6C^{high} monocytes, develop larger atherosclerotic lesions and produce less hypocretin—a stimulatory and wake-promoting neuropeptide—in the lateral hypothalamus. Hypocretin controls myelopoiesis by restricting the production of CSF1 by hypocretin-receptor-expressing pre-neutrophils in the bone marrow. Whereas hypocretin-null and haematopoietic hypocretin-receptor-null mice (Extended Data Fig. 1)–3), To understand the influence of sleep on circadian leukocyte migration to tissues[12,13], we profiled leukocytes in various organs at ZT3 and ZT14. Both control and SF mice had elevated Ly-6C^{high} monocyte and neutrophil levels in various tissues during the dark period, and those increases were higher in SF mice (Extended Data Fig. 2). These observations align with human studies that have linked sleep curtailment or interruption with leukocyte numbers[10,11].

Next, we focused on haematopoiesis. In *Apoe*$^{-/-}$ mice, sleep fragmentation increased proliferation of lineage$^-$ (Lin$^-$) Kit$^+$Sca1$^+$ (LSK) haematopoietic progenitors in the bone marrow, and this increase corresponded to an approximately twofold higher number of bone marrow LSK cells (Fig. 1e) and other progenitor subsets (Extended Data Fig. 3a). The spleens of SF mice contained more LSK cells and

PERSPECTIVES

OPINION

Exploring phylogeny to find the function of sleep

Ron C. Anafi, Matthew S. Kayser and David M. Raizen

Abstract | During sleep, animals do not eat, reproduce or forage. Sleeping animals are vulnerable to predation. Yet, the persistence of sleep despite evolutionary pressures, and the deleterious effects of sleep deprivation, indicate that sleep serves a function or functions that cannot easily be bypassed. Recent research demonstrates sleep to be phylogenetically far more pervasive than previously appreciated; it is possible that the very first animals slept. Here, we give an overview of sleep across various species, with the aim of determining its original purpose. Sleep exists in animals without cephalized nervous systems and can be influenced by non-neuronal signals, including those associated with metabolic rhythms. Together, these observations support the notion that sleep serves metabolic functions in neural and non-neural tissues.

The death of each day's life, sore labour's bath,
Balm of hurt minds, great nature's
second course,
Chief nourisher in life's feast.
Macbeth (2.2.50–52)

In three short lines, William Shakespeare captures the diverse spirit of contemporary theories regarding the function of sleep. The "death of each day's life" reflects the null hypothesis that sleep serves no particular function but is simply an absence of wake. The phrases "sore labour's bath" and "balm of hurt minds" imply that sleep functions in the repair of body and brain, respectively. "nature's second course" suggests a more vital and specific role for sleep, one not served by wake. Shakespeare ends by suggesting that sleep is singularly essential to wake-time functioning, describing it as the "chief nourisher in life's feast".

Humans were the focus of Shakespeare's literary observations, and most of the modern scientific debate on the purpose of sleep has similarly centred on human sleep. However, researchers have identified sleep in every animal carefully examined. Sleep has been described in the phyla Chordata[1], Arthropoda[2], Nematoda[3], Mollusca[4], Platyhelminthe[5] and Cnidaria[6]. To understand sleep and its function, we must redirect our focus to span the tree of animal life.

Although much work regarding the function of sleep has relied on studies of the consequences of sleep deprivation, this approach has limitations (BOX 1). The study of sleep across phylogeny provides an alternative approach to understanding sleep function. The phylogenetic framework depends on the postulation that sleep states emerged early in animal evolution (FIG. 1a), such that mechanistic insights gleaned from evolutionarily distant species are informative regarding principles of sleep in all animals. Specifically, examination of sleep in different species may enable the distillation of the core functions of sleep.

The goal of this article is to provide an overview of sleep states identified in different species, highlighting the fact that certain functional aspects are probably conserved from an ancestral sleep state. This conservation, coupled with recent observations of the effects of sleep on non-neural tissues as well as the control of sleep by non-neural tissues, suggests that sleep evolved fundamentally as a metabolic state of the animal and serves functions outside the nervous system. We discuss these metabolic roles of sleep in the context of sleep phylogeny. As previously proposed, metabolic roles of sleep include a means for saving energy[7], temporally separating chemically incompatible reactions[8], allocating metabolic resources[9] and maximizing the efficiency of metabolic processes. Several clinical observations[10–12] also support the notion that sleep serves metabolic roles in humans.

Sleep across phylogeny

Electroencephalographic (EEG) signals in mammals and birds provide surrogate markers for sleep states, whereby wake is characterized by mixed-frequency low voltage signals, and deep non-rapid eye movement (NREM) sleep is characterized by low frequency high voltage EEG oscillations. However, at its core, sleep is defined behaviourally: sleep is a quiescent behavioural state associated with reduced responsiveness to weak stimuli and rapid reversibility in response to strong stimuli[13]. The reduced sensory responsiveness during sleep distinguishes it from immobility during wakefulness, and the rapid reversibility of the quiescent state distinguishes sleep from other physiological and pathophysiologic quiescent states such as torpor, hibernation, toxic immobility and coma (INBOX 1). Following the consequences of sleep deprivation, this approach has limitations (BOX 1). The study of sleep across phylogeny provides an alternative approach to understanding sleep function. The phylogenetic framework depends on the postulation that sleep states emerged early in animal evolution (FIG. 1a), such that mechanistic insights gleaned from evolutionarily distant species are informative regarding principles of sleep in all animals. Specifically, examination of sleep in different species may enable the distillation of the core functions of sleep.

The invertebrate first suggested to display a behavioural sleep state was the cockroach *Leucophaea maderae*, which, when forced to continue locomotion during its resting time, showed an increase in subsequent immobility[7], suggesting homeostatic guarding of the resting behavioural state. A follow-up study showed that immobility during the inactive period was associated with a reduced level of arousal[8], as would be expected for a sleep state (TABLE 1). In the honeybee (*Apis mellifera*), a similar quiescent behavioural state with reduced arousability was associated with decreased responsiveness of visual interneurons, demonstrating a physiological basis to this behaviour[14].

The modern era of mechanistic studies of sleep began at the turn of this century


Nature and Science of Sleep

Dovepress

REVIEW

Obstructive sleep apnea in patients with Down syndrome: current perspectives

This article was published in the following Dove Press journal:
Nature and Science of Sleep

Ryne Simpson[1]
Anthony A Oyekan[2]
Zarmina Ehsan[1,3]
David G Ingram[1,3]

[1]Department of Pediatrics, Children's Mercy Hospital, Kansas City, MO, USA; [2]School of Medicine, University of Missouri-Kansas City, Kansas City, MO, USA

Abstract: For individuals with Down syndrome (DS), obstructive sleep apnea (OSA) is a complex disorder with significant clinical consequences. OSA is seen frequently in DS, and when present, it tends to be more severe. This increased prevalence is likely related to common anatomic abnormalities and a greater risk of additional comorbidities such as hypotonia and obesity. Because signs and symptoms do not often correlate with disease, all children and adults with DS should receive routine screening for OSA. Similar to the general population, polysomnography remains the gold standard for diagnosis. Because individuals with DS may be more susceptible to cardiovascular and neurocognitive sequelae, early diagnosis and treatment of OSA is becoming increasingly important. Treatment options generally involve upper airway surgery (primarily adenotonsillectomy) and continuous positive airway pressure (CPAP); however,

RESEARCH

PHYSIOLOGY

A sleep-inducing gene, *nemuri*, links sleep and immune function in *Drosophila*

Hirofumi Toda, Julie A. Williams, Michael Gulledge*, Amita Sehgal†

Sleep remains a major mystery of biology. In particular, little is known about the mechanisms that account for the drive to sleep. In an unbiased screen of more than 12,000 *Drosophila* lines, we identified a single gene, *nemuri*, that induces sleep. The NEMURI protein is an antimicrobial peptide that can be secreted ectopically to drive prolonged sleep (with resistance to arousal) and to promote survival after infection. Loss of *nemuri* increased arousability during daily sleep and attenuated the acute increase in sleep induced by sleep deprivation or bacterial infection. Conditions that increase sleep drive induced expression of *nemuri* in a small number of fly brain neurons and targeted it to the sleep-promoting, dorsal fan-shaped body. We propose that NEMURI is a bona fide sleep homeostasis factor that is particularly important under conditions of high sleep need; because these conditions include sickness, our findings provide a link between sleep and immune function.

We spend one-third of our lives sleeping, yet the purpose and mechanisms of sleep remain a major research challenge in neuroscience (1, 2). Sleep is broadly regulated by two major processes: the circadian system that times daily sleep and the homeostatic system that drives the need to sleep. Mechanisms that generate circadian clocks are now understood on a fundamental level (3, 4), and the neurochemistry associated with sleep and wake states has also been well studied (1, 5). However, we still know very little about the mechanisms that generate the homeostatic drive to sleep. Studies of sleep homeostasis frequently rely on depriving organisms of sleep and assaying the subsequent recovery sleep that results from the increased drive. Prolonged wakefulness promotes accumulation of sleep-promoting signals, some of which may be secreted. Thus, transfer of cerebrospinal fluid from sleep-deprived animals to rested animals triggers sleep (7), although the nature of the secreted factors is debatable. Adenosine is thought to be one such signal, but the role of adenosine and adenosine receptors is limited to specific aspects of sleep (8). Sleep drive also increases during sickness, but it is unclear whether increased sleep under these conditions is mediated by the same mechanisms that increase sleep upon sleep deprivation (9, 10).

Forward genetic screens (11) allow unbiased identification of molecular factors relevant for a particular biological phenomenon. Genetic screens for sleep mutants in *Drosophila* have successfully identified several molecules that modulate sleep and wakefulness (12–20). Because the screens were generally loss-of-function in nature and were targeted toward isolation of short-sleeping mutants, they identified factors whose loss reduces sleep. However, where tested, overexpression of these factors does not increase sleep above wild-type levels (14, 17, 21), which suggests that they are insufficient to induce sleep on their own. In addition, several fly sleep-regulating genes are required broadly in the brain (14, 17, 21), perhaps serving to modulate neural activity in response to upstream sleep-inducing signals. The paucity of sleep-inducing signals in any organism prompted us to undertake a screen for such molecules.

Identification of *nemuri* as a sleep-inducing molecule from a gain-of-function genetic screen

To identify genetic factors that promote sleep, we conducted an unbiased and genome-wide gain-of-function screen in *Drosophila*. We used an inducible pan-neuronal Gal4 driver, elav-GeneSwitch (elav-GS) (22), to drive expression of random genes tagged with Gal4-responsive upstream activating sequences (UASs). Enhancer-promoter (EP) collections (23), UAS-cDNA libraries in pNOBP (24), and the Bangalore Fly Resource Center (BFRC) (25) were the sources for flies carrying UAS insertions, each of which was crossed to elav-GS–carrying flies to allow pan-neuronal induction of UAS-tagged genes with the GS activator RU486 (trade name for mifepristone) (26). To circumvent potential developmental defects, we fed offspring RU486 only during the adult stage in the course of the assay. In total, we screened 32,598 lines (table S1), which correspond to 8051 *Drosophila* genes. Although overexpression of most genes did not affect sleep, some of the lines displayed a decrease or an increase in sleep (Fig. 1A). We further tested lines in which both males and females had sleep times at least two standard deviations away from the average sleep time for all lines. Rescreens of candidate lines identified only one that showed a significant increase in sleep relative to controls (fig. S1A). Upon induction of elav-GS with RU486, the total amount of sleep in this line increased in both males and females and was reflected in increases in both daytime and nighttime sleep (fig. S1B).

The line with the increased sleep phenotype contains a UAS-regulated transgene (#202024 at BFRC) corresponding to a previously uncharacterized gene, CG33913 (www.ncbi.nlm.nih.gov), accession number NP_725032/AHN56430), which we named *nemuri* (*nur*; Japanese word for "sleep"). In silico analysis of *nur* mRNA in adult *Drosophila* brains revealed that the gene was predominantly expressed in glia (fig. S2A). Although the period was slightly short in *nur*-overexpressing flies (22.8 ± 0.3 hours (mean ± SEM) relative to that in control animals (23.2 ± 0.3 hours), behavioral rhythms were as clearly defined in *nur*-overexpressing flies as in controls (fig. S2B). Thus, overexpression of *nur* has minimal effect on circadian rhythms but strong effects on sleep.

Increases of sleep length and depth as a result of *nur* overexpression

For higher-resolution analysis of sleep induced by *nur*, we evaluated sleep with a video tracking system (26). Sleep in flies occurs largely during the nighttime, but it also manifests as a mid-day siesta that is more pronounced in males. Video analysis confirmed that *nur* overexpression increased both daytime and nighttime sleep relative to control flies not treated with RU486 (Fig. 1B). Overexpression of *nur* increased the number of sleep bouts during the day with no change in bout duration (Fig. 1C). On the other hand, during the night, the number of sleep bouts was decreased, but the bout duration was much longer in *nur*-overexpressing flies (Fig. 1C), indicating that *nur* overexpression consolidates nighttime sleep.

To test whether *nur* affects sleep depth, which is measured as the extent to which sleeping animals are resistant to external stimuli, we subjected flies to a mechanical arousing stimulus (2G) in the middle of the night at midnight time (ZT) 20 (ZT0, lights on; ZT12, lights off). Although ~94% of control flies awoke upon stimulation, only ~18% of *nur*-overexpressing flies were aroused (Fig. 1D). The strong mechanical stimulus used in this assay typically elicits the consistent response seen in controls, so the very low response in experimental animals indicated that *nur* increases sleep depth. After the mechanical stimulus, the few aroused *nur*-overexpressing flies were sluggish and had reduced locomotor speed relative to control animals (fig. S3A). However, locomotor ability


Science

REPORTS

Cite as: J. K. Holth *et al.*, *Science* 10.1126/science.aax2546 (2019)

The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans

Jovrah K. Holth[1]*, Sarah K. Fritschi[1]*, Chaoang Wang[1], Nigel P. Pedersen[2], John R. Cirrito[3], Thomas E. Mahan[3], Mary Beth Finn[1], Melissa Manis[1], Joel C. Goerling[1], Patrick M. Fuller[4], Brendan P. Lucey[1], David M. Holtzman[1]†

[1]Department of Neurology, Hope Center for Neurological Disorders, and Charles F. and Joanne Knight Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, MO 63110, USA. [2]Department of Neurology, Emory Epilepsy Center and Program in Neuroscience, Emory University, Atlanta, GA 30322, USA. [3]Department of Neurology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, USA. [4]Department of Neurology, Beth Israel Deaconess Medical Center, Division of Sleep Medicine, Harvard Medical School, Boston, MA 02215, USA.

†Corresponding author. Email: holtzman@wustl.edu

*These authors contributed equally to this work.

The sleep-wake cycle regulates interstitial fluid (ISF) and cerebrospinal (CSF) levels of amyloid-β (Aβ) that accumulates in Alzheimer disease (AD). Furthermore, chronic sleep deprivation (SD) increases Aβ plaques. However, tau, not Aβ, accumulation appears to drive AD neurodegeneration. Here, we tested whether ISF/CSF tau and tau seeding/spreading was influenced by the sleep-wake cycle and SD. Mouse ISF tau was increased ~90% during normal wakefulness vs. sleep and ~100% during SD. Human CSF tau also increased over 50% during SD. In a tau seeding and spreading model, chronic SD increased tau pathology spreading. Chemogenetically-driven wakefulness in mice also significantly increased both ISF Aβ and tau. Thus, the sleep-wake cycle regulates ISF tau and sleep deprivation increases ISF and CSF tau as well as tau pathology spreading.

Neuron

Review

Sleep and Human Aging

Bryce A. Mander,[1] Joseph R. Winer,[1] and Matthew P. Walker[1,2,*]

[1]Sleep and Neuroimaging Laboratory, Department of Psychology, Helen Wills Neuroscience Institute
University of California, Berkeley, Berkeley, CA 94720-1650, USA
[2]Lead Contact
*Correspondence: mpwalker@berkeley.edu
http://dx.doi.org/10.1016/j.neuron.2017.02.001

Older adults do not sleep as well as younger adults. Why? What alterations in sleep quantity and quality occur as we age, and are there functional consequences? What are the underlying neural mechanisms that explain age-related sleep disruption? This review tackles these questions. First, we describe canonical changes in human sleep quantity and quality in cognitively normal older adults. Second, we explore the underlying neurobiological mechanisms that may account for those human sleep alterations. Third, we consider the functional consequences of age-related sleep disruption, focusing on memory impairment as an exemplar. We conclude with a discussion of a still-debated question: do older adults simply need less sleep, or rather, are they unable to generate the sleep that they still need?

Normative aging is associated with a reduced ability to initiate and maintain sleep. Moreover, deficits in sleep physiology, including those of non-rapid eye movement (NREM) sleep and its associated neural oscillations, are especially prominent in later life. Though sleep disruption is a common signature of "normal aging", the underlying neural mechanisms explaining age-related sleep impairment are only now being revealed.

This review focuses on physiological changes associated with normative human aging. First, we characterize associated alterations in sleep structure and oscillatory activity in later life. Second, we describe emerging neurobiological mechanisms that may account for these sleep alterations. Third, we consider the functional consequences of age-related sleep disruption, focusing on memory impairment as an exemplar. We conclude with a discussion of a still-debated question: do older adults simply need less sleep, or rather, are they unable to generate the sleep that they still need?

What about Sleep Changes with Age?

Both the macro-level structure of sleep, such as sleep duration and sleep stages, and the micro-level architecture of sleep, including the quantity and quality of sleep oscillations, change as we progress into our older age.

Macro Sleep Changes

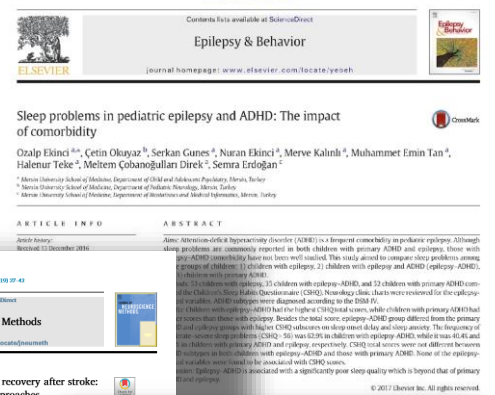
Advancing into the fifth decade of older age and beyond are a collection of well-characterized changes in sleep architecture (Figure 1A): (1) advanced sleep timing (i.e., earlier bedtimes and rise times), (2) longer sleep-onset latency (i.e., longer time taken to fall asleep), (3) shorter overall sleep duration, (4) increased sleep fragmentation (i.e., less consolidated sleep with more awakenings, arousals, or transitions to lighter sleep stages), (5) more fragile sleep (i.e., higher likelihood of being woken by external sensory stimuli), (6) reduced amount of deeper NREM sleep known as slow wave sleep (SWS), (7) increased time spent in lighter NREM stages 1 and 2, (8) shorter and fewer NREM-REM sleep cycles, and (9) increased time spent awake throughout the night (Conte et al., 2014; Feinberg and Carlson, 1968; Kales et al., 1967; Kleinman and Dijk, 2008; Landolt et al., 1996; Ohayon et al., 2004; Redline et al., 2004; Van Cauter et al., 2000; Vienne et al., 2016; Webb and Campbell, 1979; Zepelin et al., 1984). This is not to suggest a lack of individual variability in the degree of sleep disruption. It is clear that some older adults show little sleep impairment, while others show dramatic alterations, despite chronological age being similar (Redline et al., 2004; Vitiello, 2009), a topic that we will return to throughout this review.

Though age-related reductions in REM sleep time have been reported, these are subtler relative to changes in NREM sleep. Often, REM sleep impairments only emerge as adults progress into their 80s and beyond (Ohayon et al., 2004; Van Cauter et al., 2000) or as a symptom of degenerative dementias (Brayet et al., 2015; Hita-Yañez et al., 2012; Petit et al., 2004) (discussed in Box 1).

The frequency of diurnal naps also increases in later life: 10% of adults ages 55–64, and 25% ages 75–84, report the occurrence of daytime naps (Foley et al., 2007). Across these older age groups, roughly half of these naps are unplanned. This is consistent with the finding that 1 in 4 older adults report experiencing daytime sleepiness severe enough to impair daytime plans on a regular basis (Foley et al., 2007) and may reflect many of the characteristic nighttime sleep abnormalities described above (e.g., more fragmented sleep, less total sleep time, and less slow wave sleep).

Excessive daytime sleepiness and daytime napping are not, however, a universal feature of old age. For some portion of older adults, daytime sleep propensity and daytime ratings of subjective sleepiness diminish with the transition from midlife into older adulthood (Dijk et al., 2010). One factor that appears to determine whether older adults are prone to daytime napping and excessive daytime sleepiness is the presence of comorbid conditions such as chronic pain, depression, sleep disorders, and frequent nighttime urination breaks (Foley et al., 2007; Vitiello, 2009).

Nevertheless, daytime sleep propensity can be higher in healthy older relative to younger adults in the evening, when the circadian alerting signal is otherwise at its peak in young


Journal of Neuroscience Methods 313 (2019) 37–43

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

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

Sleep as a model to understand neuroplasticity and recovery after stroke: Observational, perturbational and interventional approaches

Armand Mensen[b,c], Andrea Pigorini[a], Laura Facchin[b], Cornelia S
Jasmine Jendoubi[b], Valeria Jaramillo[b], Kathrin Chiffi[b], Aleksand
Simone Sarasso[a], Antoine Adamantidis[b], René M. Müri[c], Reto Hu
Claudio Bassetti[b]

[a] University Hospital Bern, Switzerland
[b] Children's Hospital Zurich, Switzerland
[c] University of Milan, Italy


JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2019 PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 73, NO. 2, 2019

Association of Sleep Duration and Quality With Subclinical Atherosclerosis

Fernando Domínguez, MD, PhD,[a,b,c] Valentín Fuster, MD, PhD,[a,d] Juan Miguel Fernández-Alvira, PhD,[a] Leticia Fernández-Friera, MD, PhD,[a,c,e] Beatriz López-Melgar, MD, PhD,[a,c,e] Ruth Blanco-Rojo, PhD,[f] Antonio Fernández-Ortiz, MD, PhD,[a,c,e,g] Pablo García-Pavía, MD, PhD,[b,h,i] Javier Sanz, MD,[a,j] José M. Mendiguren, MD,[j] Borja Ibañez, MD, PhD,[a,c,d] Héctor Bueno, MD, PhD,[b,c,k] Enrique Lara-Pezzi, PhD,[a,c] José M. Ordovás, PhD[a,l,m]

ABSTRACT

BACKGROUND Sleep duration and quality have been associated with increased cardiovascular risk. However, large studies linking objectively measured sleep and subclinical atherosclerosis assessed in multiple vascular sites are lacking.

OBJECTIVES The purpose of this study was to evaluate the association of actigraphy-measured sleep parameters with subclinical atherosclerosis in an asymptomatic middle-aged population, and investigate interactions among sleep, conventional risk factors, psychosocial factors, dietary habits, and inflammation.

METHODS Seven-day actigraphic recording was performed in 3,974 participants (age 45.8 ± 4.3 years; 62.6% men) from the PESA (Progression of Early Subclinical Atherosclerosis) study. Four groups were defined: very short sleep duration <6 h, short sleep duration 6 to 7 h, reference sleep duration 7 to 8 h, and long sleep duration >8 h. Sleep fragmentation index was defined as the sum of the movement index and fragmentation index. Carotid and femoral 3-dimensional vascular ultrasound and cardiac computed tomography were performed to quantify noncoronary atherosclerosis and coronary calcification.

RESULTS When adjusted for conventional risk factors, very short sleep duration was independently associated with a higher atherosclerotic burden with 3-dimensional vascular ultrasound compared to the reference group (odds ratio: 1.27; 95% confidence interval: 1.06 to 1.52; p = 0.008). Participants within the highest quintile of sleep fragmentation presented a higher prevalence of multiple affected noncoronary territories (odds ratio: 1.34; 95% confidence interval: 1.09 to 1.64; p = 0.006). No differences were observed regarding coronary artery calcification score in the different sleep groups.

CONCLUSIONS Lower sleeping times and fragmented sleep are independently associated with an increased risk of subclinical multiterritory atherosclerosis. These results highlight the importance of healthy sleep habits for the prevention of cardiovascular disease. (J Am Coll Cardiol 2019;73:134–44) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

From the [a]Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain; [b]Heart Failure and Inherited Cardiac Diseases Unit, Department of Cardiology, Hospital Universitario Puerta de Hierro, Madrid, Spain; [c]Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain; [d]Icahn School of Medicine at Mount Sinai, New York, New York; [e]IdiPAZ (Instituto de Investigación Hospital Universitario La Paz), Madrid, Spain; [f]Unidad de Bioestadística Clínica, Hospital Universitario La Paz, Madrid, Spain; [g]Universidad Complutense, Madrid, Spain; [h]Cardiology Department, Hospital Universitario 12 de Octubre, and Instituto de Investigación Sanitaria Hospital 12 de Octubre, Madrid, Spain; [i]Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain; and the [j]U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts. *The PESA study is cofunded equally by the CNIC and Banco Santander. The study also receives funding from the Institute of Health Carlos III (PI13/01090) and the European Regional Development Fund. The CNIC is supported by the Ministry of Economy, Industry and Competitiveness (MEIC) and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (MEIC award SEV-2015-0505). Dr. Bueno has received consulting fees from AstraZeneca, Bayer, Bristol-Myers Squibb-Pfizer, and Novartis; has received speaking fees or support for attending scientific meetings from AstraZeneca, Bayer, Bristol-Myers Squibb-Pfizer, Ferrer, Novartis, and MEDICALTIC; the heart.org, and has received

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.10.060

Conseqüències de la privació de son

x4.9 Depressió severa

x2.8 Infart de miocardi

x2.1 Fibromiàlgia

x2.0 Artritis reumatoide

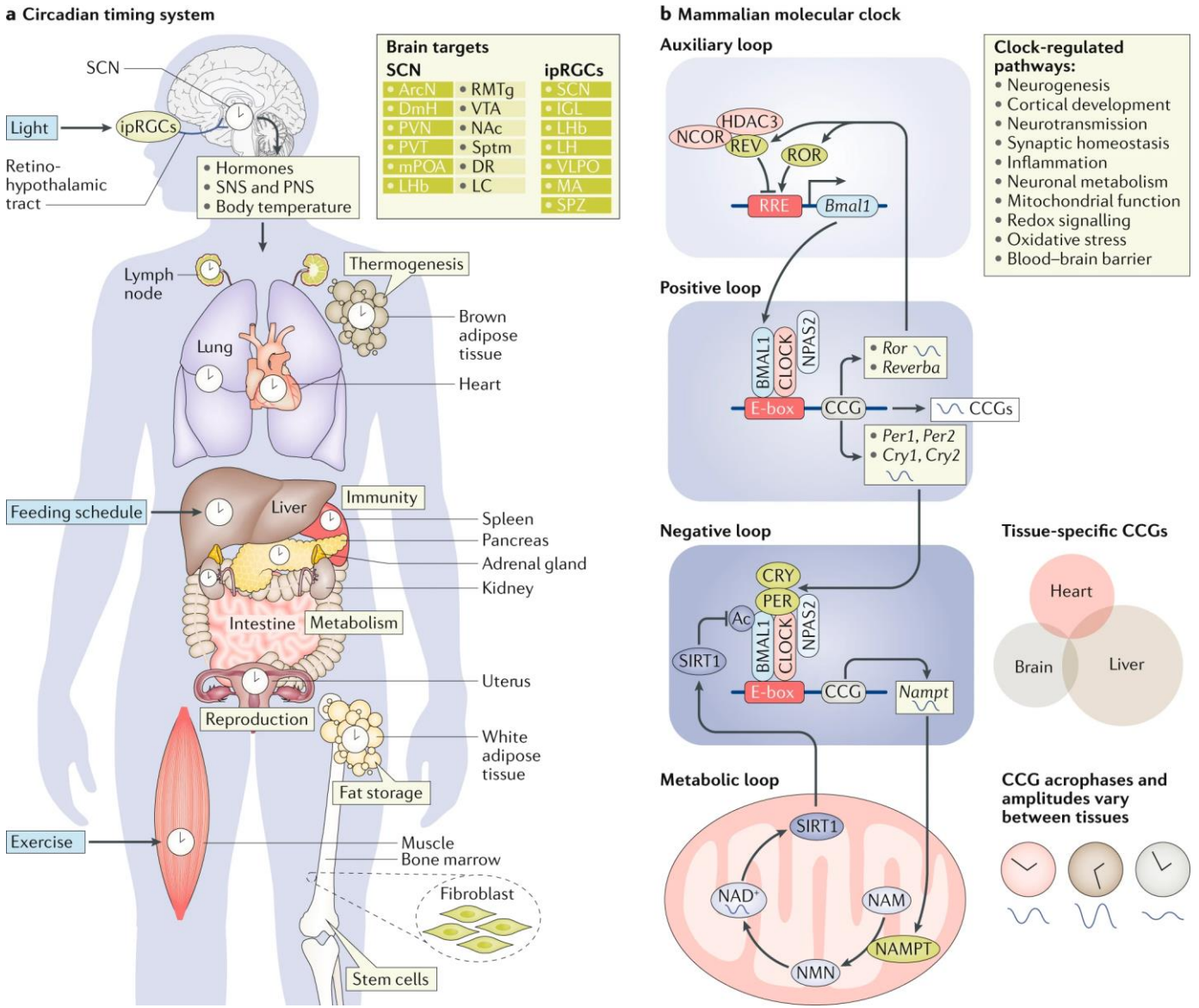
x1.6 Osteoartritis

x5.0 Alzheimer

Sleep is integral to life!

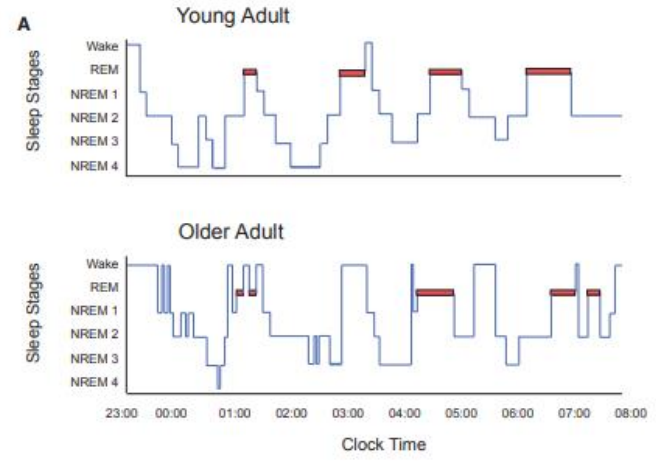
Què entenem per trastorns de son?

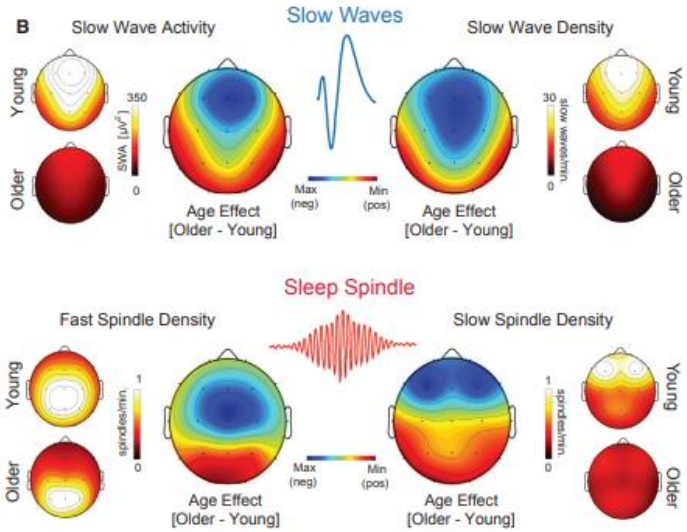
Relació fisiopatològica del son amb malalties rellevants

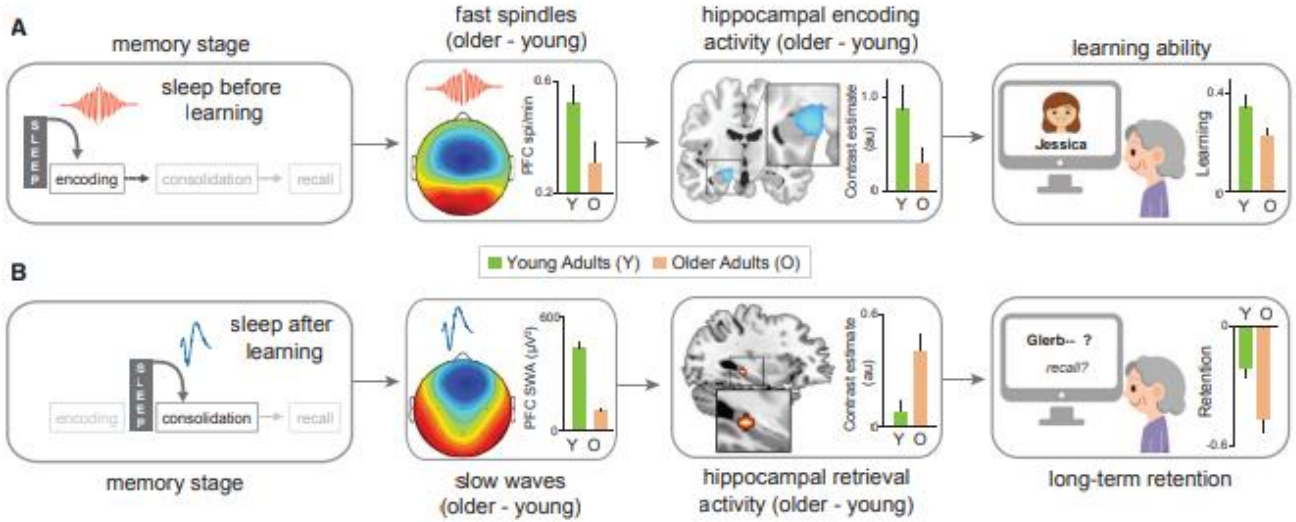


Relació fisiopatològica del son amb malalties rellevants (1)

Son i envelliment







Mander, B. A., Winer, J. R., & Walker, M. P. (2017). Sleep and Human Aging. *Neuron*, *94*(1), 19–36. https://doi.org/10.1016/j.neuron.2017.02.004

Relació fisiopatològica del son amb malalties rellevants (2)

Malalties cardiometabòliques

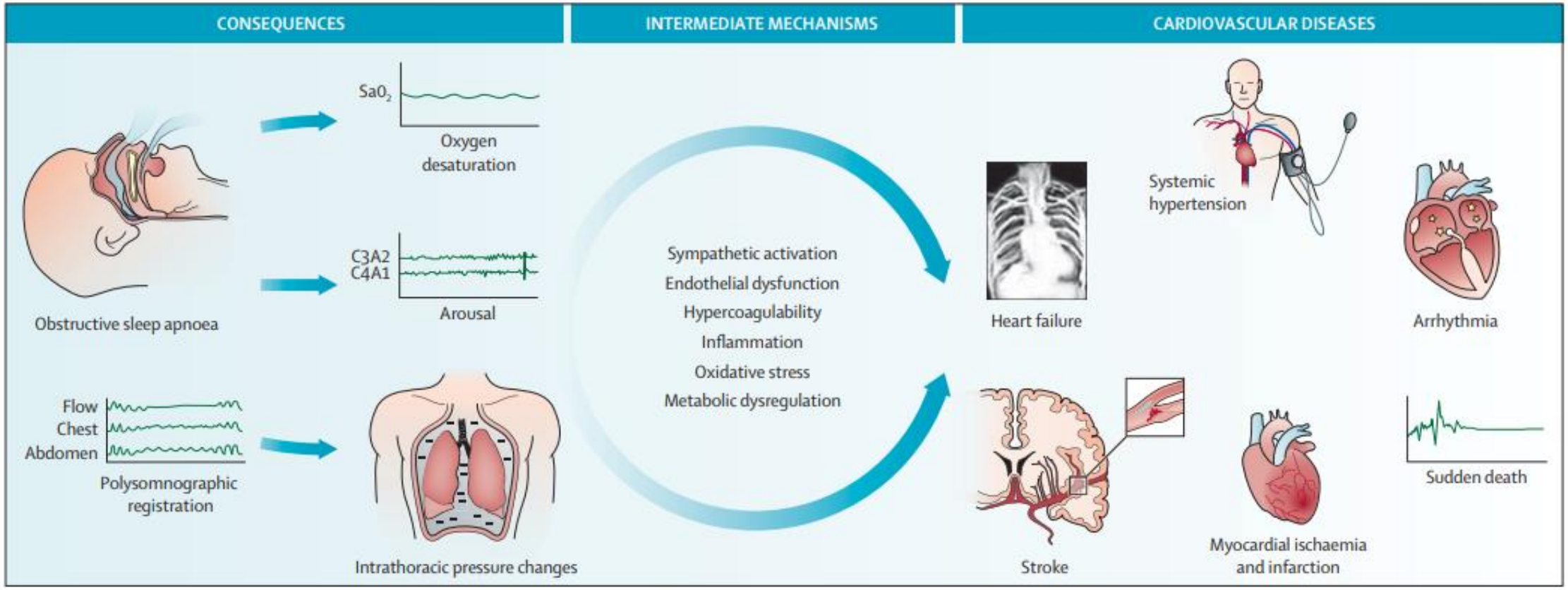


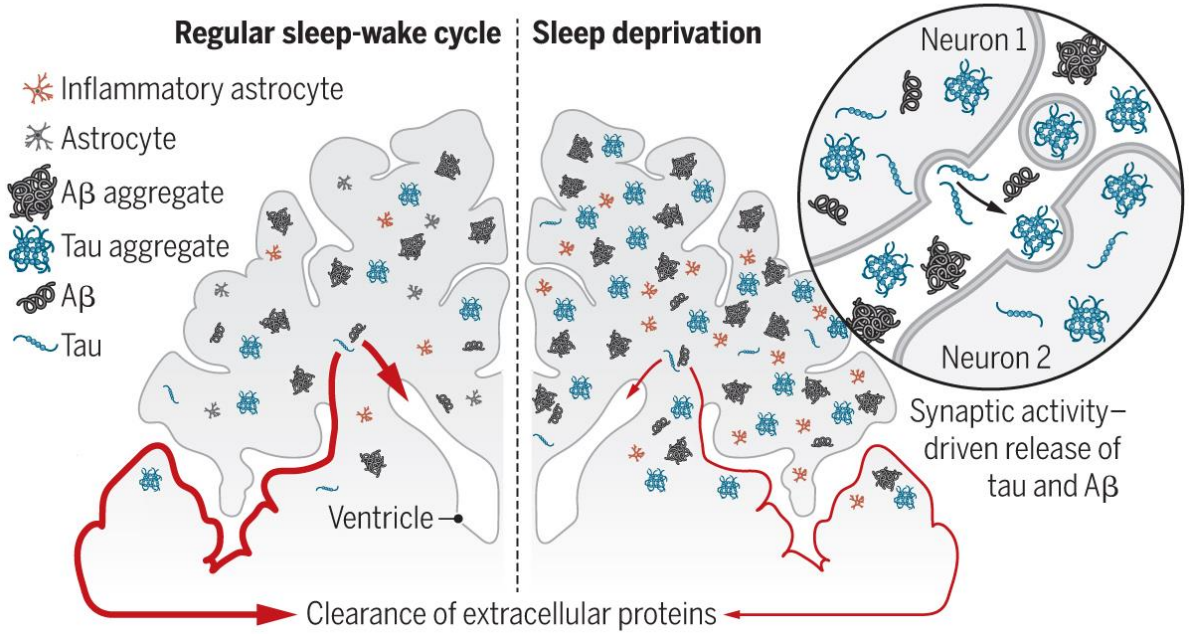
***Figure*: Obstructive sleep apnoea consequences and intermediate mechanisms that potentially contribute to risk of cardiovascular disease**
The events associated with collapse of the upper airway lead to brain arousal, intrathoracic pressure changes, and hypoxaemia and reoxygenation. Several intermediate mechanisms link obstructive sleep apnoea with the initiation and progression of cardiovascular diseases. SaO_2=oxygen saturation. C3A2 and C4A1=electroencephalographic channels.

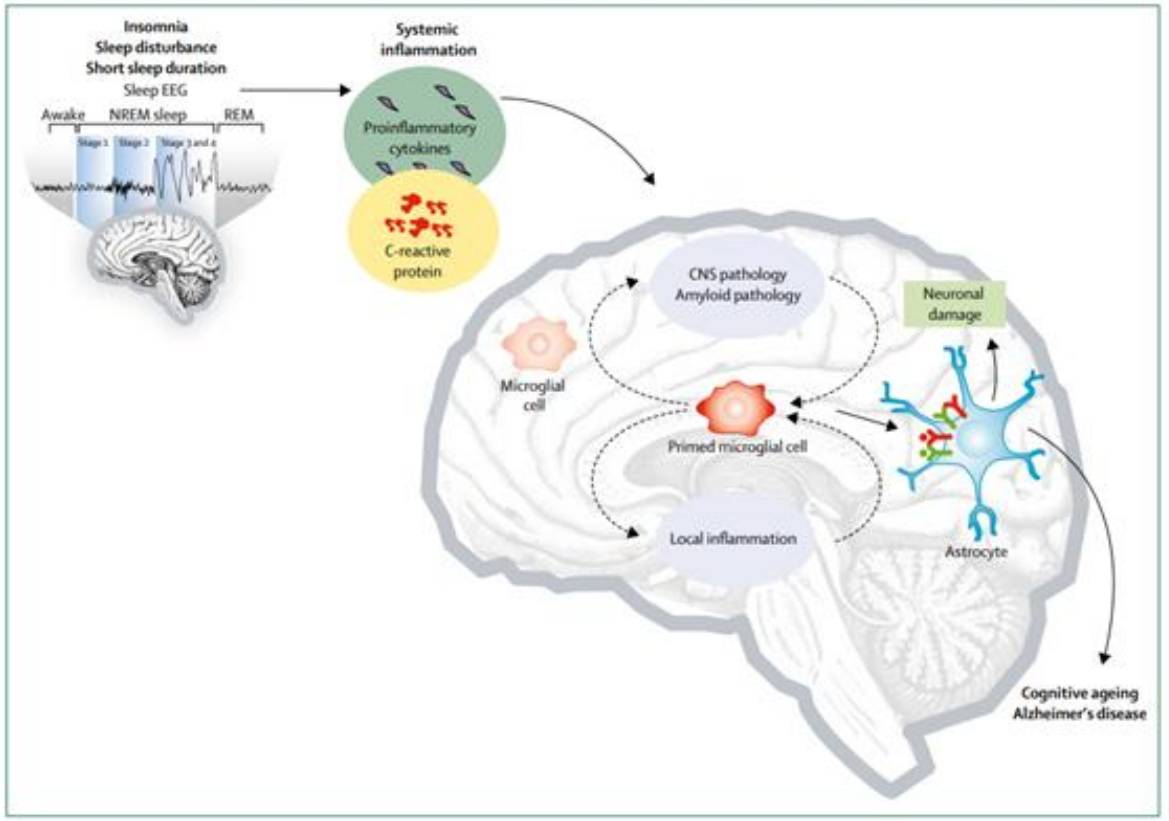
Relació fisiopatològica del son amb malalties rellevants (3)

Malalties neurodegeneratives

Sleep deprivation promotes Alzheimer's pathology

Sleep is accompanied by lowered activity-driven release and heightened clearance of Aβ and tau from the brain. Sleep deprivation reduces aggregate clearance and promotes astrogliosis, network activity–driven tau and Aβ release, further protein aggregation, and the spread of Alzheimer's disease pathology.

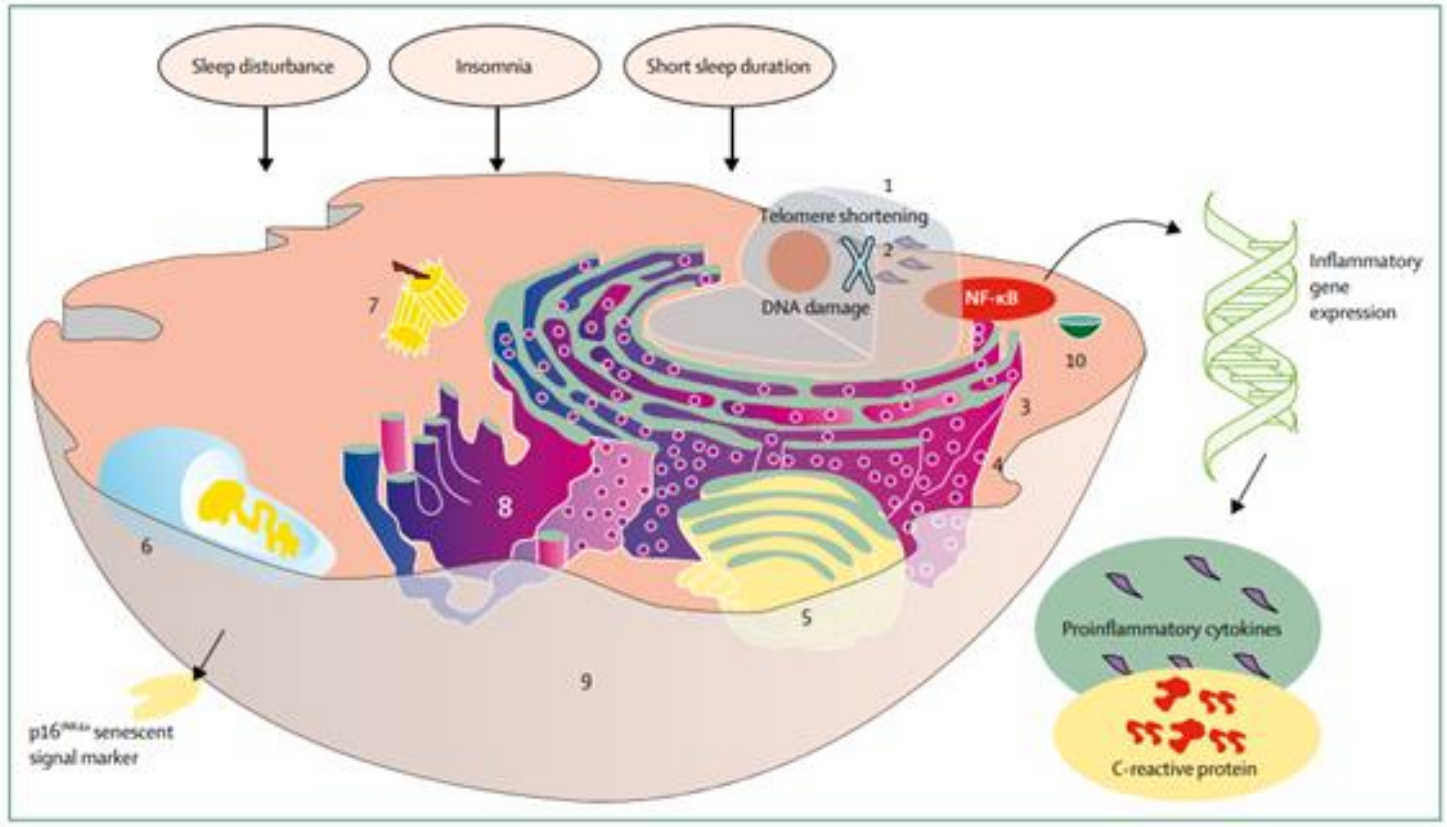




Irwin MR, Vitiello MV. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. Lancet Neurol. 2019 Mar;18(3):296-306. doi: 10.1016/S1474-4422(18)30450-2. Epub 2019 Jan 17. PMID: 30661858.

Relació fisiopatològica del son amb malalties rellevants (4)

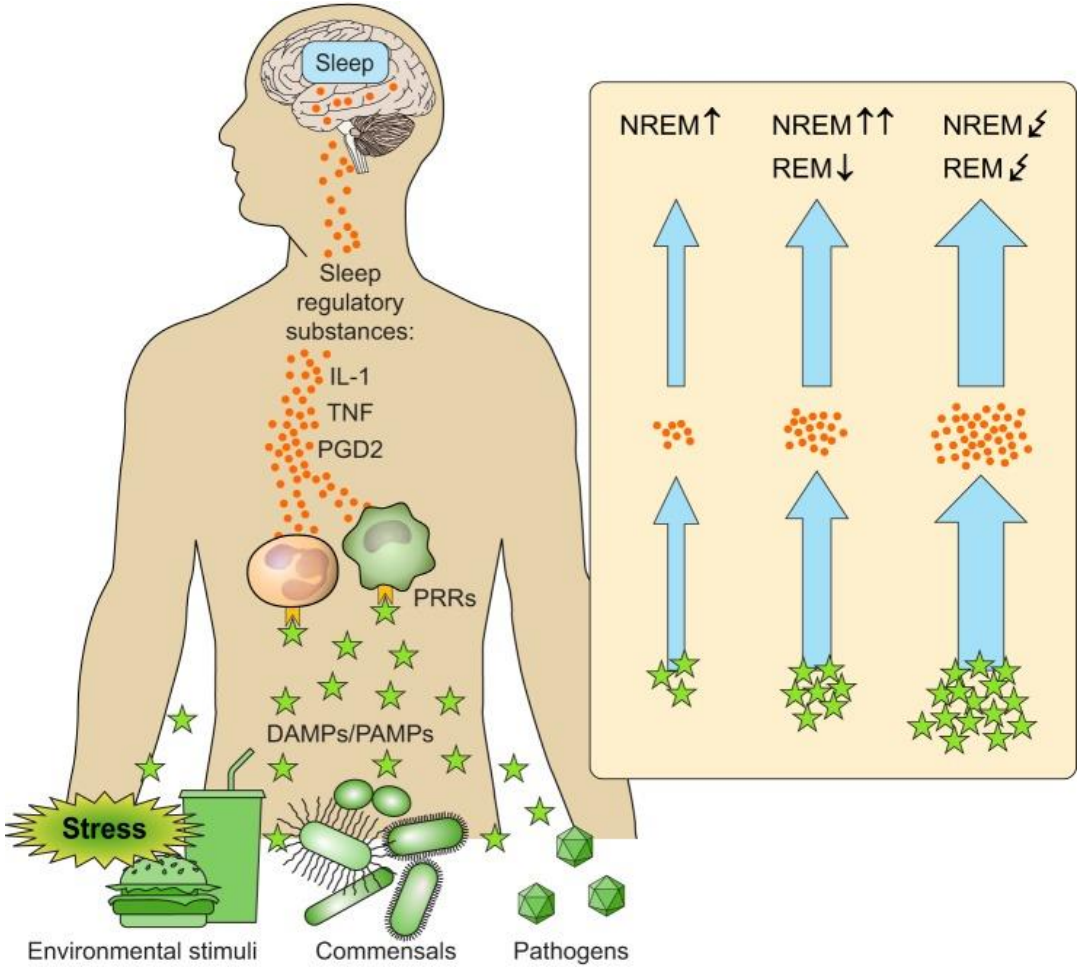
Processos inflamatoris

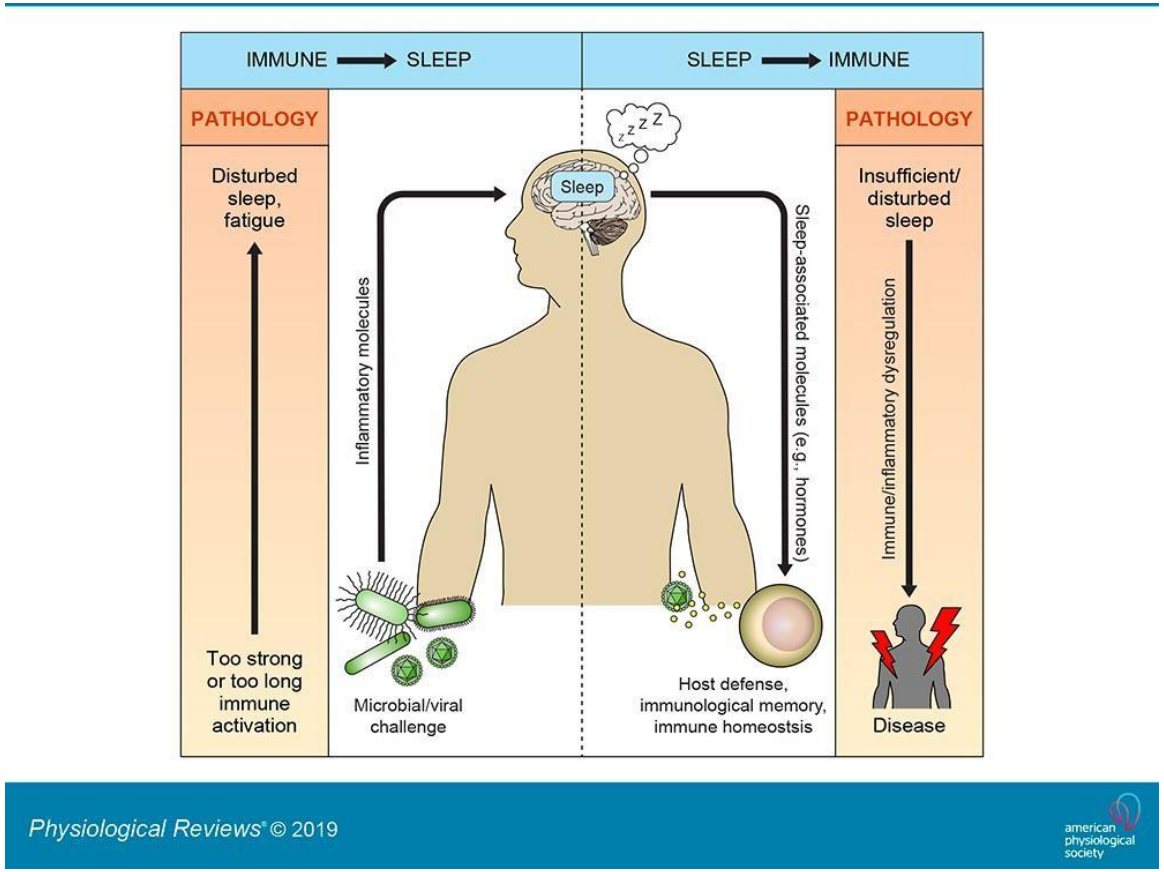


Irwin MR, Vitiello MV. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. Lancet Neurol. 2019 Mar;18(3):296-306. doi: 10.1016/S1474-4422(18)30450-2. Epub 2019 Jan 17. PMID: 30661858.

Relació fisiopatològica del son amb malalties rellevants (5)

Sistema immunològic

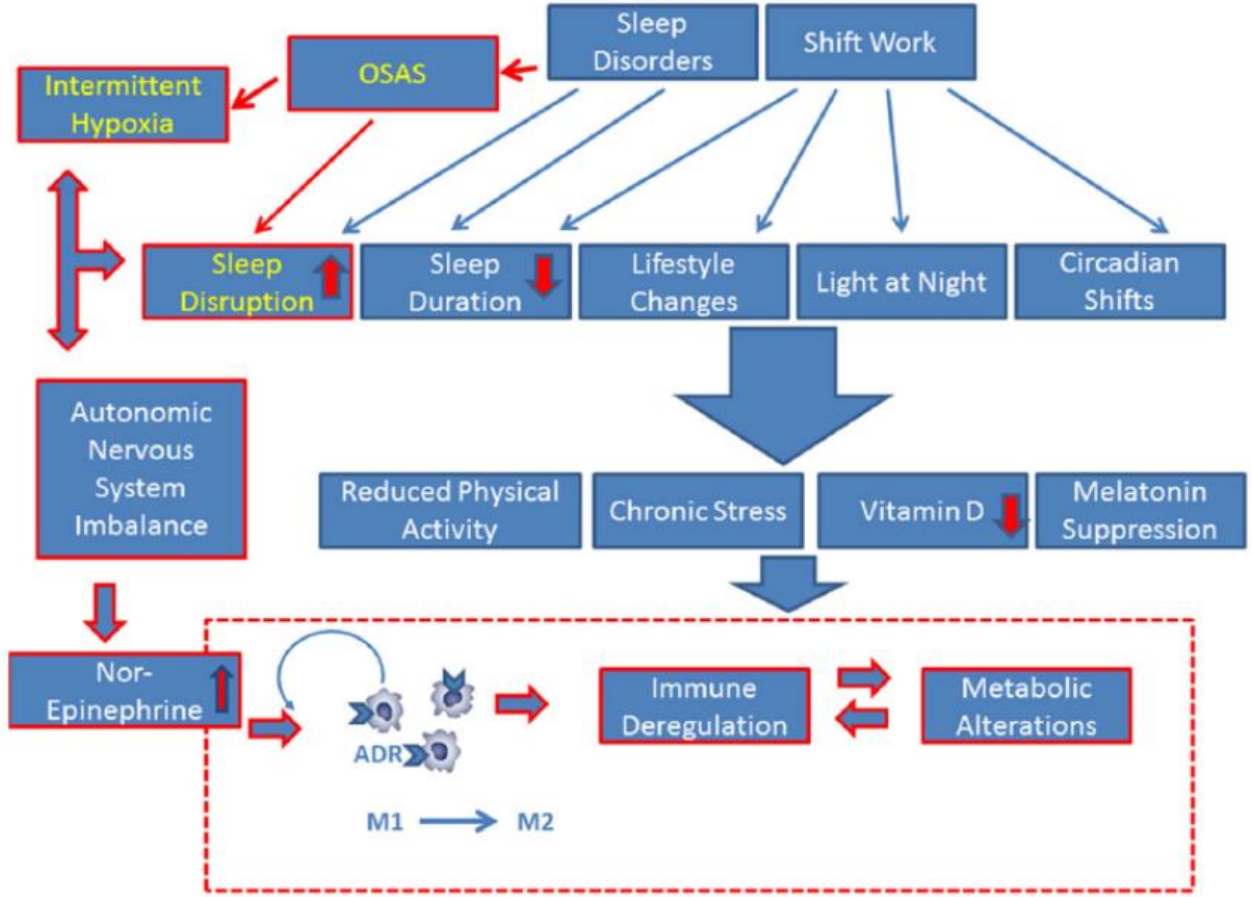




Besedovsky L, Lange T, Haack M. The Sleep-Immune Crosstalk in Health and Disease. Physiol Rev. 2019 Jul 1;99(3):1325-1380. doi: 10.1152/physrev.00010.2018. PMID: 30920354; PMCID: PMC6689741.

Sleep disturbances promote cancer

Why?



Gozal et al. Sleep Med Rev. 2016; 27:43-55.

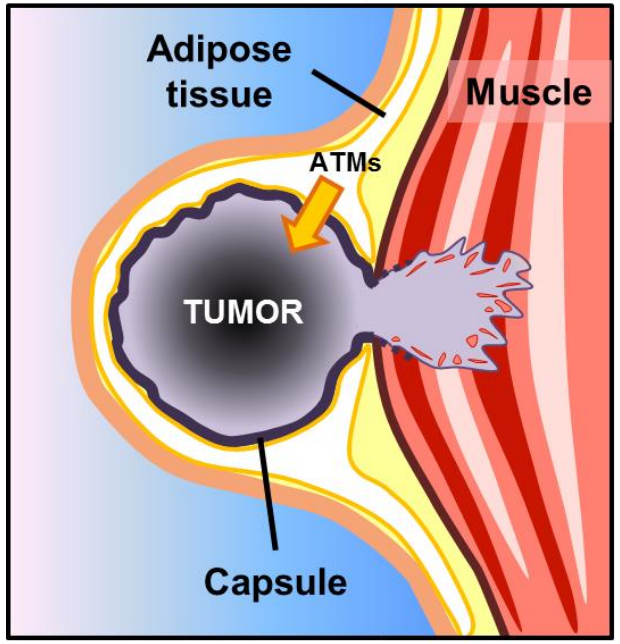
Sleep disturbances promote cancer

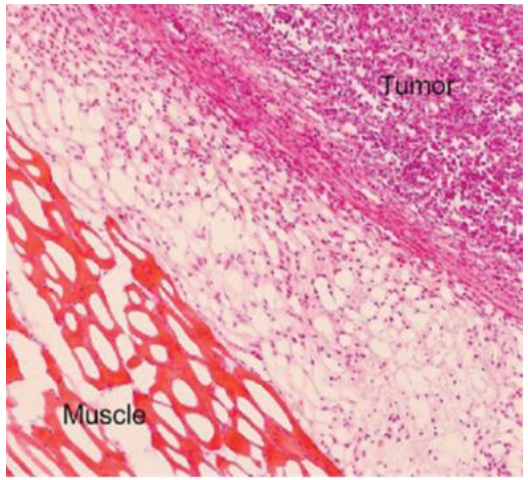
Experimental data from animal models

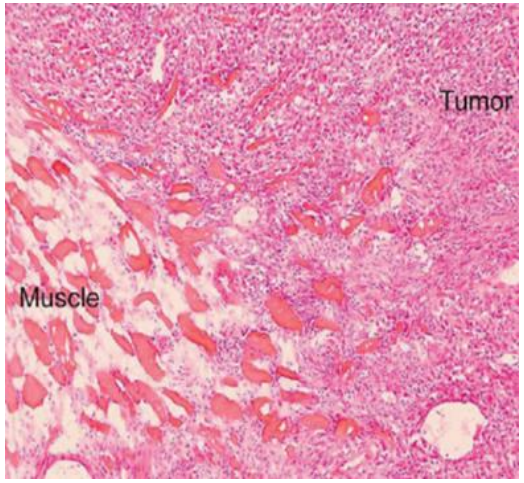
- **Tumor <u>invasion</u>**

INTERMITTENT HYPOXIA ↑

SLEEP FRAGMENTATION ↑



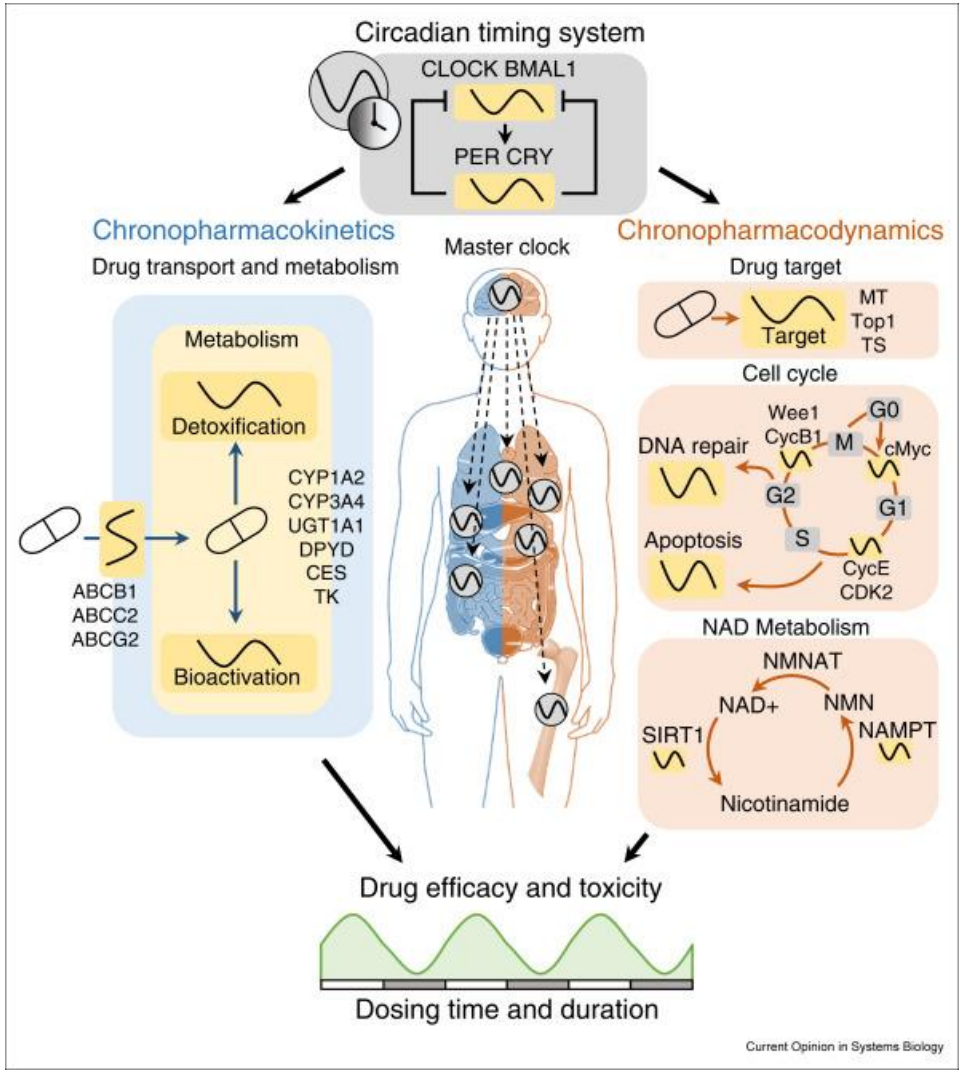




Almendros I et al. Am J Respir Crit Care Med;189:593-601, 2014
Cortese R et al. Oncotarget.;6:556-69 2015
Hakim et al. Cancer Res. 2014;74:1329-37

AdSalutem Sleep Institute

Cronoterapia



Dae Wook Kim, Eder Zavala, Jae Kyoung Kim (2020). Wearable technology and systems modeling for personalized chronotherapy. Current Opinion in Systems Biology.

HEALTH

Chemotherapy could work twice as well if given at the right time

25 October 2016

by *Joanna Roberts*

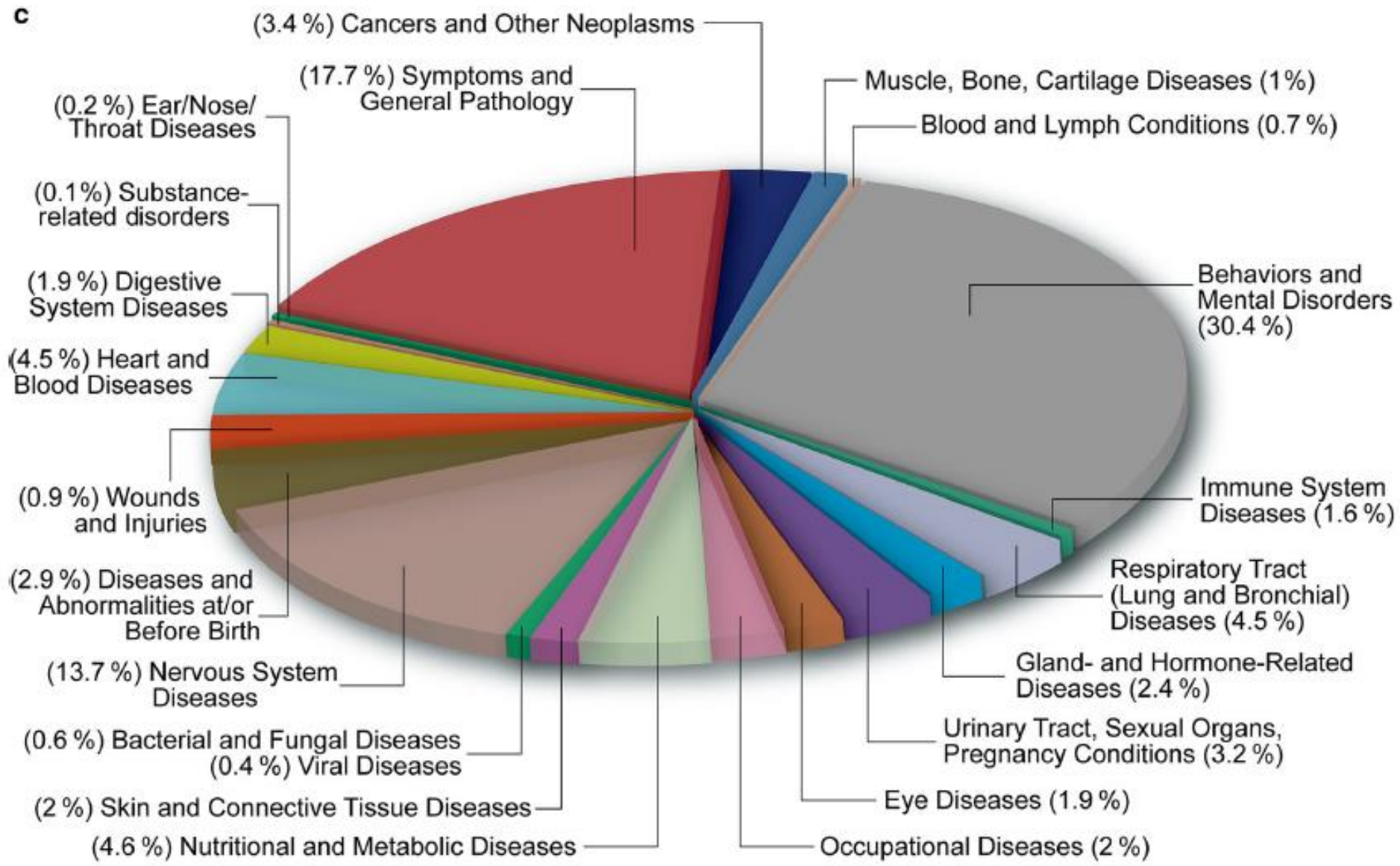
Republish

Adjusting the time that chemotherapy is given to male colorectal cancer patients has been shown to increase their survival rates by three months. Photo credit: Pixabay/ public domain

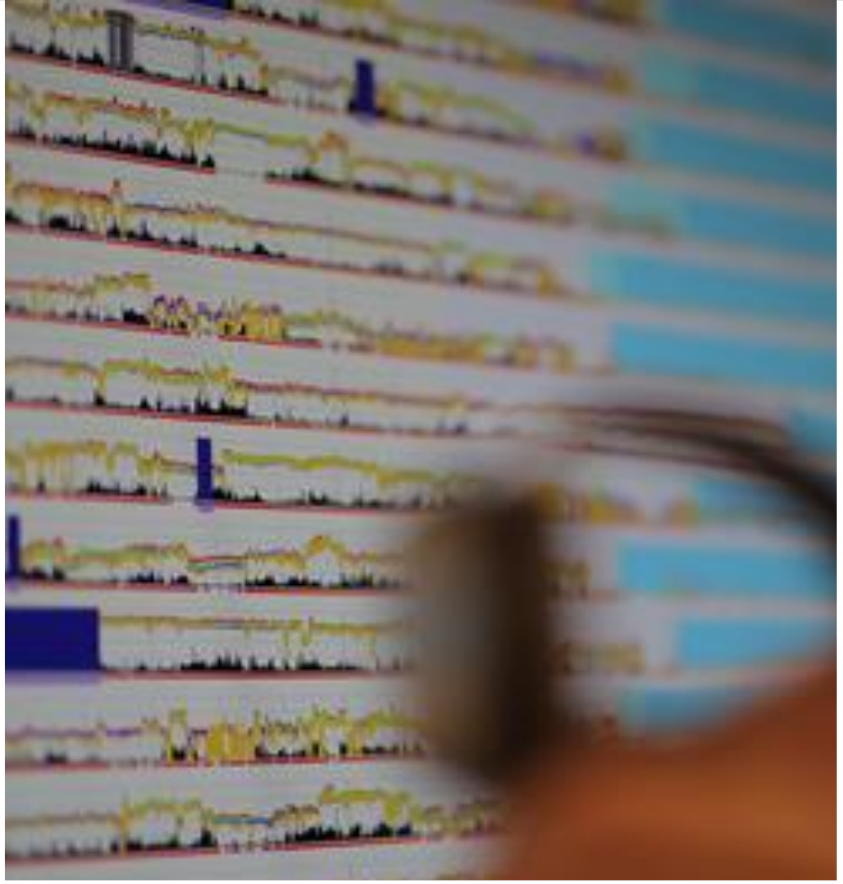
The anti-tumour properties of chemotherapy drugs could work twice as well if you take them at times when the body is most receptive, but that means different timetables for different people, according to researchers working to understand how to use the body's daily rhythms to make medicine optimally effective and reduce unpleasant side effects.

[Chemotherapy could work twice as well if given at the right time | Research and Innovation (europa.eu)]

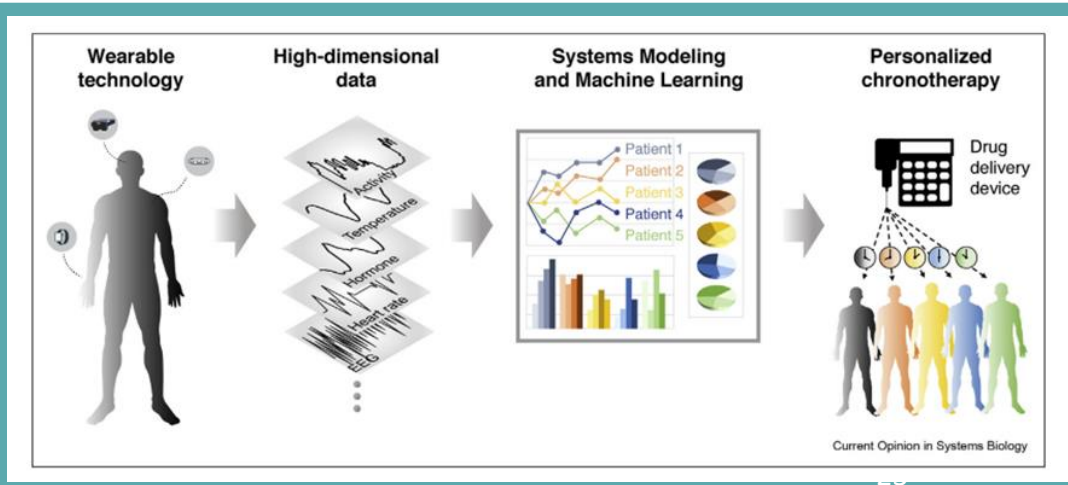
Chronotherapy: Intuitive, Sound, Founded…But Not Broadly Applied



Julia M. Selfridge, Tetsuya Gotoh, Samuel Schiffhauer, JingJing Liu, Philip E. Stauffer, Andrew Li, Daniel G. S. Capelluto, Carla V. Finkielstein



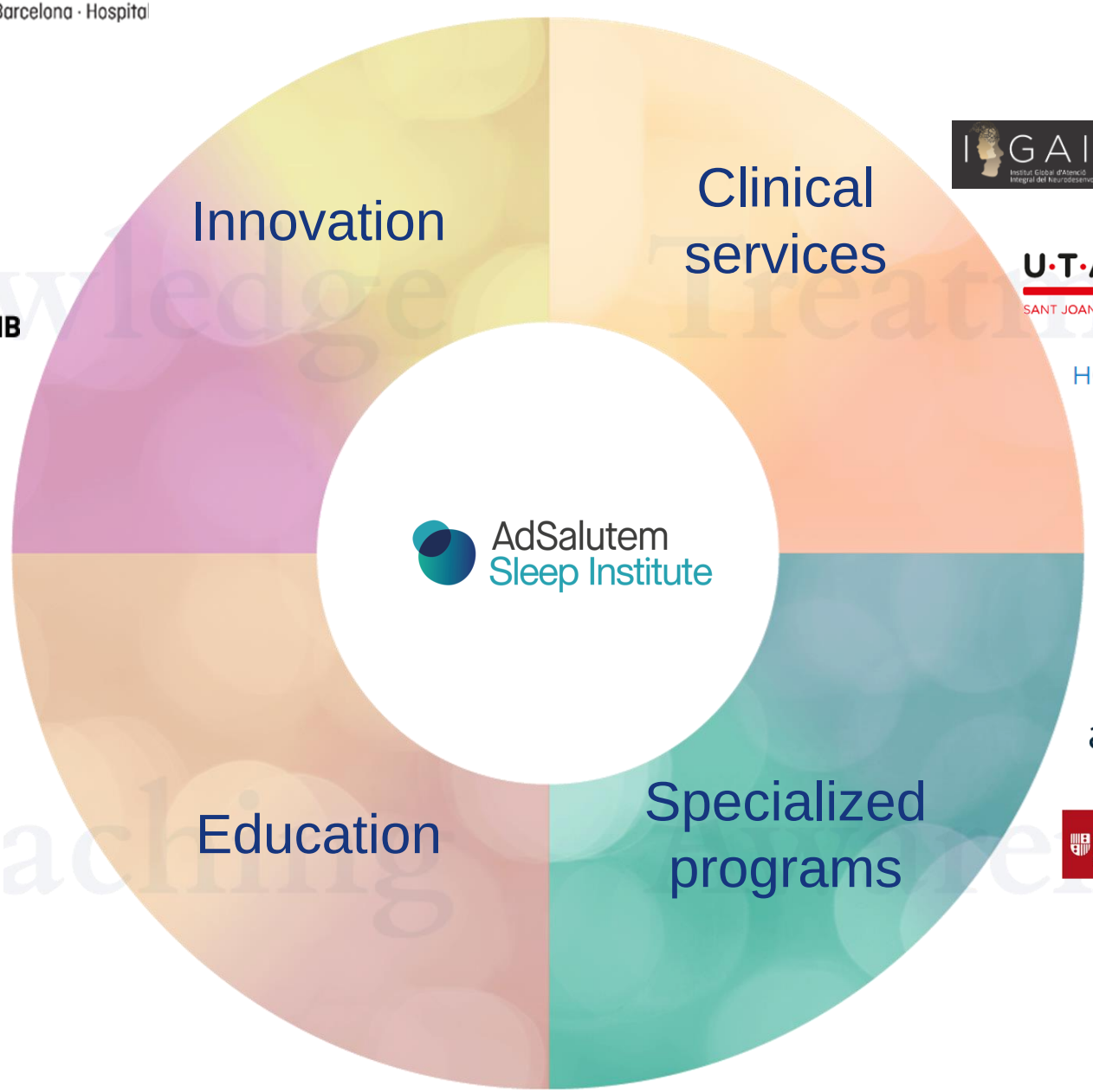
Tecnologies per monitoritzar el son



AdSalutem Sleep Institute

Sleep is integral to life!

Should sleep be considered a life protector?
… a therapeutical remedy to fight disease?
… a booster of pharmacological effect?
… a golden medicine by itself.


Innovation
Clinical services
Education
Specialized programs
AdSalutem Sleep Institute

Gràcies per la vostra atenció!

Dr. Antoni Esteve

28 d'Octubre de 2021

AdSalutem Sleep Institute