Sleep Disorders in the Elderly

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24.01.2025
Belgian Interuniversity Course in Geriatric Medicine

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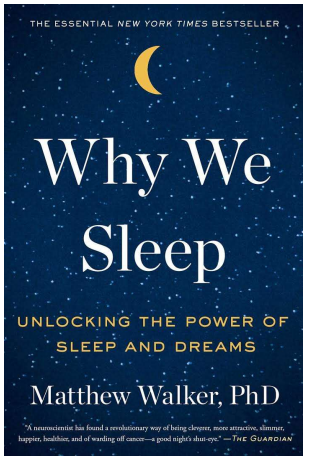
Outline

- **Some basic physiology: sleep homeostasis and circadian rhythm**
- Sleep changes with ageing
- Diagnostic assessment
- Sleep disorders in the elderly
  - Insomnia and psychiatric comorbidity
  - Sleep disordered breathing
  - RLS
  - RBD and other parasomnias
- Non-pharmacological interventions
  - Do not forget environmental factors
- Impact of medication
  - Risk for sleep disturbance
  - Pharmacological treatment
- Summary and Recommendations

Why we sleep



- Sleep has actually been a mystery for a long time and still holds a lot of secrets but as Matthew Walker says:

> *‘ It must be very important because otherwise, evolutionary, should not have persisted, because when you sleep you are very vulnerable, cannot forage for food and cannot reproduce.’*

Matthew Walker. Why we sleep. Unlocking the power of sleep and dreams. 2017. ISBN: 9780141983769.

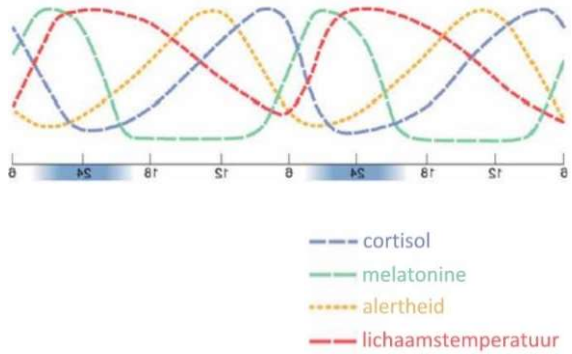
Sleep: so much more than slowing down

- Primary and vital need
- ≠ passive absence of wakefullness
- Active physiological process with various functions:
  - Contributions to cognitive functioning, learning, memory, making logical decisions and choices
  - Emotion regulation, psychological and social functioning
  - Correct functioning of:
    - Immune system
    - Metabolism
    - Control of appetite and weight
    - Strong connection with cardiovascular system (blood pressure, sympathetic balance, vascular tone….)
- Sleep is a combination of
  - Learned behavior (conditioning)
  - Biological processes determined by:
    - Genetics
    - Human development stage

Sleep and age

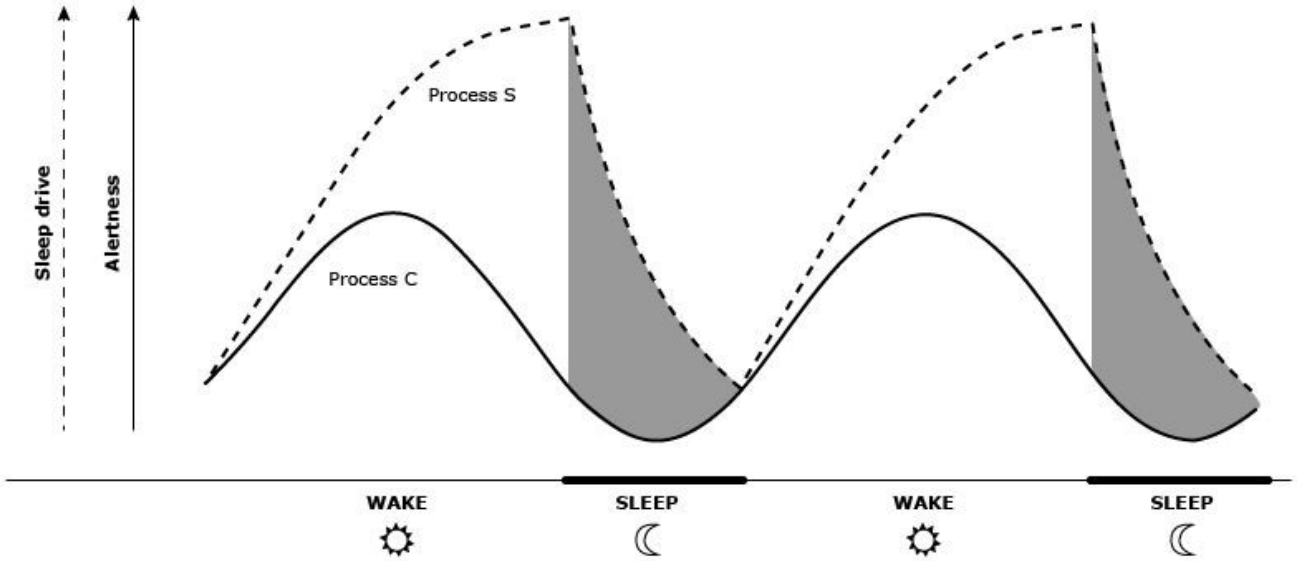
- Characteristics of human sleep gradually change with aging:
  - Reflects maturation process of our body from birth to old
  - Partly changing independently of any pathological process
  - But may effect people's subjective quality of life
  - Increasing morbidity
- *To better understand and study sleep complaints and potential pathologies in the elderly: overall knowledge of evolution of physiology of normal sleep with ageing is crucial*

Regulation

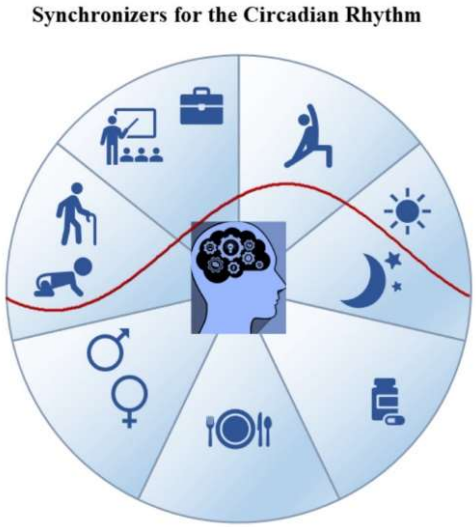


Sleep is determined by 2 rhythms:

- **Process S:** Homeostasis / sleep propensity
- **Process C:** Internal biological clock / circadian rhythm



Process S and process C (Cheng & Drake, 2016)



Montaruli et al., Biomolecules 2021

Achermann, & Borbely 2003
(Beersma, 2002)

Homeostatic control – ‘process S’

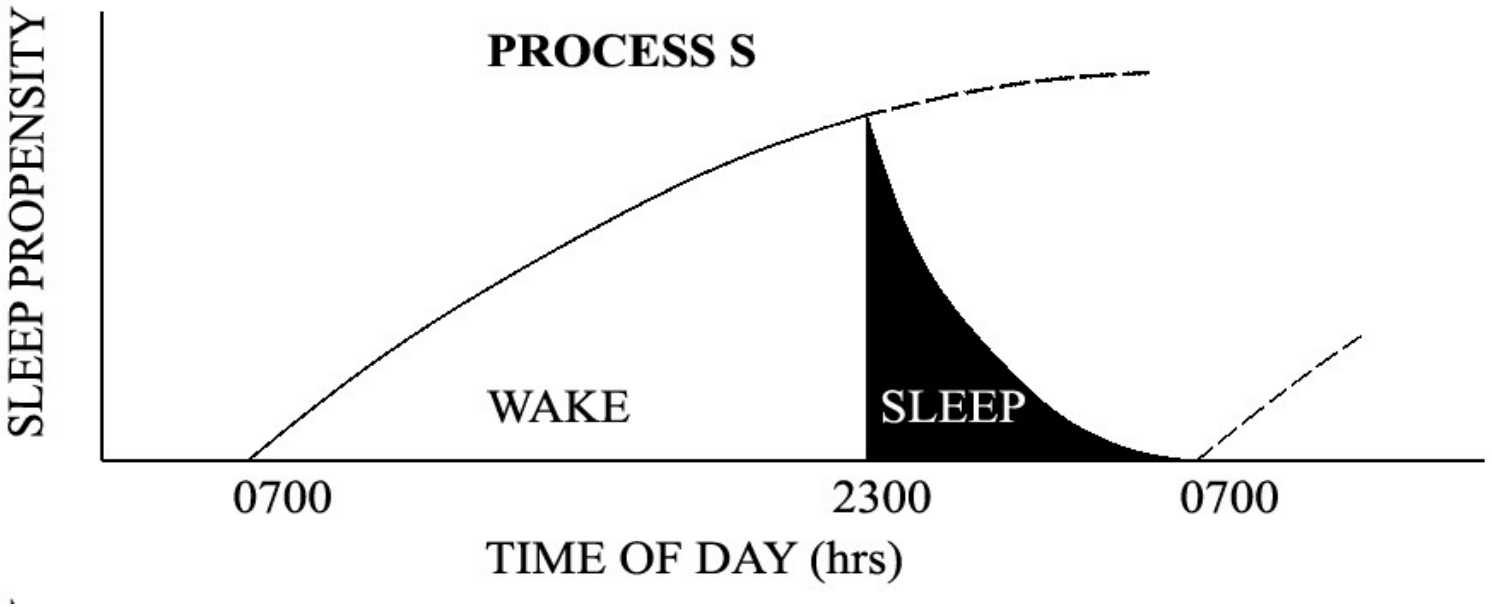
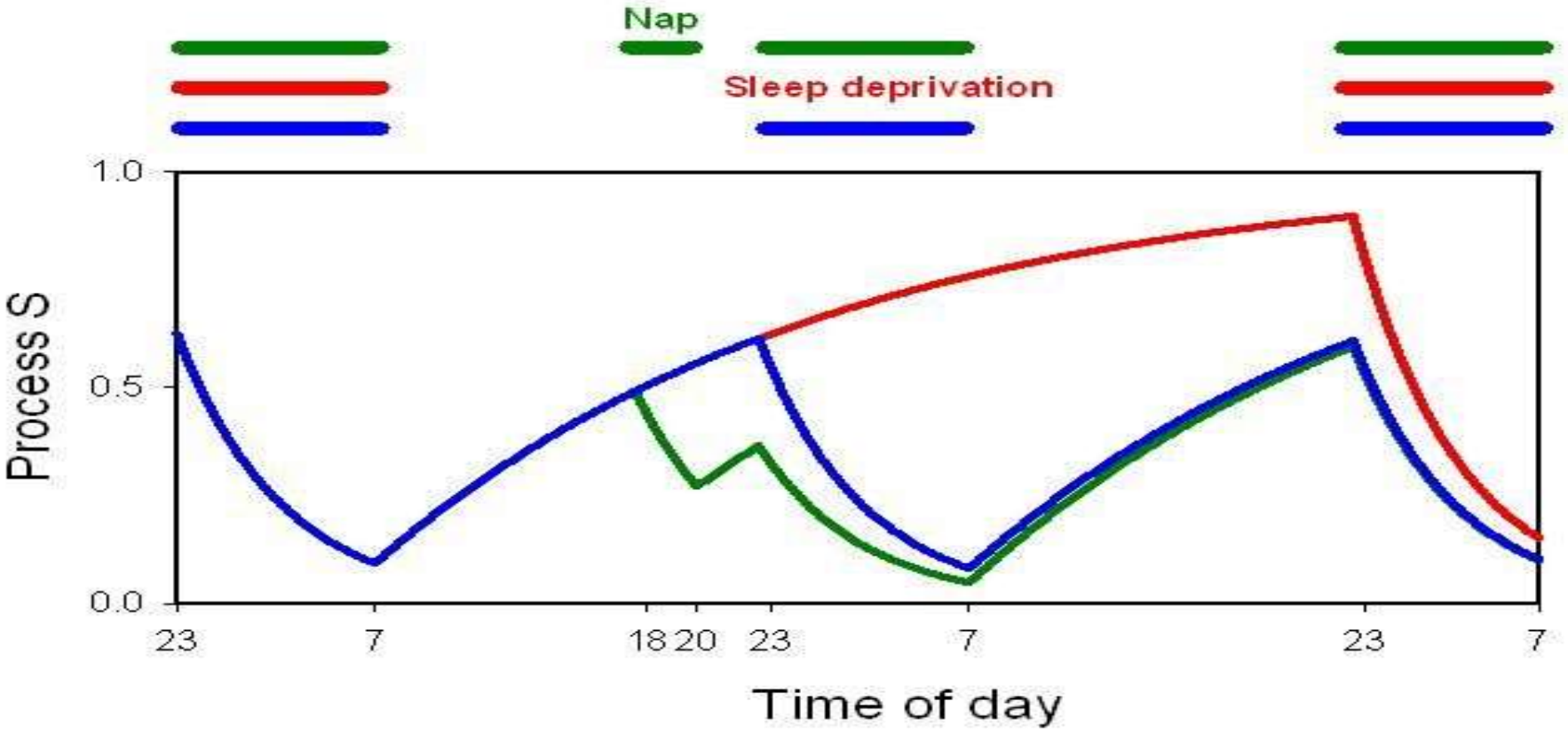


Figure 1. Schematic representation of process S adapted from Achermann & Borbély (2003): time course (*X*-axis) of process S-regulated sleep propensity (*Y*-axis).

Homeostatic regulation – ‘process S’



Sleep in the elderly: daytime sleep and napping

- More frequently with ageing *(Li, Vitiello, & Gooneratne, 2018)*
- Influenced by educational and cultural context and former lifestyle *(Naska, et al., 2007)*
  - **Short naps:**
    - positive impact with improvements in subjective well-being, psychomotor and cognitive performance *(Li, Chang, et al., 2018)*
    - improve the amount of sleep per 24 hour *(Picarsic et al., 2008)*
  - **Long naps (>60-90 min)** might mitigate or reverse the effects *(Li, Chang, et al., 2018)*:
    - ↓ homeostatic sleep propensity leads to worse night sleep architecture
    - reduction of homeostatic sleep propensity certainly relevant in elderly with insomnia
  - **Essential:** distinguish between intended and unintended naps
    - Intended naps have an overall favourable profile
    - Unintended naps are more likely the result of excessive daytime sleepiness (EDS) and are associated with more negative effects related to an underlying condition:
      - primary sleep disorders:
        - sleep-related breathing disorders
        - periodic limb movements

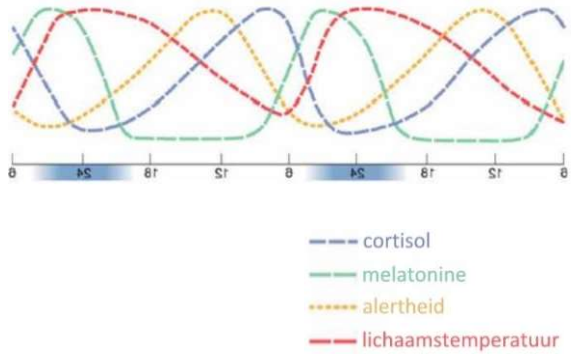
Sleep in the elderly: EDS

- **EDS always suggests the existence of an underlying sleep-wake disorder rather than a normal age-related trend**

- **Excessive Daytime Sleepiness (EDS):**
  - Difficulties staying awake during normal daytime activities
  - Evaluated by the Epworth Sleepiness Scale (ESS, with a score of >10 indicating EDS)
  - EDS can result in unintended naps
  - Often related to pathological conditions *(Zalai, Bingeliene, & Shapiro, 2017)*
    - metabolic syndrome
    - depression
    - sleep apnea
    - RLS
    - circadian rhythm disorders
    - any other sleep-disturbing or sleep fragmenting factors
    - side effects of prescription drugs
    - neurodegenerative diseases
      - predictive or worsening factor of cognitive decline, in α-synucleinopathies (i.e., Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy)

ESRS Sleep Medicine Textbook 2021

Regulation



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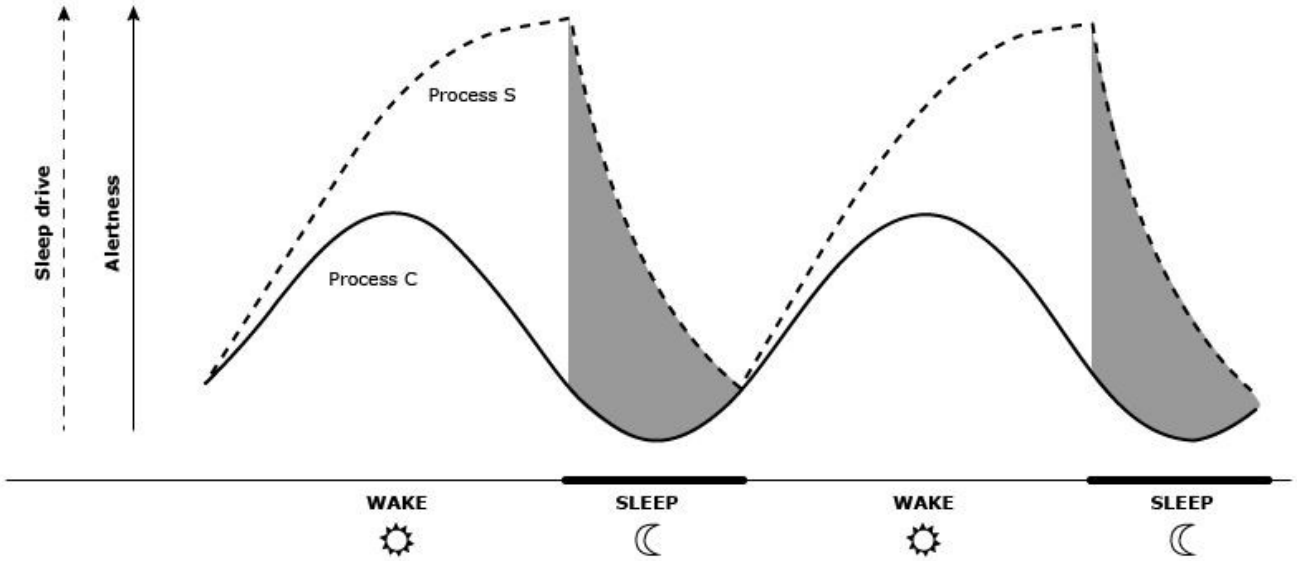

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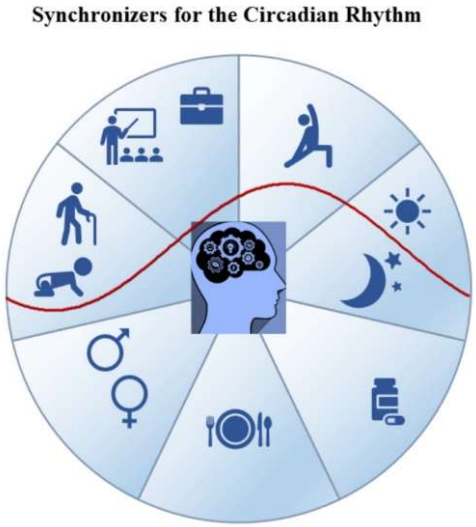

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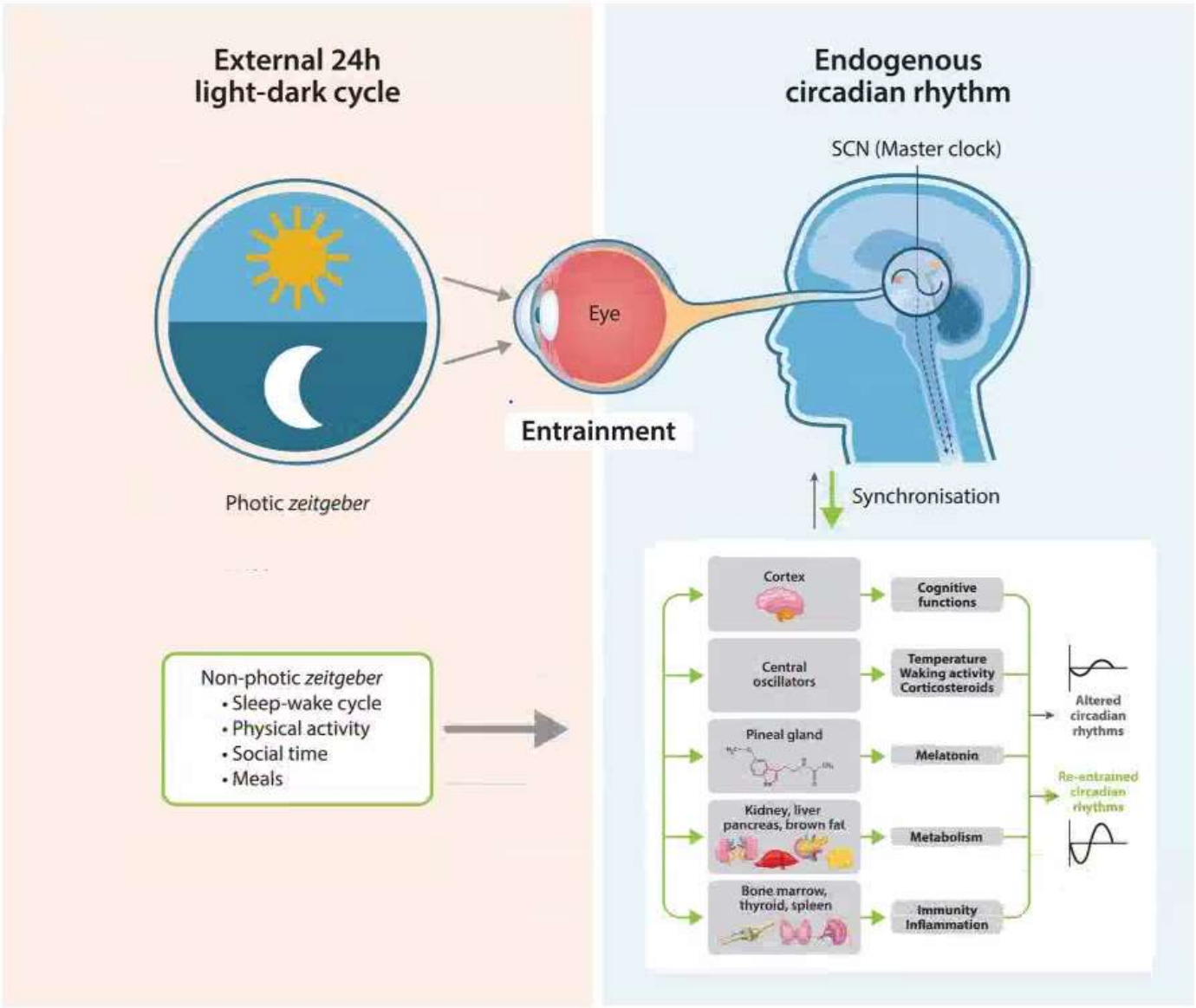
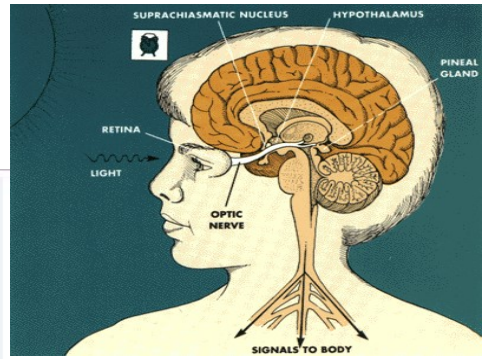
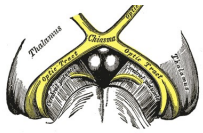
Circadian rhythm





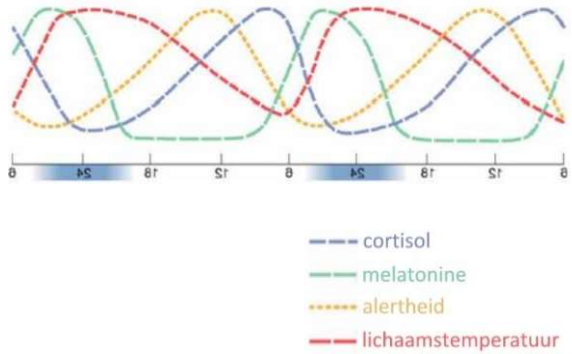


SCN=Nucleus suprachiasmaticus

Fig. 1 Schematic diagram of the circadian clock entrainment pathways. Light directly entrains the suprachiasmatic nucleus (SCN), whereas other non-photic zeitgebers exhibit rhythmic changes and entrain the SCN and peripheral clocks throughout 24 h—adapted with permission from Buttgereit et al. [40] and Hood and Amir [41]

Jande van Rensburg, 2021

Regulation



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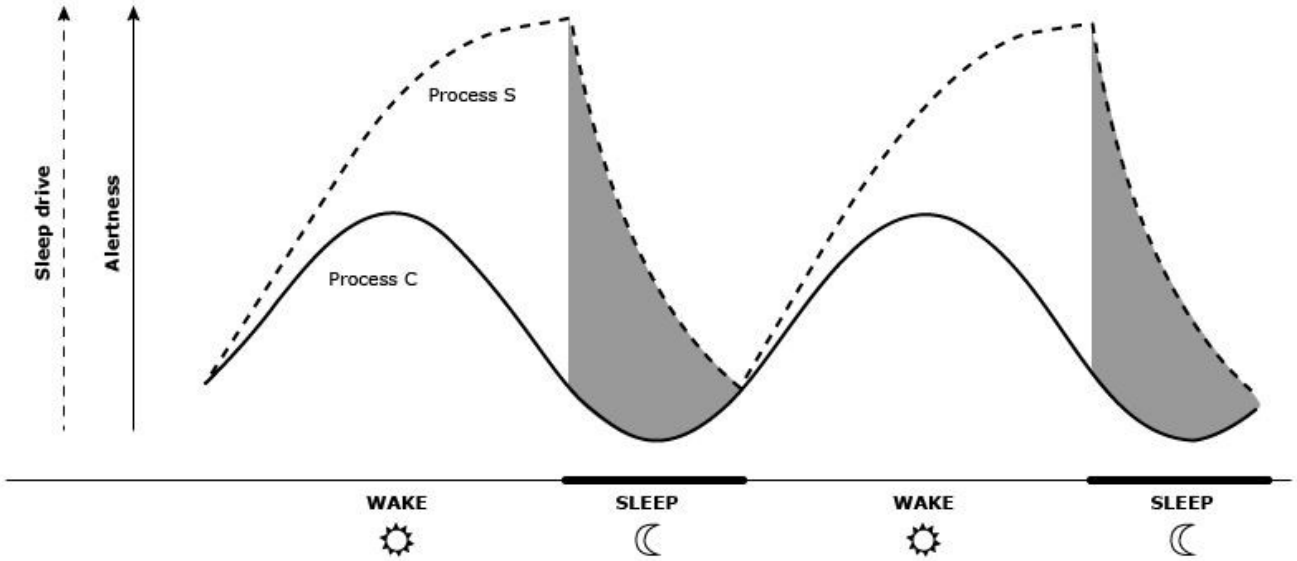

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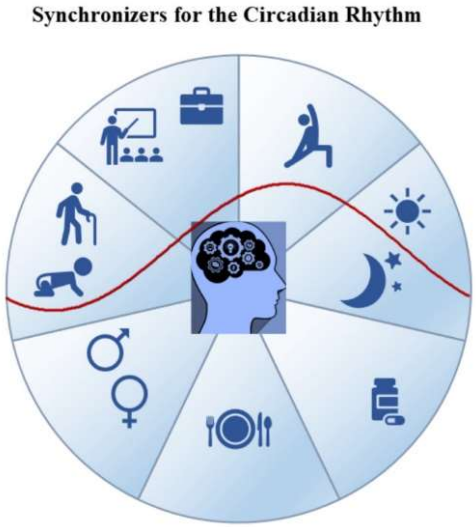

Montaruli et al., Biomolecules 2021

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How do neurotransmitters & hormones make us sleep?

Turn on sleep promoting neurotransmitters
Turn off wakefulness promoting neurotransmitters

Promote wakefulness

- Glutamate
- Noradrenaline
- Serotonin
- Acetylcholine
- Histamine
- Dopamine
- Orexin/hypocretin

Promote sleep

- GABA
- Adenosin
- Melatonin

If it only were that simple……..

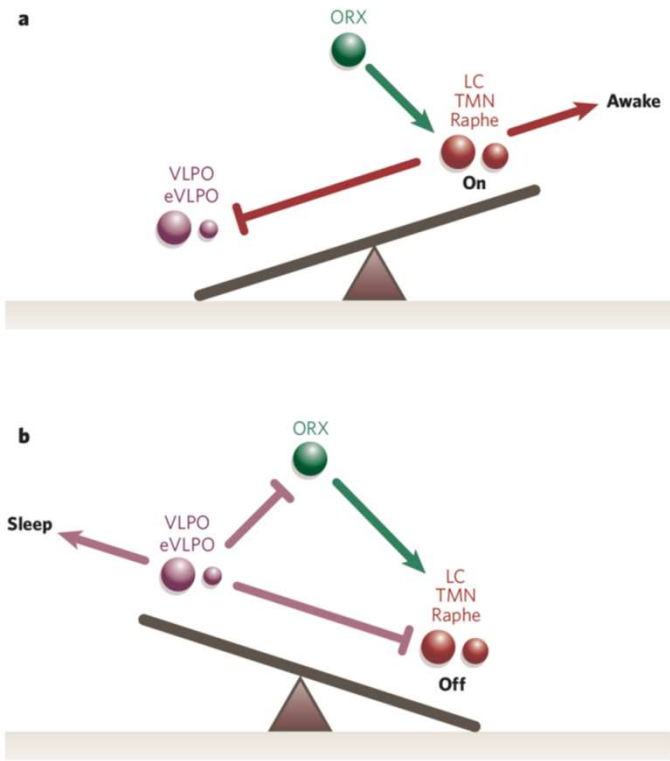
The relationship between each neurotransmitter and sleep/wakefulness is not always direct

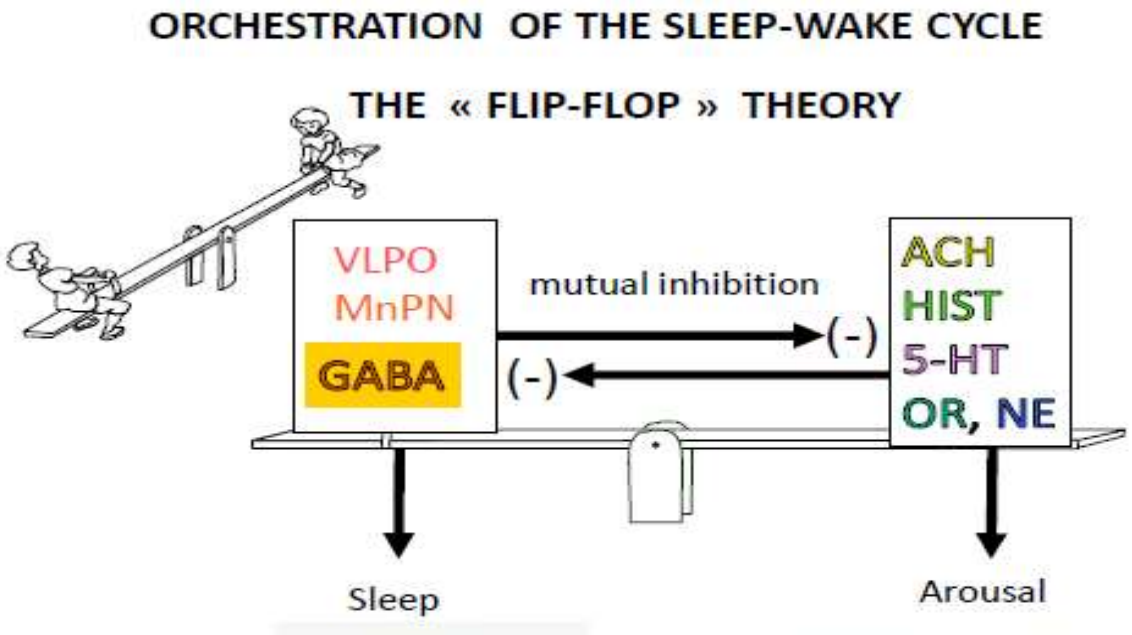
Each neurotransmitter stimulates and inhibits other neurotransmitters

Therefore, when addressing sleep problems, it is often not possible to focus on just one neurotransmitter

Regulation of sleep

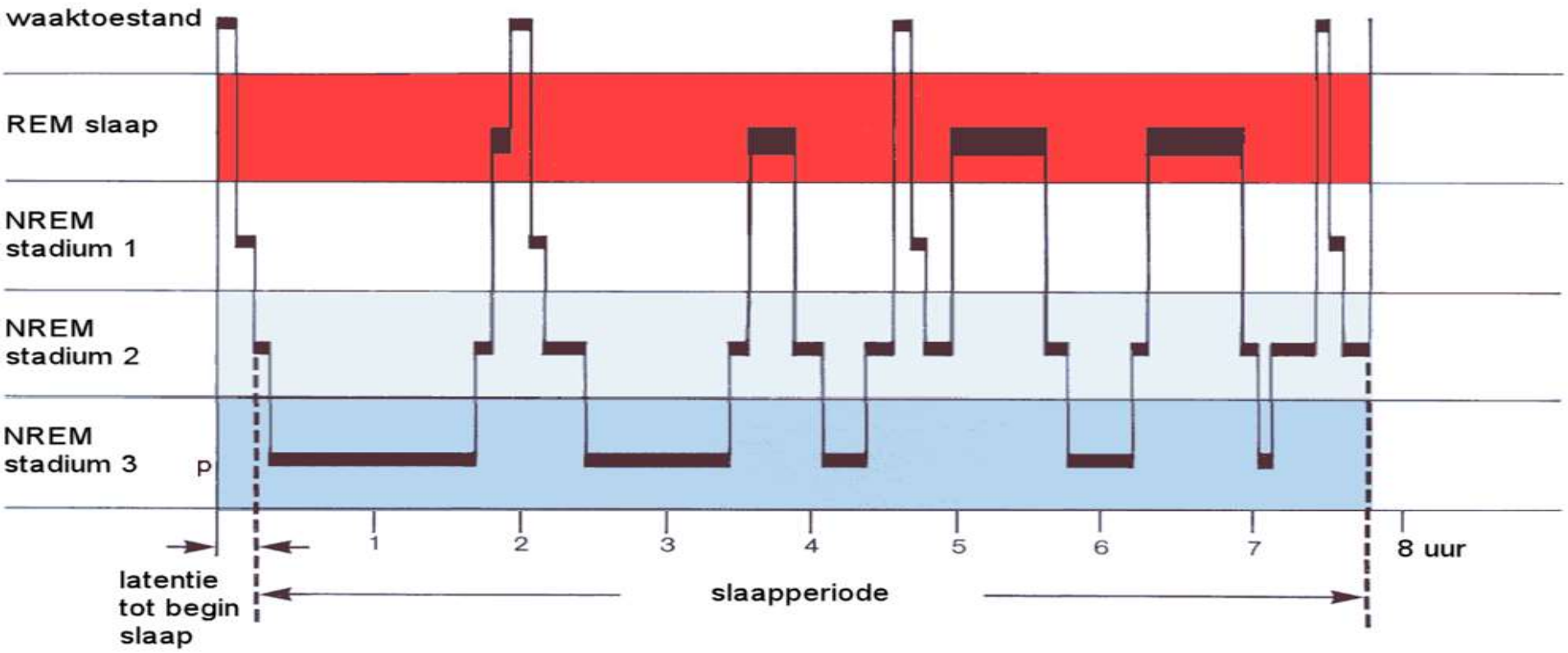
S. Saper et al., 2005





D. Mc Ginty, S. Saper, 2006

Normal sleep: as evidenced by the hypnogram



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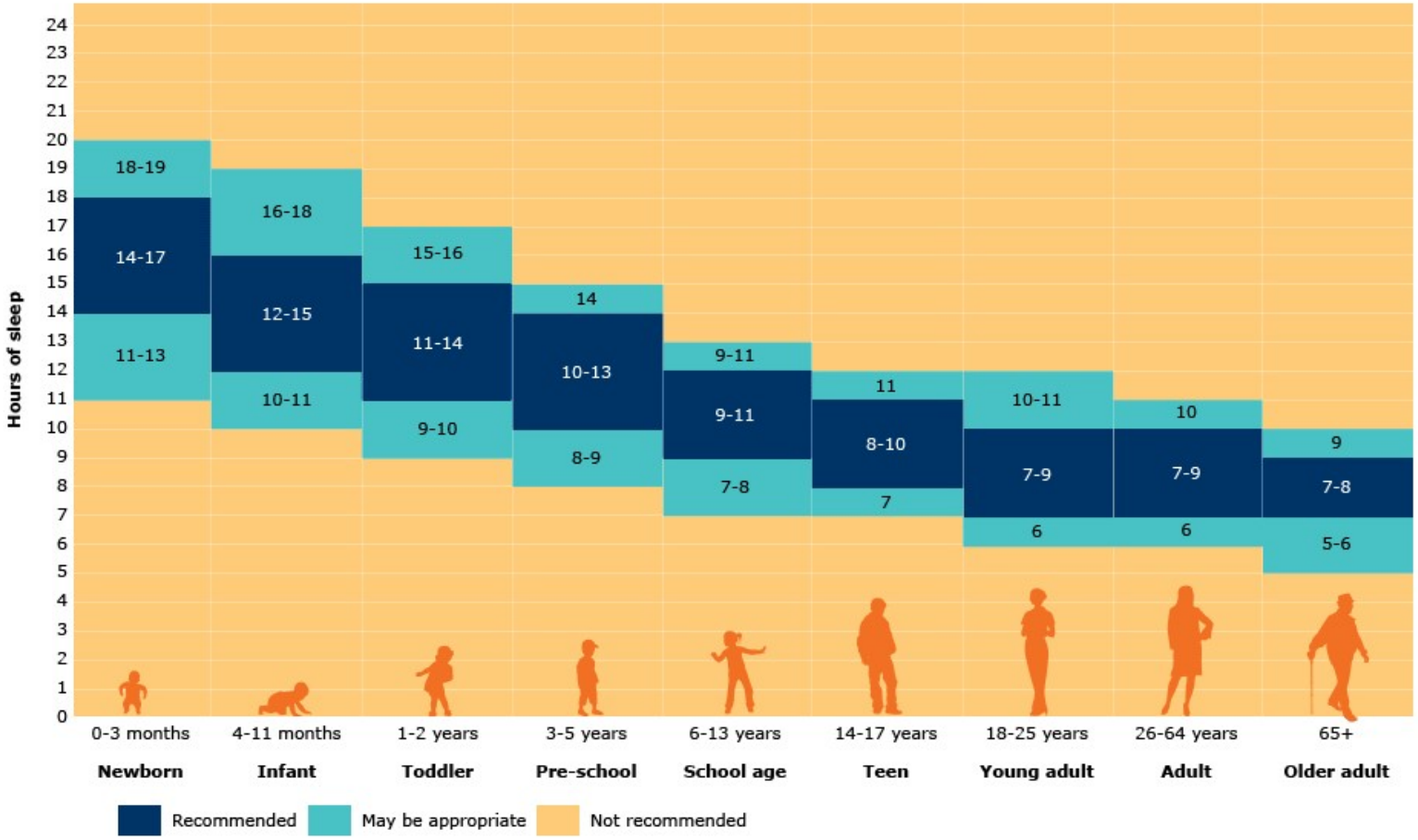
How much should we sleep?

- **Total sleep time** for adults is 7-9 hours for optimal physical, mental and cognitive performance / functioning

Sleep Foundation's sleep time duration recommendations.

Sleep Health.2015



Chronotype

Morning type

Evening type

Neither type

Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan *(Ohayon et al. Sleep 2004)*

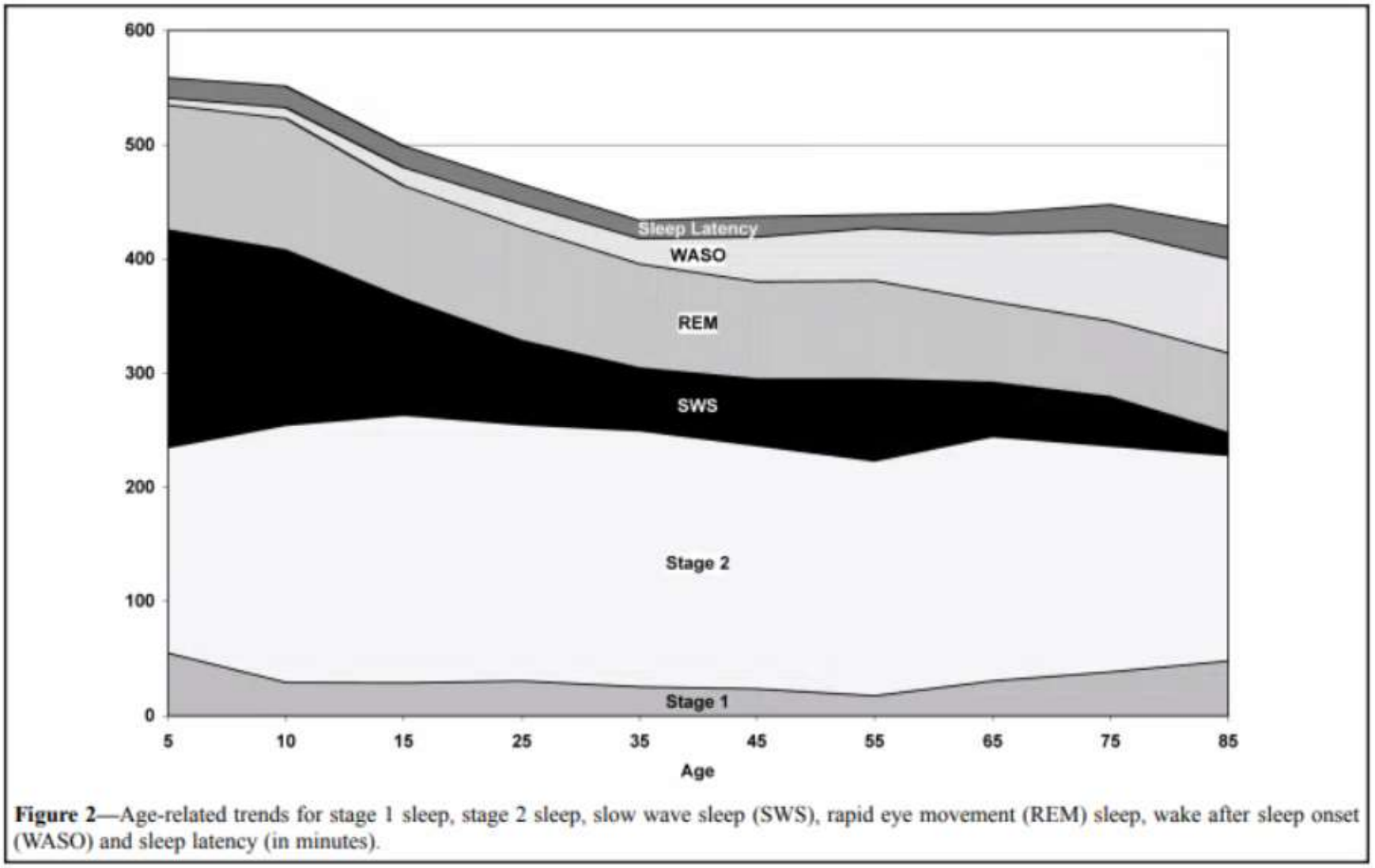


Figure 2—Age-related trends for stage 1 sleep, stage 2 sleep, slow wave sleep (SWS), rapid eye movement (REM) sleep, wake after sleep onset (WASO) and sleep latency (in minutes).

Sleep changes with aging: objective sleep parameters in the elderly

- 2 meta-analyses:
  - N= 3,577 (aged 5-102 years), 65 studies, 1960-2003 *(Ohayon et al., 2004)*
  - N= 5,273, five age subgroups from 18 to 80 years, 169 studies, 2007-2016 *(Boulos et al., 2019)*
  - Exclusion: studies of patients with a pre-existing condition known to affect sleep
- **Sleep parameters that change with age**
  - **Total sleep time (TST)** progressively ↓ ,roughly 10 min per decade
  - **Sleep efficiency (SE)** ↓ *(90-95% in adolescents vs 80% at 70 y)*
  - **Wake after sleep onset (WASO)** ↑ corresponds to the total amount of time spent awake after falling asleep at the beginning of the night. WASO more than doubles in people aged >65 years compared to early adulthood.
  - **Arousal index (ARI)** (number of arousal interruptions of sleep per hour) ↑
  - **Sleep fragmentation** (reflected by WASO and ARI): contribute to feeling of poor sleep and tiredness
  - **Sleep onset latency (SOL)** ↑
  - ↑ in superficial sleep **(N1, N2)**
  - **N3** ↓*Luca et al., 2015)*, lower delta waves and slow wave activity
  - Less intense sleep propensity
  - **REM** sleep shifts to earlier night-time sleep, remains relative stable

Sleep changes with aging: objective sleep parameters in the elderly

- Changes at micro-level: EEG spectral power:
  - Progressive ↓ **SWA** from age of 30 onwards
  - Changes in morphology of **slow waves** (steepness, length and amplitude)
  - Substantial ↓ **SWA** is reflected in structural changes *(loss of synaptic density or strength)*
    - Eg. link with cortical atrophy
    - Cortical atrophy in medial prefrontal cortex: possible neuroanatomical substrate for sleep-related cognitive impairment
    - Associated with impaired overnight sleep-dependent memory retention

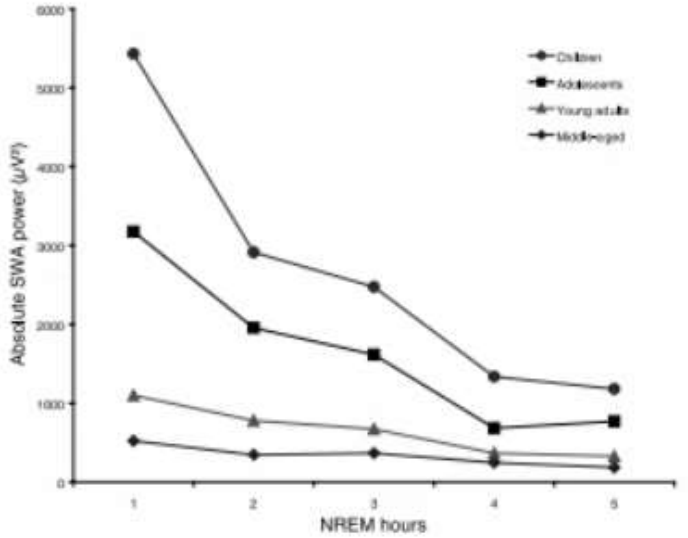


Figure 2. Absolute SWA power across 5 NREM hours for children (●), adolescents (■), young adults (▲) and middle-aged (◆) adults.

Gaudreau et al. 2001; Age-related modifications of NREM sleep EEG

Baillet & Schmidt, 2020

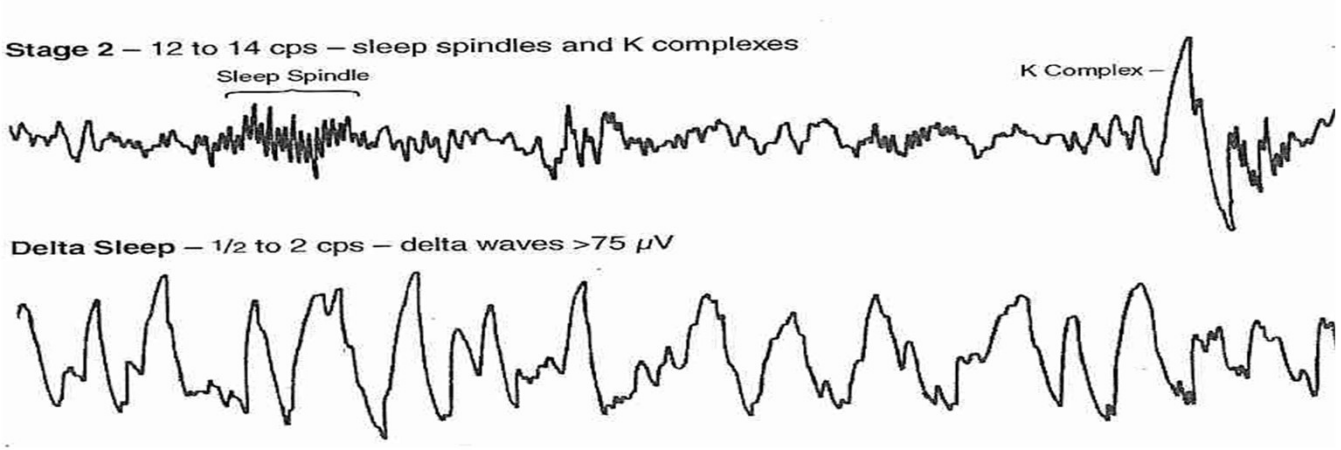
Sleep changes with aging: objective sleep parameters in the elderly

- Changes at micro-level: EEG spectral power:
  - Association between ↓ frontal fast sleep spindles, ↓ sleep-dependent motor memory consolidation and age-related white matter loss

Mander et al., Sleep and Human aging (2017)

  - Declarative Memory consists of memory for events *(episodic memory)* and facts *(semantic memory)*
  - Age related change in sleep spindle parameters possibly related to progressive decline in declarative memory in elderly

Seeck-Hirschner et al. (2012)



Circadian rhythm: Gradually more fragile and unstable with ageing

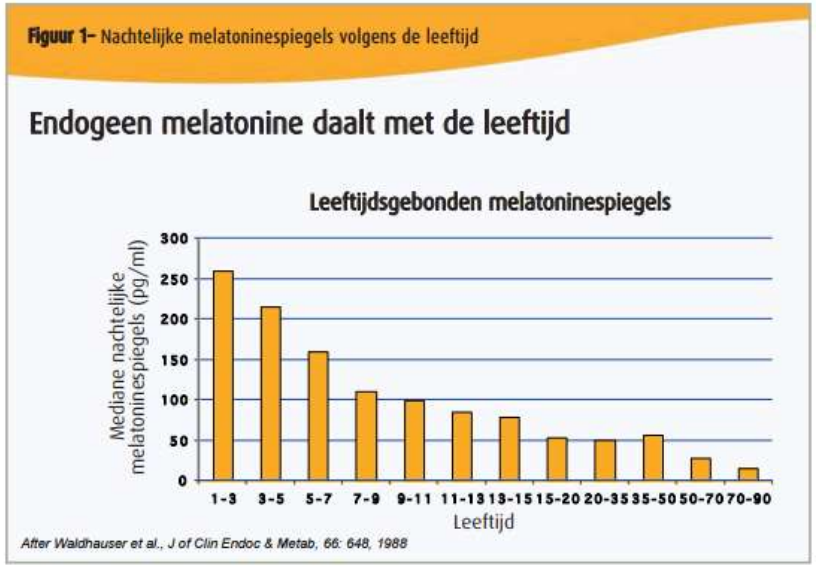
- Overall responsiveness of the circadian system to environmental stimuli **dampens with age** *(Hood & Amir, 2017)*

- Subsequent **consequences** *(Farajnia, Deboer, Rohling, Meijer, & Michel, 2014)*:
  - Reduced and fragmented locomotor activity
  - Phase advance in sleep onset, which occurs up to 1 to 2 hour earlier than in younger individuals
  - Decline of the ability to reset the circadian clock on the dark-light cycle leading to difficulties in adjusting to phase shifts (shift work, jetlag, legal variations of standard clock time during summer or winter)

- Complex regulatory mechanisms: age-related effects on cc system occur in multiple ways affecting each part of these pathways and their respective feedback loops
  - On the **input side**:
    - Reduction of light transmission through the eyes (cataract and other eye diseases)
    - Deterioration of the intrinsically photosensitive retinal ganglion cells responsible for providing light information to the SCN
  - **Asymptomatic atherosclerosis**: ↓ energy supply to the anterior hypothalamus
  - Decline of SCN cells caused by oxidative stress + accumulation of endogenous reactive oxygen/nitrogen species *(Pandi-Perumal, Monti, & Monjan, 2009)*

Circadian rhythm: Gradually more fragile and unstable with ageing

- ↓ nocturnal **melatonin secretion**
- Circadian variations of the SCN influence **hormonal secretions** *(Morris, Aeschbach, & Scheer, 2012)*
  - For example: **cortisol** secretion peak with a phase advanced onset resulting in sleep fragmentation due to its inherent arousal effect
- ↓**testosterone** in ♂ and ↓**oestradiol** in ♀ associated with fragmented sleep and difficulty in falling asleep *(Li, Vitiello, et al., 2018; Morris et al., 2012)*



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Changing sleep during life in women

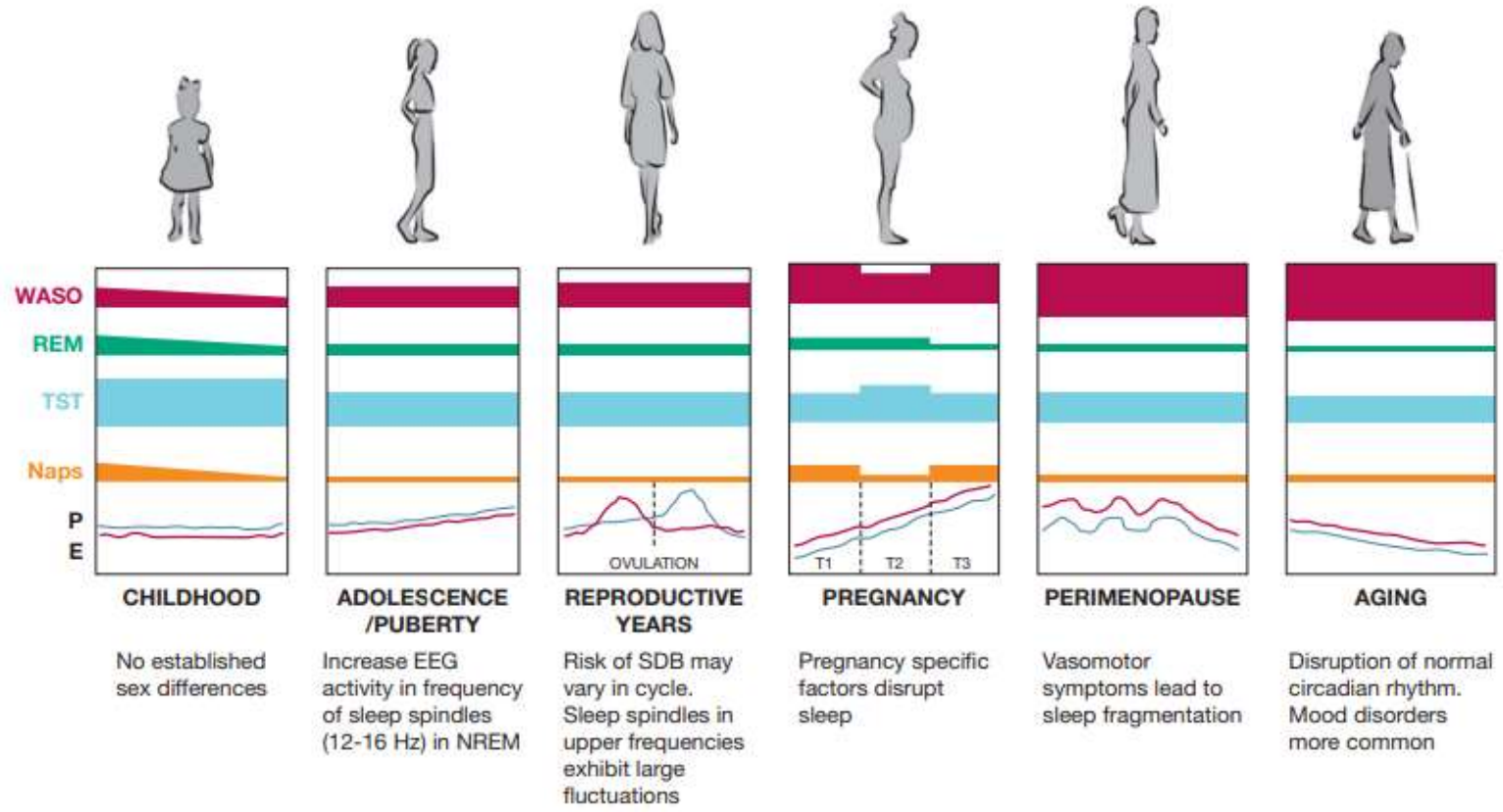


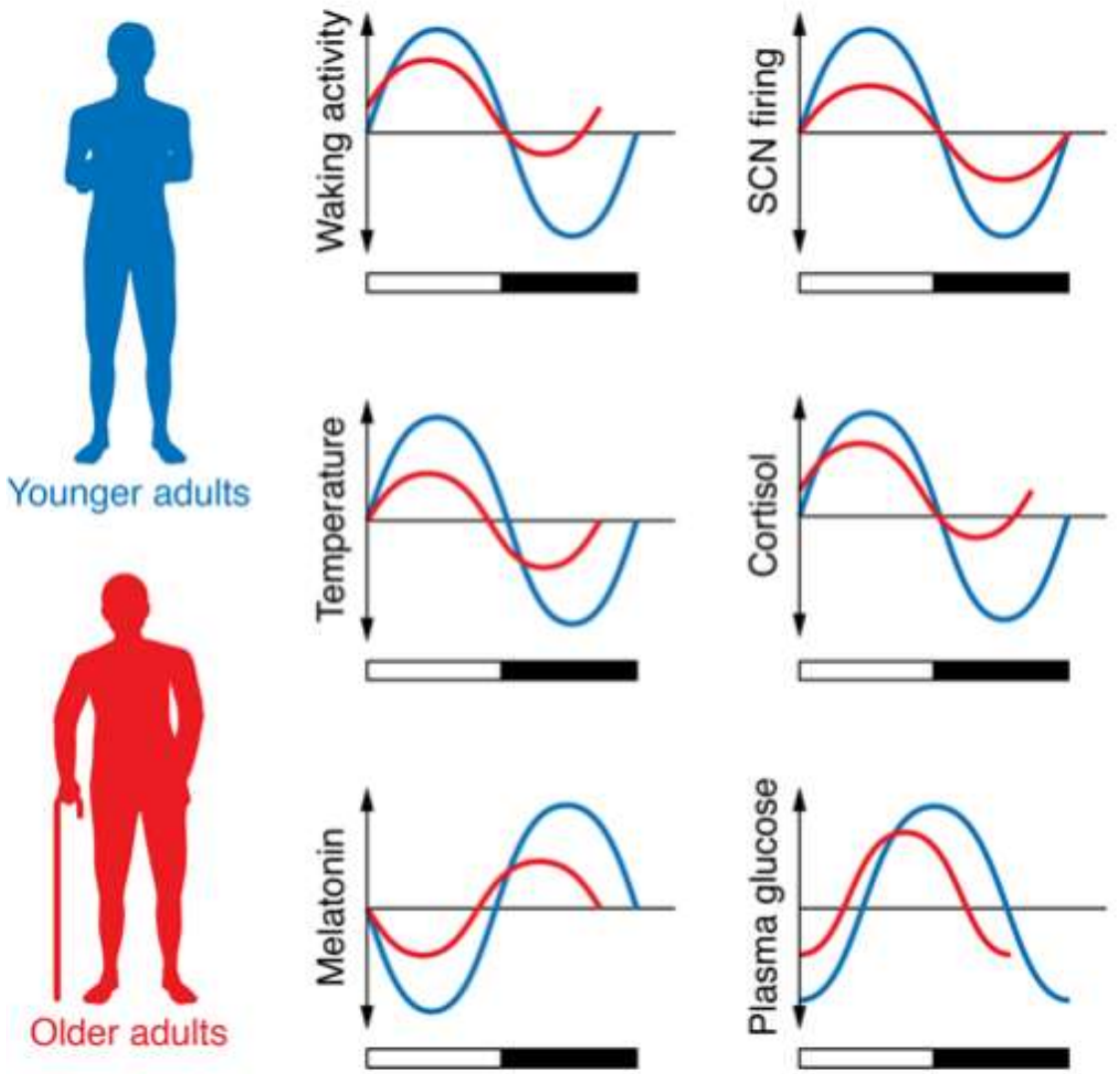
Figure 1 – *Sleep in women across the life span. E = estrogen; NREM = non-rapid eye movement; P = progesterone; REM = rapid eye movement; SDB = sleep-disordered breathing; T = trimester; TST = total sleep time; WASO = wake after sleep onset.*

Pengo et al. (2018) Chest. Sleep in women across the life span

The aging clock: circadian rhythms and later life

(Hood and Amir, J of Clinical Investigation 2017)

- Examples of circadian rhythms in older adults relative to rhythms in younger adults. In the 24-hour cycle, documented changes include rhythms of waking activity; core body temperature; SCN firing; release of hormones, such as melatonin and cortisol; and fasting plasma glucose levels. Relative to younger adults (blue lines), the amplitude of many rhythms dampens in older adults (red lines). In some cases, the peak of the rhythm also advances.



Sleep changes with aging: objective sleep parameters in the elderly

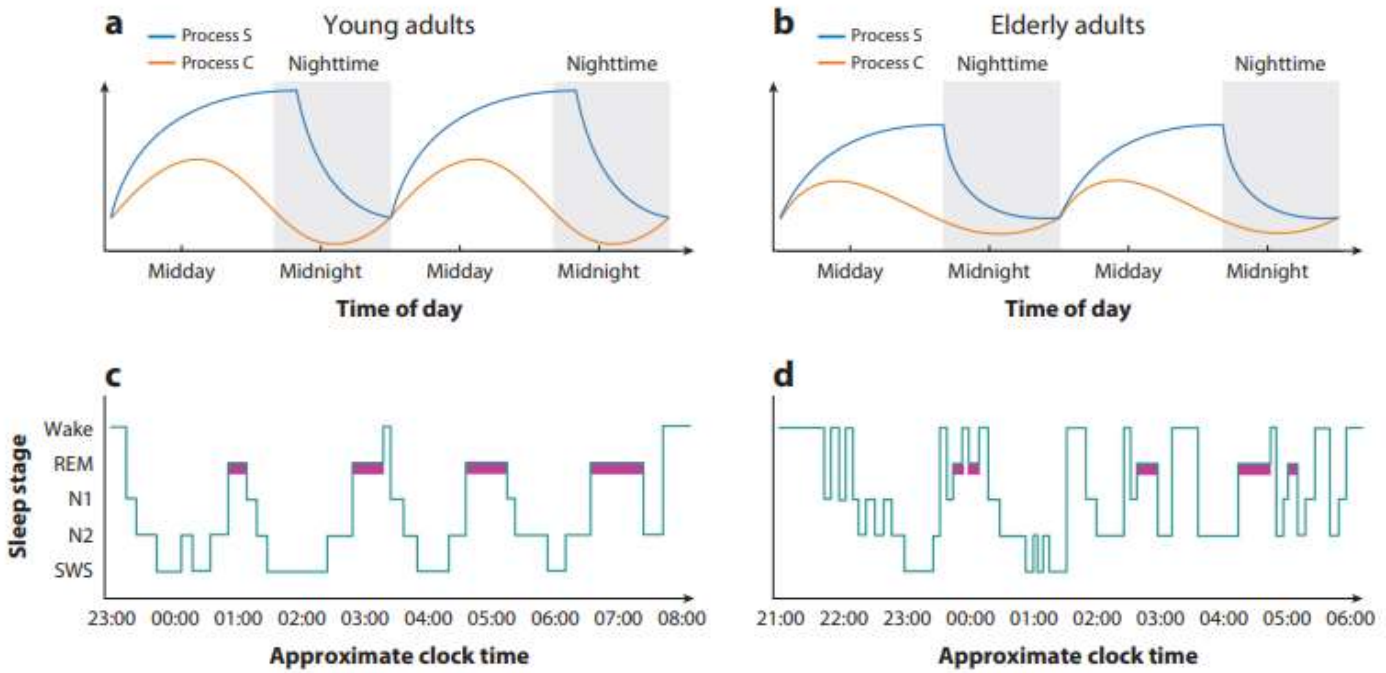


Figure 2

Schematics of sleep processes in young and elderly adults. Compared with younger adults (*a*), elderly adults (*b*) exhibit a blunted (lower amplitude) homeostatic drive to sleep (Process S, *blue line*), which peaks earlier in the night. The circadian Process C (*orange line*) of elderly people (*b*) is also reduced in amplitude and peaks earlier in the day than in younger adults (*a*). (*c*,*d*) Sleep architecture reflects these changes. Compared with younger adults (*c*), elderly adults (*d*) go to bed earlier, have a longer sleep latency, exhibit more fragmented sleep with increased transitions between sleep/wake stages, and spend more time awake (WASO) and less time asleep (especially in SWS). Abbreviations: N1, non-rapid eye movement sleep stage 1; N2, non-rapid eye movement sleep stage 2; REM, rapid eye movement; SWS, slow-wave sleep; WASO, wake after sleep onset. Figure adapted from References 3, 203, and 204 and from images created with Biorender.com.

Kron et al. 2023 Orexin Receptor Antagonism: Normalizing Sleep Architecture in Old Age and Disease

The aging clock: circadian rhythms and later life

(Hood and Amir, J of Clinical Investigation 2017)

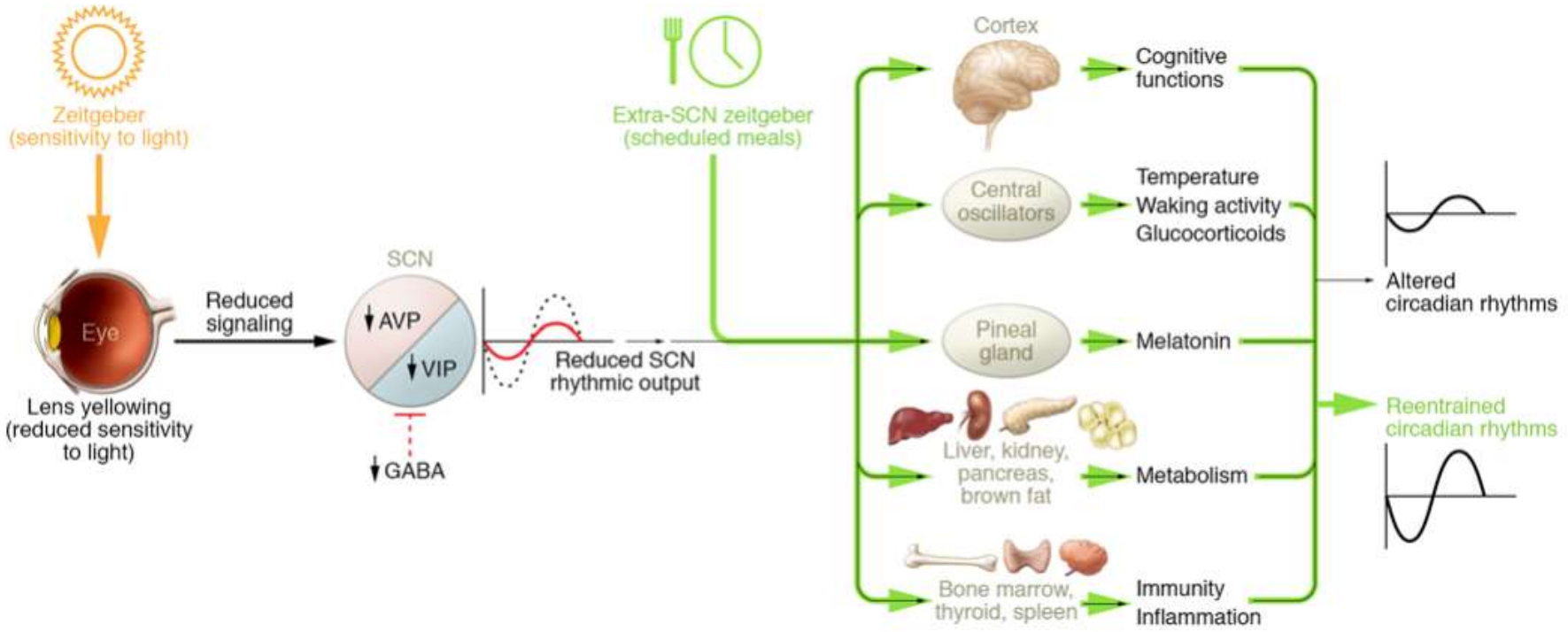
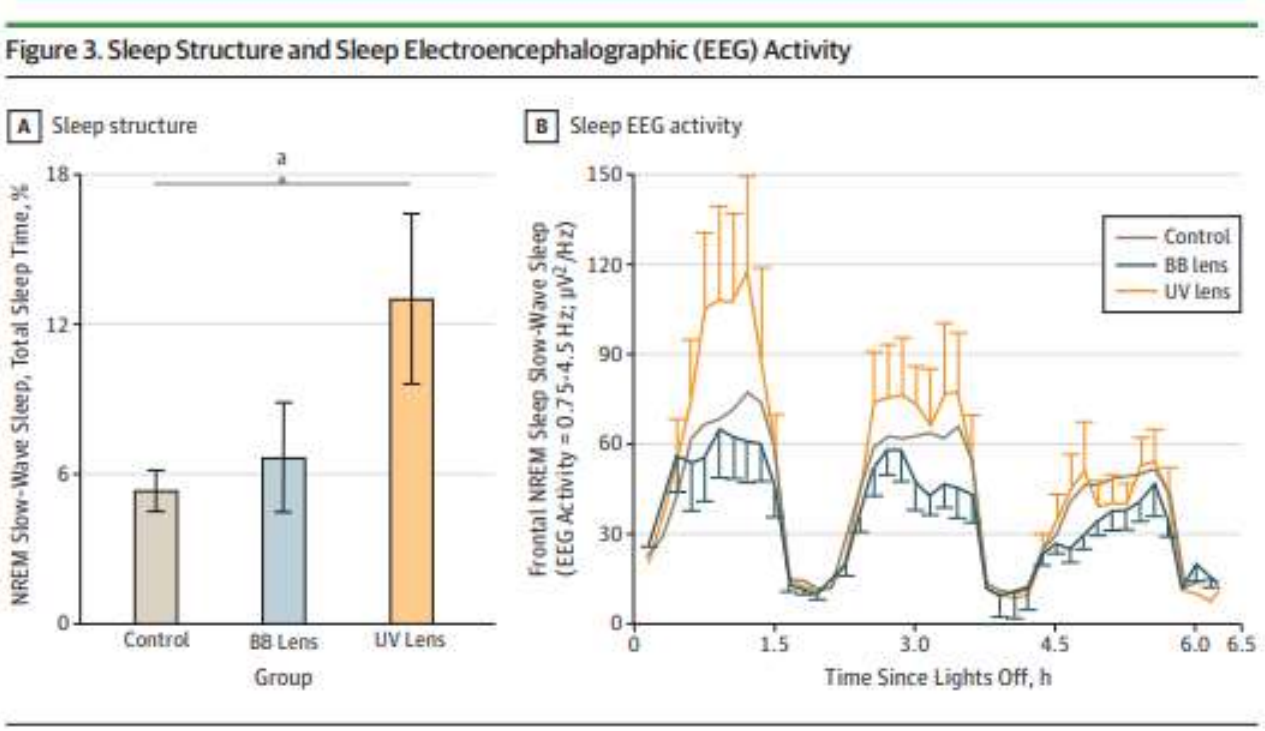


Figure 3. Schematic of possible mechanisms underlying age-related changes in circadian rhythms. Progressive yellowing and thickening of the lens may reduce sensitivity to light, the strongest zeitgeber. Reduction of AVP and VIP expression and fewer GABAergic synapses may decrease signaling within the SCN, leading to a decrease in the overall amplitude of its firing rhythm. A weaker SCN output signal may in turn reduce the strength of downstream oscillators in central and peripheral tissues, including the cortex, pineal gland, liver, kidney, thyroid, and spleen. Providing other zeitgebers such as scheduled meals (green arrows), which act on the circadian system via extra-SCN pathways, may help entrain an aging circadian system.

Circadian and homeostatic changes of sleep in the elderly

- After cataract surgery observation of improvement of sleep quality, melatonin sensitivity and cognitive function

Chellappa et al., 2019



Association of intraocular cataract lens replacement with sleep structure (slow-wave sleep) (A) and sleep EEG activity (slow-wave activity) (B). B, EEG activity = 0.75 Hz to 4.5 Hz; μV^2/Hz. Data are reported as mean (standard error of the mean). BB indicates blue blocking; NREM, non-rapid eye movement; UV, ultraviolet.

[a] $P < .05$ (see Results section for more information).

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Sleep and age: diagnostic assessment

- Mandatory thorough medical history for elderly patients with sleeping problems
- Including medical, pharmacological, mental and social dimensions (referring to framework of geriatric assessment)
- **Necessary because of the many complex links between most sleep-patterns (short versus long sleepers, sleepiness and naps), specific sleep disorders (OSA, insomnia, RLS), co-morbidities, autonomic dysfunction and cardiovascular risk and mortality**

History taking

- Reports about hours sleeping and quality of sleep frequently biased by very individual expectations and subjective perceptions
- Correlations with objective findings often unconvincing
- Issues to be addressed in first interview
  - Chronicity/duration
  - Daytime sleepiness
  - Napping behaviour
  - Sleeping pills or drinks
  - Time of going to bed
  - Sleep latency
  - Nocturnal awakening
  - Time waking up and getting up
  - Restless legs
  - Sleep hygiene
  - Bed partner and carer interview about snoring and apnea, vocalizations and movements during sleep

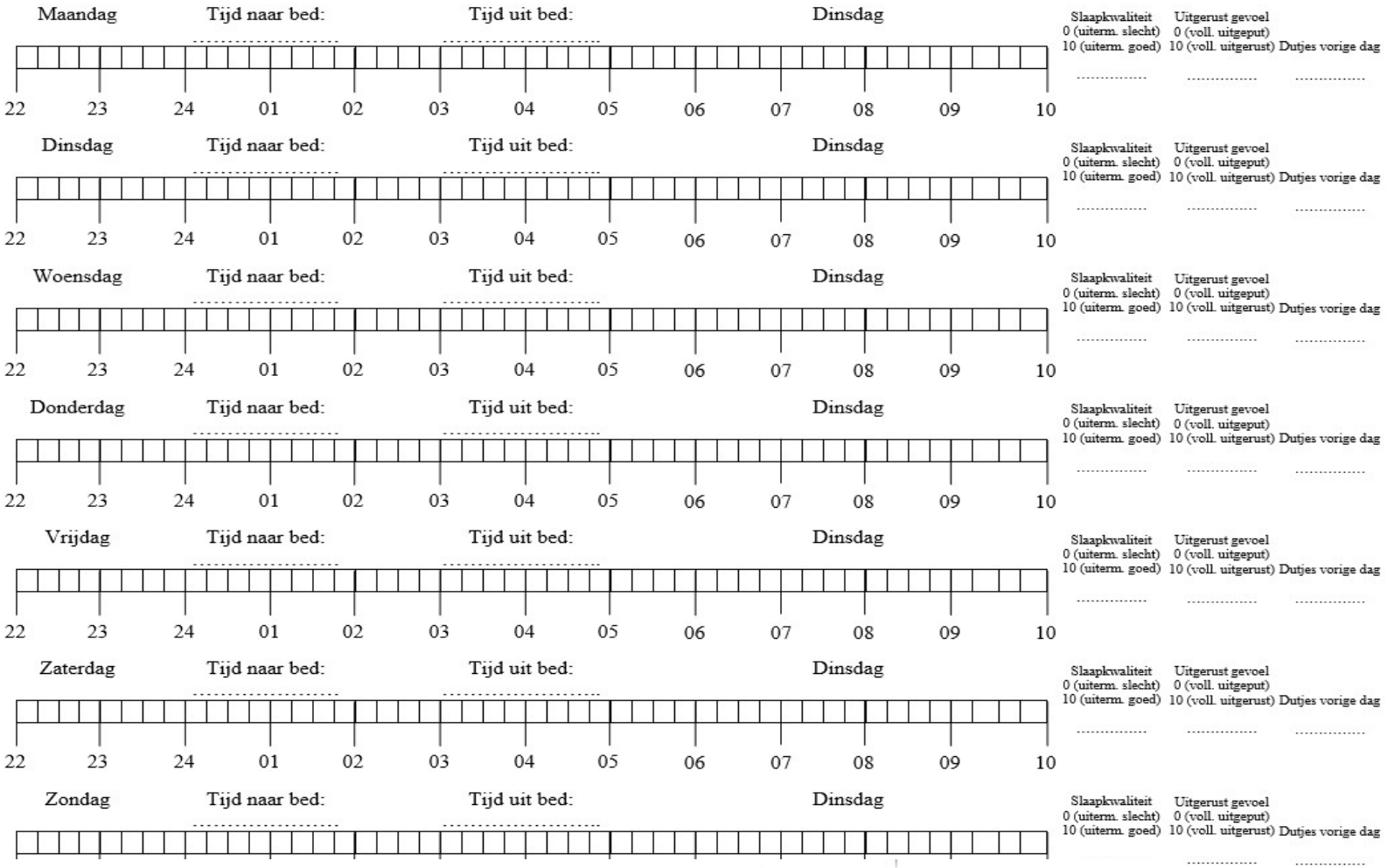
Assessment of sleep: subjective questionnaires

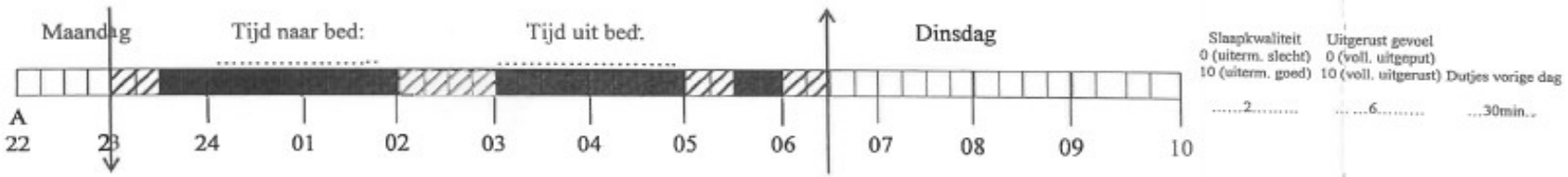
- Limited contribution
- Subjective questionnaires not necessarily represent specific characteristics of insomnia in advanced age
- **Limited section** of most common **sleep questionnaires** *(e.g. PSQI, ISI, ESS, SF-36)* specifically adapted to elderly *(Luyster et al, 2015)* or validated for patients with dementia *(Frohnhofe et al, 2020)*
- On the other hand, **sleep diary** essential in documenting and treating insomnia and other sleep disorders, in order to document sleepiness and daytime naps, time to bed, time spent in bed between waking up and getting up
- Beware of **potential symptom aggravation** due to fixation and neurotic documentation; similar consideration for technical devices and actigraphy
- PSG for objective measurements
- ECG and 24 hr blood pressure recording to identify autonomic hyperactivity with high heart rates and non-dipping or serious BP nocturnal dipping

ESRS Sleep Medicine Textbook 2021

Subjective assessment of sleep: sleep log

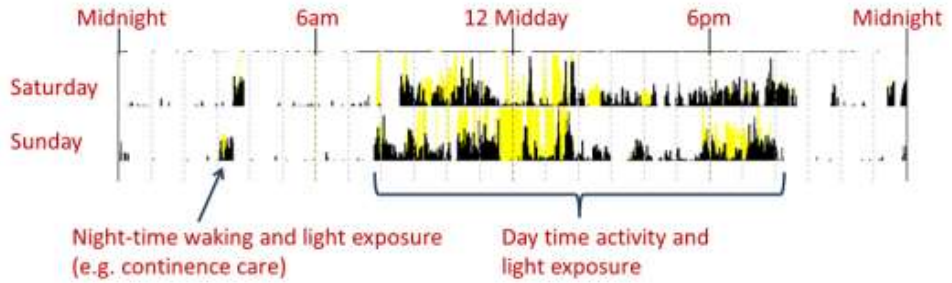
Verbeek I., Kempenhaeghe, CSW, Heeze, The Nederlands





Subjective assessment of sleep: sleep log

- **Activity trackers**
  - Non-intrusive
  - Measures the amount of sleep over longer periods



- **Polysomnography ± multiple sleep latency test :**
  - EEG, EOG, EMG, chest and abdominal movements, transcutaneous oxygen saturation, oronasal air flow, noise/phonometr, video, pulse rate, body position

Outline

- Some basic physiology: sleep homeostasis and circadian rhythm
- Sleep changes with ageing
- Diagnostic assessment
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  - **Insomnia and psychiatric comorbidity**
  - Sleep disordered breathing
  - RLS
  - RBD and other parasomnias
- Non-pharmacological interventions
  - Do not forget environmental factors
- Impact of medication
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DSM-5 Insomnia Disorder: Diagnostic Criteria

A. Predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:

   1. Difficulty initiating sleep. (> 30 minutes)
   2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (SE < 85%)
   3. Early-morning awakening with inability to return to sleep (< 6 ½ hr sleep)

B. Sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral or other important areas of functioning.

C. Sleep difficulty occurs at least 3 nights per week

D. Sleep difficulty is present for at least 3 months

E. Sleep difficulty occurs despite adequate opportunity for sleep

F. Insomnia not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia)

B. Insomnia not attributable to physiological effects of a substance (e.g., a drug of abuse, a medication)

C. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia

Prevalence of chronic insomnia disorder, ICSD-3)

Table 5 Prevalence of insomnia disorder in different European countries

Country	*Author (year)*	*Sample size*	*% Insomnia diagnosis*
England	Calem *et al.* (2012)	20 503	5.8%
Finland	Ohayon and Partinen (2002)	982	11.7%
France	Léger *et al.* (2000)	12 778	19%
Germany	Schlack *et al.* (2013)	7988	5.7%
Hungary	Novak *et al.* (2004)	12 643	9%
Italy	Ohayon and Smirne (2002)	3970	7%
Norway	Pallesen *et al.* (2001, 2014)	2000	15.5%
Romania	Voinescu and Szentágotai (2013)	588	15.8%
Spain	Ohayon and Sagales (2010)	4065	6.4%
Sweden	Mallon *et al.* (2014)	1550	10.5%

Riemann D. et al. 2017, J Sleep Res. European Insomnia Guideline

Insomnia is a common sleep problem among the old people, with an overall prevalence reported between 30% and 50%

Dopheide, 2020; Patel, Steinberg, & Patel, 2018

Screen in the broad spectrum of conditions associated with insomnia

TABLE 5 Major medical comorbidities or contributory factors to chronic insomnia

Mental	Medical	Neurological	Substance use/dependence
Depressive disorders	Cardiovascular disorders	Neurodegenerative diseases	Alcohol
Bipolar disorders	Diabetes mellitus	Cerebrovascular diseases	Nicotine
Anxiety disorders	Chronic kidney diseases	Traumatic brain injury	Caffeine
Borderline personality disorder	Chronic obstructive pulmonary diseases	Multiple sclerosis	Tetrahydrocannabinol /marihuana
Posttraumatic stress disorder	Rheumatic disorders	RLS/PLMD	Opioids
Schizophrenia	Chronic pain	Fatal familial insomnia	"Designer" drugs
Substance use disorders	Any kind of malignant disorder		Cocaine
	SRBD/OSA		Amphetamines

Abbreviations: OSA, obstructive sleep apnea; PLMD, periodic limb movement disorder; RLS, restless legs syndrome; SRBD, sleep-related breathing disorder.

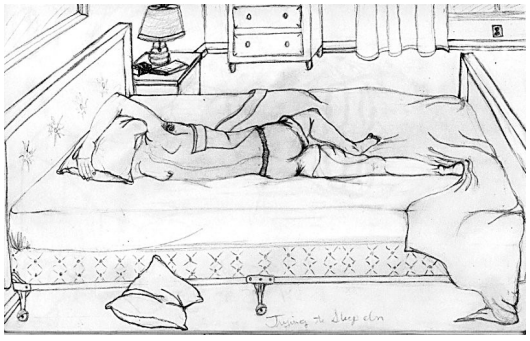
Riemann D. et al. 2023, J Sleep Res. European Insomnia Guideline: An update

Insomnia: increased risk of a variety of conditions

Table 2 Insomnia at HUNT2 as a risk factor for reporting conditions/disorders 11 years later at HUNT3

	Risk factor: Insomnia at HUNT2					
	Unadjusted model		*Adjusted model**		*Adjusted model†*	
Disorder/condition (HUNT3)	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Physical conditions						
Angina	**1.72**	1.38–2.14	**1.75**	1.39–2.20	**1.52**	1.19–1.94
Arthrosis	**2.45**	2.19–2.75	**2.10**	1.85–2.37	**1.83**	1.61–2.08
Asthma	**1.70**	1.47–1.98	**1.68**	1.44–1.95	**1.46**	1.25–1.71
Ankylosing spondylitis	**1.94**	1.42–2.66	**1.96**	1.43–2.70	**1.68**	1.20–2.36
Cancer	**1.32**	1.09–1.60	1.15	0.94–1.39	1.20	0.98–1.47
Diabetes (type 2)	1.12	0.90–1.41	1.04	0.83–1.31	0.99	0.77–1.26
Fibromyalgia	**5.91**	5.09–6.85	**5.16**	4.42–6.02	**3.76**	3.19–4.45
Headache	**1.93**	1.72–2.15	**2.20**	1.96–2.47	1.86	1.64–2.10
Hypertension	**1.28**	1.15–1.44	1.09	0.97–1.23	1.04	0.92–1.18
Myocardial infarction	**1.30**	1.01–1.68	**1.42**	1.09–1.85	**1.35**	1.02–1.78
Obesity (BMI > 30)	**1.23**	1.10–1.38	**1.18**	1.06–1.33	1.09	0.97–1.24
Osteoporosis	**2.55**	2.08–3.12	**1.86**	1.50–2.30	**1.61**	1.28–2.03
Rheumatoid arthritis	**2.45**	2.01–2.97	**2.17**	1.79–2.64	**1.91**	1.55–2.36
Stroke	**1.72**	1.33–2.21	**1.50**	1.24–2.07	**1.33**	1.02–1.75
Whiplash	**2.35**	1.92–2.87	**2.45**	2.00–3.00	**1.92**	1.54–2.38
					Adjusted model‡	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Mental disorders						
Anxiety	**3.81**	3.38–4.28	**3.75**	3.33–4.23	**3.07**	2.67–3.55
Depression	**3.17**	2.78–3.63	**3.12**	2.73–3.57	**2.68**	2.28–3.14
Mental disorder (seeking help for)	**3.60**	3.45–4.33	**3.80**	3.38–4.26	**3.05**	2.64–3.52

BMI, body mass index; HUNT, Nord-Trøndelag Health Studies; CI, confidence interval; OR, odds ratio.
Statistically significant associations highlighted in bold type.
*Adjusted for demographics (age, gender and education).
†Adjusted for demographics + anxiety and depression at baseline.
‡Adjusted for demographics + angina, arthrosis, asthma, ankylosing spondylitis, cancer, diabetes (type 2), fibromyalgia, headache, hypertension, myocardial infarction, obesity (BMI > 30), osteoporosis, rheumatoid arthritis, stroke and whiplash at baseline.



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Sleep-disordered breathing (SDB)

- Prevalence ↑ age:
  - 20 % *(Posadas et al, 2020)* to 63 % *(Attier-Zmudka et al, 2019)* in elderly
  - High prevalence rates reported in different forms of dementia
- Contributing factors:
  - reduced pharyngeal muscle tone
  - anatomical changes in upper airways
  - iatrogenic factors:
    - (inadvertent) use of benzodiazepines and opiods
- A mild to moderate increase in OAHI not always clinically significant

  (Feinsilver and Hernandez, 2017)
- EDS important pointer towards symptomatic SDB
- Frequent association of SDB with cognitive impairment *(Mubashir et al, 2019)*
- OSA and CSA are to be considered in old age, both causing intermittent nocturnal hypoxia and sleep fragmentation

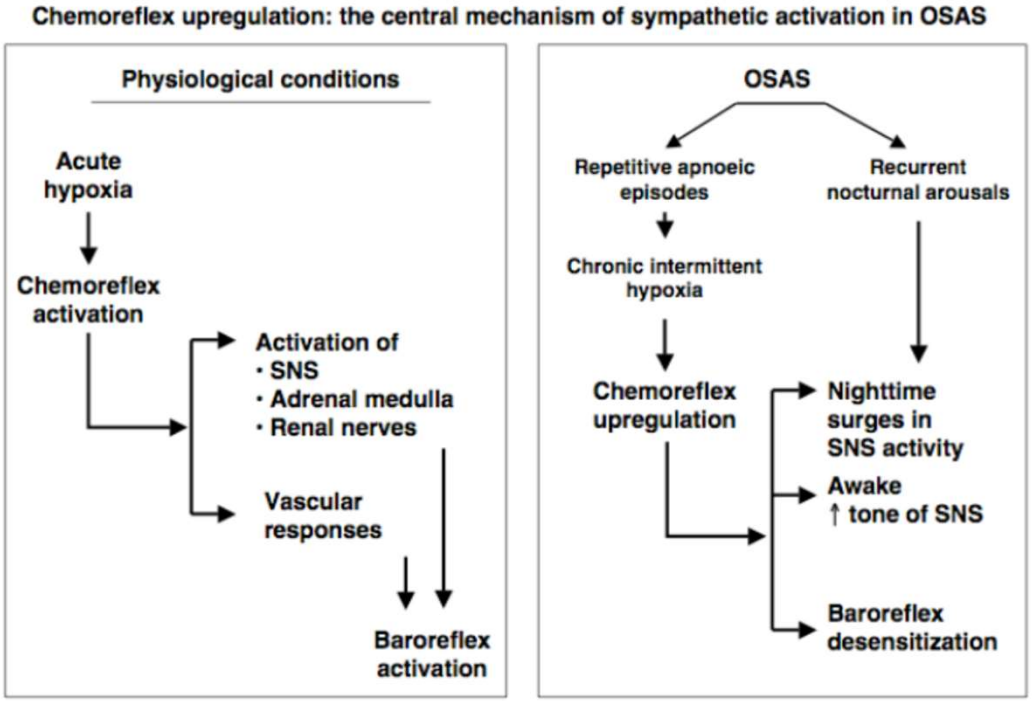

Fig. (1). Chemoreflex upregulation: the central mechanism of sympathetic activation in obstructive sleep apnoea syndrome (OSAS). In physiological conditions, when acute hypoxia develops, chemoreceptors are activated with consequent transient cardiovascular and respiratory changes, activation of the sympathetic nervous system, adrenal medulla and renal artery nerves, and a vascular response. Baroreflex also intervenes to antagonize the effects on the sympathetic nervous system (SNS). In OSAS, chronic exposure to intermittent hypoxia causes chemoreflex sensitization to hypoxia. This chemoreflex hyperactivity is the main mechanism that mediates sympathetic activation, which is not limited to the nocturnal surges provoked by apnoeic episodes and arousals, but extents to the whole day. Concomitantly to chemoreflex sensitization, baroreflex desensitization occurs [149].

Greco C., Spallone V. Obstructive sleep apnoea syndrome and diabetes. Fortuitous association or interaction? **Curr Diabetes Rev 2015**, 12(2):129-55.

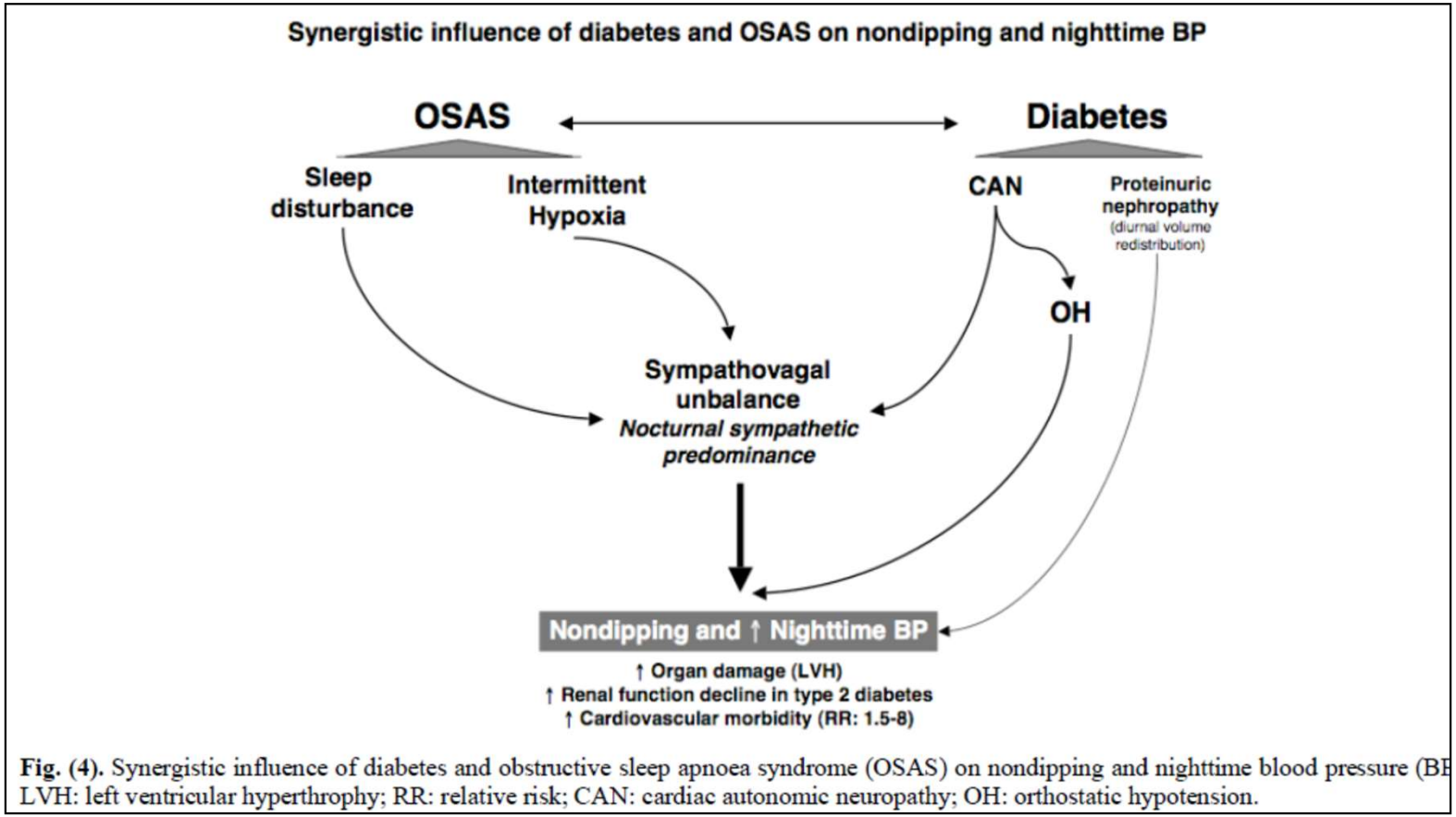

Fig. (4). Synergistic influence of diabetes and obstructive sleep apnoea syndrome (OSAS) on nondipping and nighttime blood pressure (BP LVH: left ventricular hyperthrophy; RR: relative risk; CAN: cardiac autonomic neuropathy; OH: orthostatic hypotension.

Greco C., Spallone V. Obstructive sleep apnoea syndrome and diabetes. Fortuitous association or interaction? **Curr Diabetes Rev 2015**, 12(2):129-55.

Sleep disordered breathing in the elderly

- Linked with negative outcomes (stroke, nocturnal hypertension (non dipping), cardiac failure, atrial fibrillation, type 2 diabetes, EDS and mortality *(Chowdhuri et al, 2018; Ernst et al 2019)*
- Increased risk of Alzheimer's disease *(Richards et al, 2019)*, vascular dementia and all-cause dementia *(Shi et al, 2018)*
- Possible importance of early treatment of symptomatic SDB with both general measures (avoidance of alcohol and sedatives, weight loss) and CPAP *(Bloom et al, 2009)*
  - Possible delay of progression of cognitive impairment *(Osorio et al, 2015)*
  - Similar adherence to CPAP in older and middle-aged adults *(Weaver and Chasens, 2007)* so worthwile to try

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Restless legs (RLS)

- Clinically significant *(at least twice weekly with at least moderate distress)* in 3-5 % > 65 yrs *(During and Winkelman, 2019)*
- Associated with increased risk of falls due to nocturnal wandering *(Kuzniar and Silber, 2007)*
- 80 % associated PLMD *(Gulia and Kumar, 2018)*
- Possible pointers in patients with cognitive impairment unable to verbalize sensory symptoms:
  - signs of discomfort (rubbing or groaning whilst holding the lower extremities)
  - excessive motor activity (kicking, pacing, turning in bed)
- Management:
  - Focus on lifestyle modifications (avoidance of alcohol, moderate physical activity)
  - Reduction of potential iatrogenic factors (stimulating antidepressants and antidopaminergic antipsychotics)
  - Maintenance of high-normal peripheral Fe-stores (ferritin > 70) *(Winkelmann et al, 2017)*
  - Gabapentin and pregabalin first choice; dopamine agonists second choice (augmentation), low dose opioids *(During and Winkelman, 2019)*

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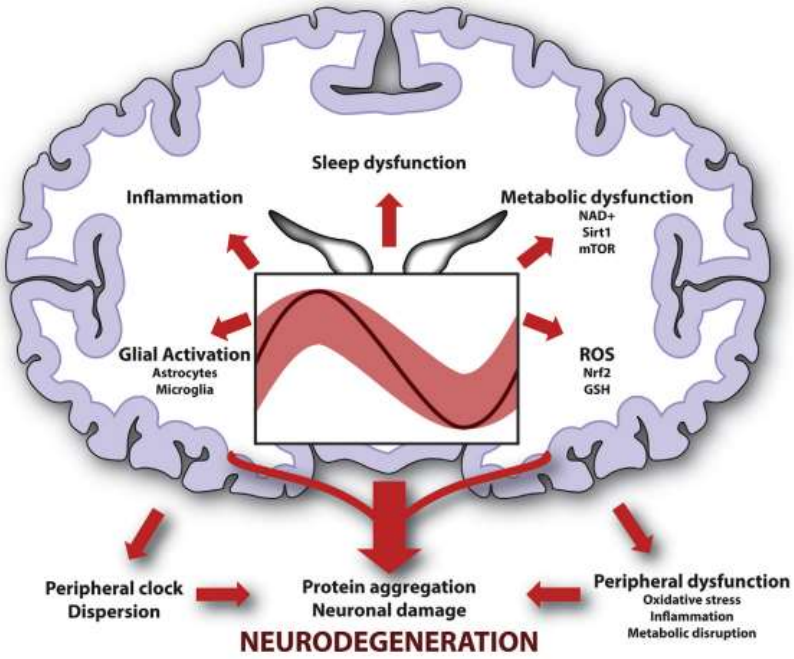
RBD (REM-sleep behavior disorder) and other parasomnias

- When elderly people experience aggressive dreams and start acting out their dreams, RBD should be suspected and confirmed with PSG
- Potentially dangerous for patients and bedpartners, who may be injured by violent movements
- Often harbinger of synucleionopathies, including Parkinson's disease, multiple system atrophy or Lewy body dementia *(Iranzo et al, 2016)*
- Common medical conditions triggering RBD
  - SSRI-TCA-MAO-i
  - Biperiden-Cholinergic medications
  - Rarely abrupt withdrawal of sedative-hypnotic medications or alcohol
  - Excessive caffeine and chocolate consumption *(Stolz and Aldrich, 1991; Verona and Ware, 2002)*
- Symptomatic improvement with clonazepam or melatonin *(Gilat et al. 2020)*
- Differential diagnosis with **other parasomnias** (somnambulism or night terror and pharmacologically induced parasomnias (the latter tending to occur later in life)
- Zolpidem, orexin-antagonists and other sleep-initiating medications may induce sleep walking, sleep driving and sleep-related eating

Sleep and neurodegeneration

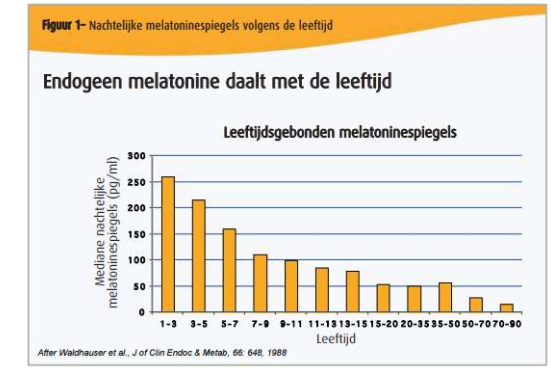
- Disturbances of sleep and circadian rhythms: considered hallmarks of neurodegenerative conditions

- Not only manifestation of disease but also contribute directly to pathogenesis:
  - Oxidative stress
  - Inflammation
  - Glial activation
  - Metabolic dysfunction



Lananna and Musiek 2020

Sleep disorders and dementia



- **Melatonin:**
  - Decreases with age
  - May exert neuroprotective effects (however: very few evidence-based studies)
  - Particularly low in manifest Alzheimer”s dementia *(Cardinali, 2019)*
- **SCN:**
  - Affected in Alzheimer disease *(van Erum, van Dam, & de Deyn, 2018)*
  - Asynchronous expression of clock genes regulating circadian processes between different brain regions in Alzheimer’s disease *(Cermakian et al, 2011)*

Association of sleep duration in middle and old age with incidence of dementia *(Sabia et al. 2021)*

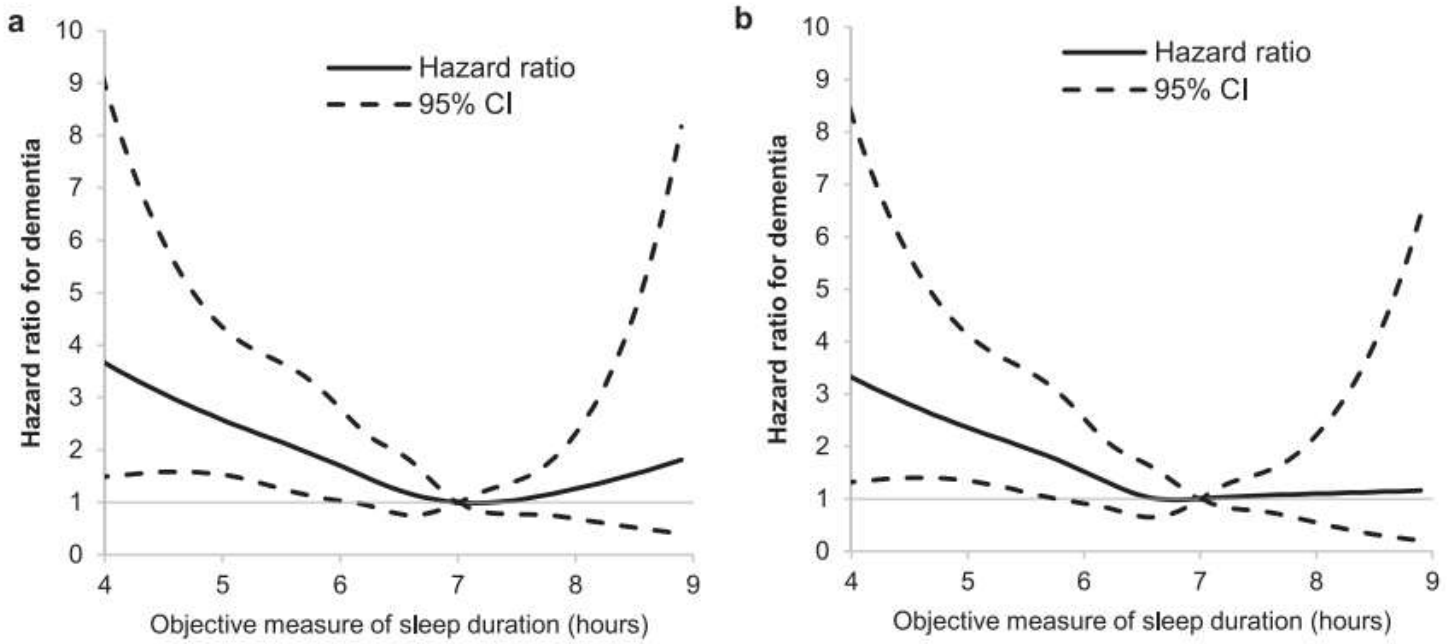


Fig. 2 Association of objectively assessed sleep duration (2012–2013, *N* cases/*N* total = 111/3888) with incident dementia over a mean follow-up of 6.4 (SD = 1.0) years: accelerometer sub-study. a The hazard ratio for dementia (black plain line) with the corresponding 95% confidence interval (black dotted line) as a function of sleep duration from a Cox regression adjusted for age (timescale), sex, ethnicity, education, marital status, alcohol consumption, physical activity, smoking status, fruit and vegetable consumption, BMI, hypertension, diabetes, cardiovascular disease, GHQ depression, and CNS medications (Source data). **b** The hazard ratio for dementia (black plain line) with the corresponding 95% confidence interval (black dotted line) as a function of sleep duration from a Cox regression using inverse-probability weighting to account for missing data and adjusted for age (timescale), sex, ethnicity, education, marital status, alcohol consumption, physical activity, smoking status, fruit and vegetable consumption, BMI, hypertension, diabetes, cardiovascular disease, GHQ depression, and CNS medications (Source data).

Sleep Duration and subsequent cortical thinning in cognitively normal older adults

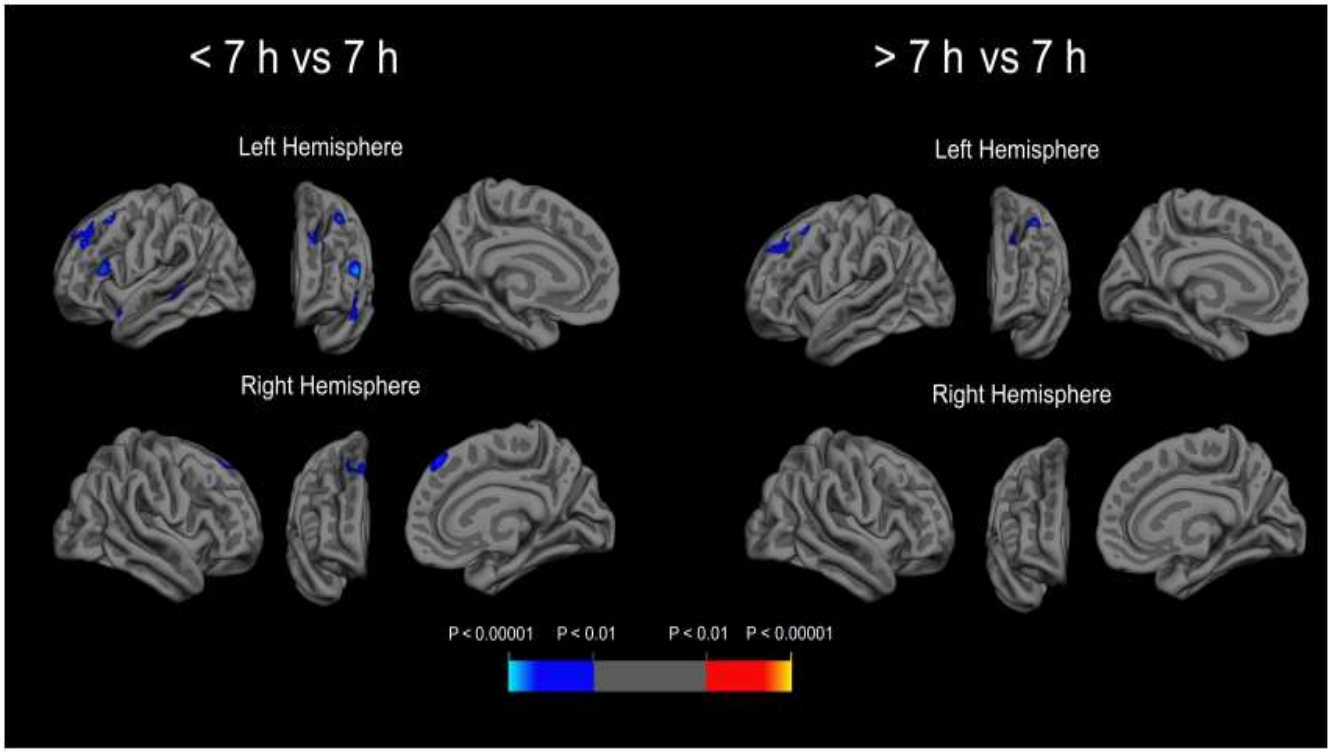


Figure 1—Prospective association of sleep duration with subsequent cortical thinning in cognitively normal older adults. Longitudinal magnetic resonance images (MRIs) from 122 cognitively normal participants indicate faster rates of cortical thinning in frontal and temporal regions among those reporting < 7 h average sleep duration (n = 24) and those reporting > 7 h average sleep duration (n = 50), compared to those reporting 7 h of sleep duration (n = 48) over the prior month. Fixed effects included age, sex, time, interval between sleep assessment and initial MRI scan, education, race, sleep, education × time, race × time, age × time, sex × time, and sleep × time; subject-specific slopes and intercepts were random effects. A primary (vertex-level) threshold of $P < 0.01$ was applied; figure displays regions with a cluster $P < 0.05$.

Prior studies: significant associations between sleep duration and cognitive performance.

Study: N= 122 cognitive normal participants. Mean age + 66,6 years(range, 51-84) at baseline and 69,5 years (range 56-86) at initial MRI scan.

Results: older adults: TST= < 7 h or > 7 h have more rapid cortical thinning in particular brain regions over time, compared to those reporting 7 h of sleep.

Hypothesis: data suggest the possibility that **sleep duration alters rates of neuronal loss.**

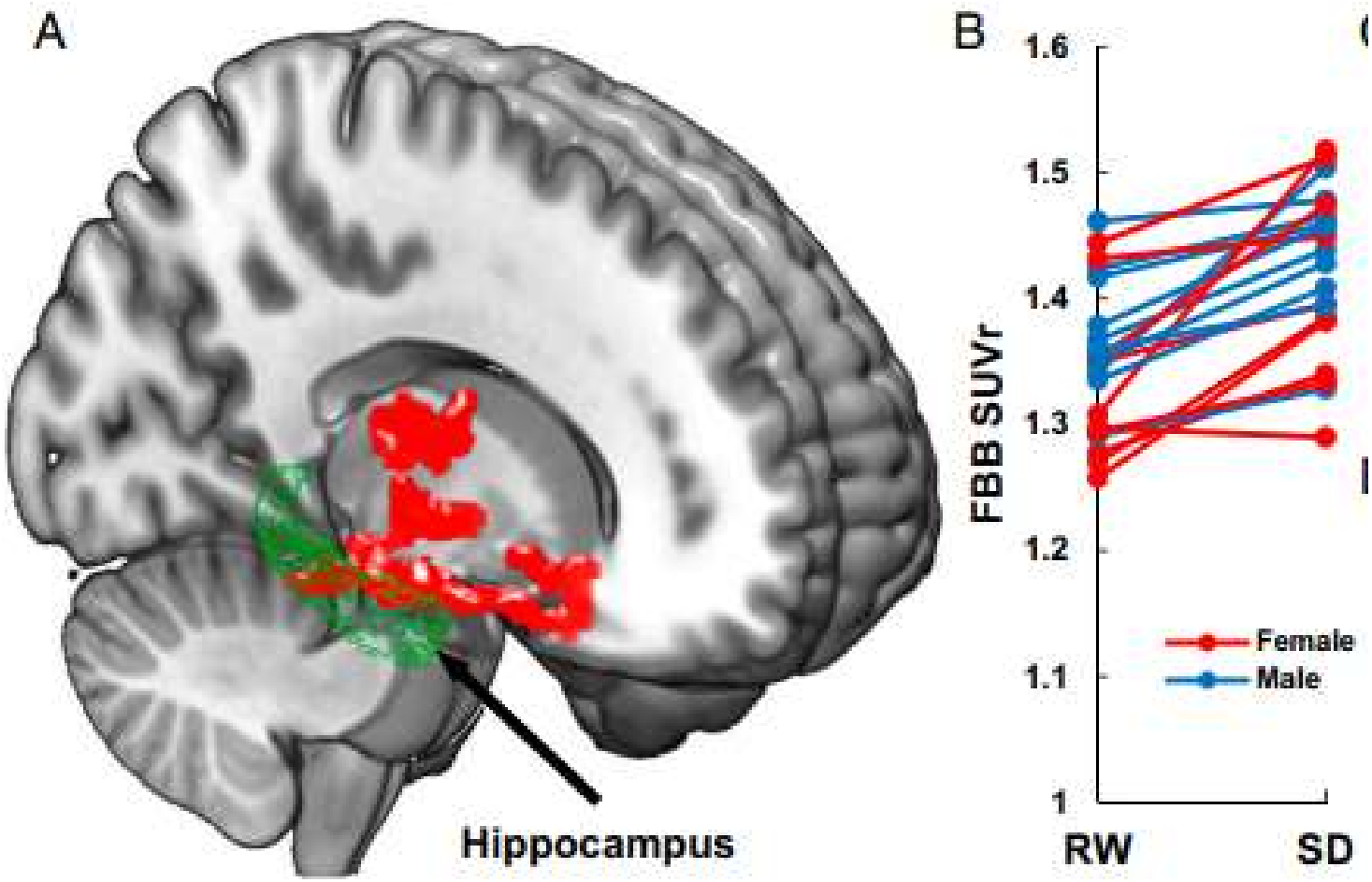
Spira et al. 2016

Sleep disorders and dementia

- Strong and bidirectional relationship between disturbed sleep and neurodegeneration *(Busche et al, 2017)*

- Several sleep-related risk factors:
  - OSA *(Buratti etal, 2016; Lutsey et al, 2018; Mansukhani et al, 2019) as an example of a bidirectional relationship*
  - Mid- and late-life insomnia *(Sindi et al, 2018)*
  - Daytime sleepiness *(Smagula et al, 2019)*
  - Napping *(Leng et al, 2019)*
  - Long sleep duration in elderly *(Sindi et al, 2018)*
  - Nighttime sleep disruption *(Grimmer et al, 2020; You et al, 2019)*
- Have a variety of negative somatic, mental and social consequences:
  - cardiovascular disease
  - increased all cause mortality *(Petrovic et al, 2019)*
  - dementia *(Shi et al, 2018)*
  - beta-amyloid accumulation *(Busche et al, 2017; Carvalho et al, 2018)*

β-Amyloid accumulation in the human brain after one night of sleep deprivation *(Shokri-Kojori et al. 2018)*



Circadian and homeostatic changes of sleep in the elderly

- **What about dementia?**
  - The glymphatic system ensures normal nightly cleaning of the brain. During SWS, glia cells shrink by 60% so that metabolic residual material can be removed including amyloid proteïn, Tau and stress molecules
  - In Alzheimer's disease, amyloid plaques accumulate in the center of the frontal lobe, also the location where deep NREM sleep is generated

Creation of a vicious circle:

In Alzheimer's disease amyloïd plaques slack in the frontal lobe → ↓ deep sleep → less effective glymphatic system → ↓ amyloid clearance → ↑ Alzheimer's disease

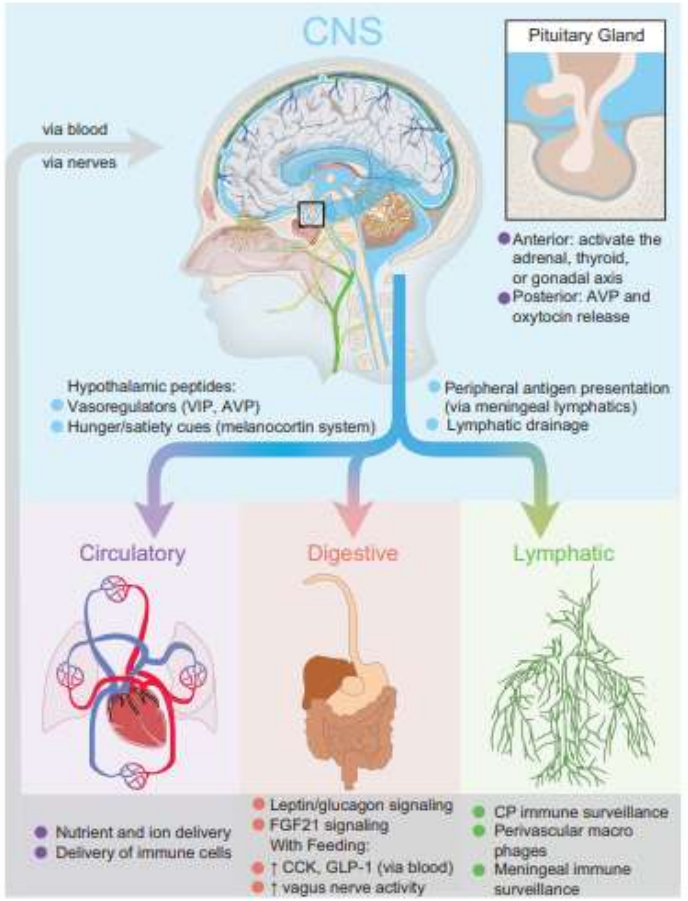


Figure 4. The glymphatic system as an interface between the brain and body. The brain can communicate to the circulatory, digestive, and lymphatic systems by secreting signaling molecules to CSF, driving fluid to the meningeal lymphatics for antigen presentation, and ultimately draining to the lymph nodes of the lymphatic system. A unique feature of the brain is the hypothalamic signaling to the pituitary gland, where neurons can either induce neuroendocrine signaling in the anterior pituitary, or directly release peptides such as AVP and oxytocin into the blood vessels of the posterior pituitary. Feedback between these systems is potentially bidirectional when considering blood composition, feeding and fasting metabolites, and immune surveillance. The pituitary gland is uniquely shielded from direct interaction with the CSF pool and direct CNS signaling by its location in an indentation of the skull covered by the diaphragma sellae, a dural membrane.

Hablitz & Nedergaard, 2021

Acoustic stimulation as a promising technique to enhance slow-wave sleep in Alzheimer's disease: results of a pilot study (phase 1) *(Van den Bulcke et al. 2023)*

Figure 1—Representation of the DREEM 2 headband device and the flowchart of the study intervention.

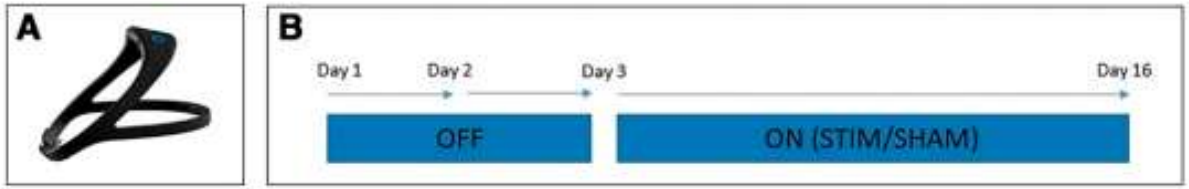
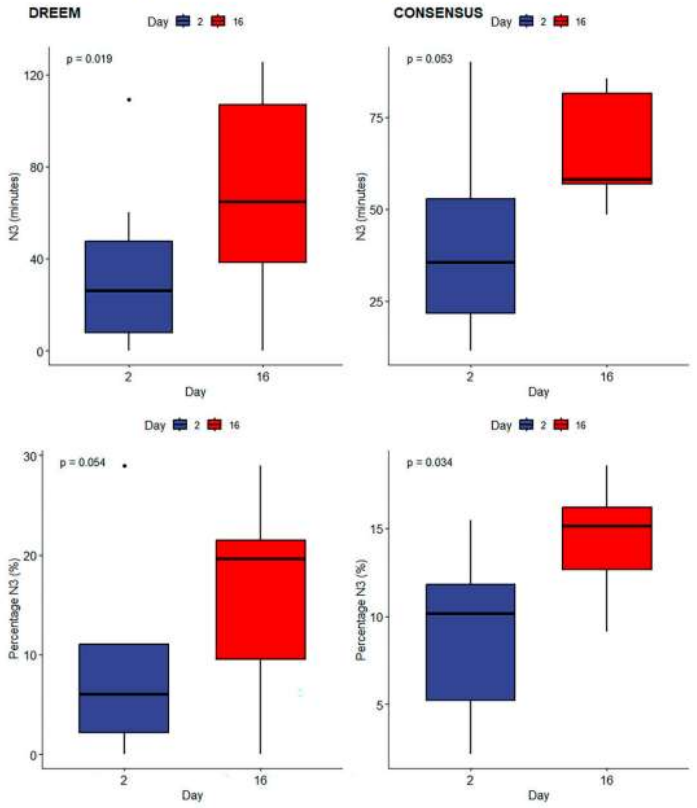


Figure 2—Representation of the effect of the intervention on N3 both in absolute time and percentage of total sleep.



(Left) Results by the embedded automatic algorithm of the DREEM headband (DREEM). **(Right)** Results of the consensus scoring of the raw electroencephalography (CONSENSUS) data.

- N= 11 mild to moderate AD
- **Method:**
  - acoustic stimulation with DREEM 2 headband
  - 14 consecutive 'stimulation nights' (phase-locked acoustic stimulation of 40-dB mink noise)
- **Results:**
  - Almost twice as much time spent in SWS (between beginning and end of intervention)
  - Consensus scoring of data confirmed trend
- **Conclusion:**
  - First evidence: targeted acoustic stimuli is feasible and could increase SWS in AD significantly

Sleep disorders and dementia

- **Neurodegeneration:** *(several disorders including Alzheimer's disease, Parkinsons's disease, mixed neurodegenerative and cerebrovascular diseases):*
  - ↑ sleep latency, ↓ TST and SE
  - ↓ slow-wave sleep (SWS)
  - ↓ REM sleep
  - ↑ daytime sleep episodes
  - ↑ frequent night-time awakenings or sleep fragmentation

  - **Irregular sleep-wake rhythm disorder (ISWRD)** describes the worsening of neuropsychiatric symptoms in patients with cognitive impairment
    - 50% of patients with dementia develop an ISWRD:
      - difficulties in initiating and maintaining sleep
      - insomnia
      - recurrent confusion
      - nocturnal agitation
      - daytime sleepiness *(Guarnieri, Cerroni, & Sorbi, 2015)*
    - More rapid cognitive deterioration
    - Leading to an enormous burden for care-givers and one of the main reasons for admissions into residential care *(Gehrman, Gooneratne, Brewster, Richards, & Karlawish, 2018)*
  - **Frequency and characteristics of sleep disorders increase with the severity of dementia**

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Irregular sleep/wake rhythm has greater negative impact on survival than sleep duration (N=60,977)

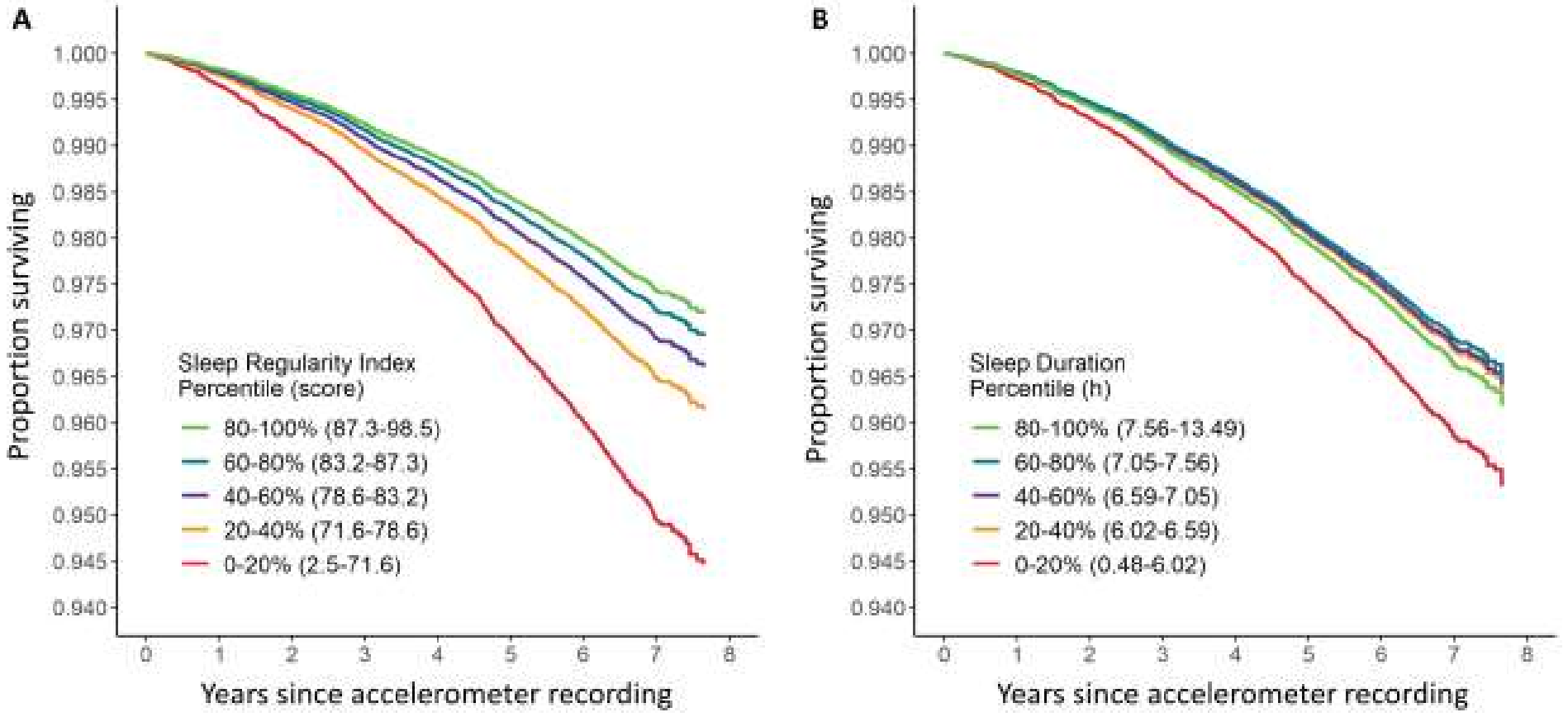


Figure 1. Cumulative survival of participants between accelerometer recording and study end point, according to (A) Sleep Regularity Index quintiles and (B) sleep duration quintiles.

Windred et al. 2024 Sleep

Non-pharmacological interventions

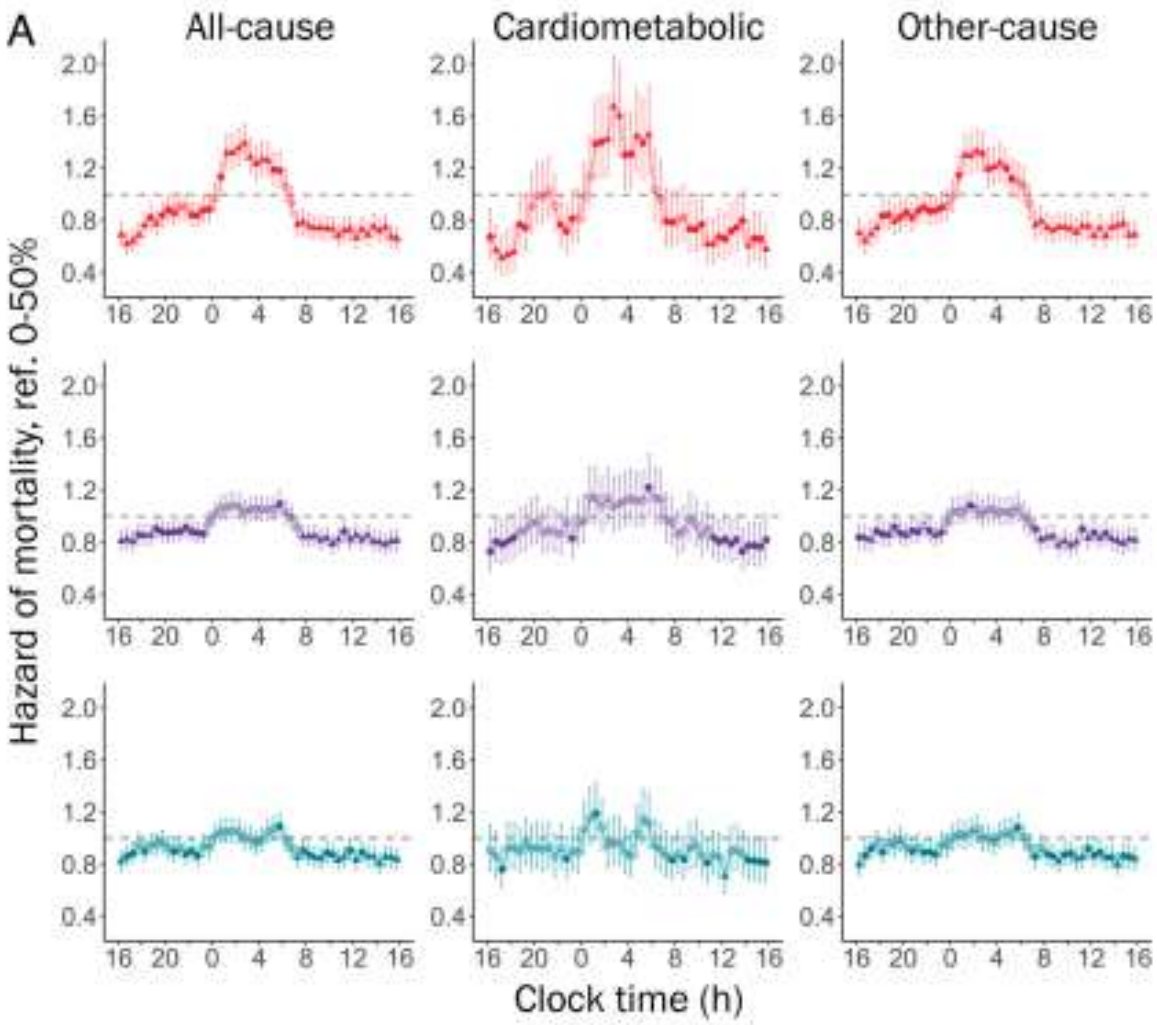
TABLE 4 Behavioural approaches for elderly people with insomnia

Measure	Guiding principle
Sleep hygiene (e.g., with regular bed times)	Conditioning, maintaining sleep architecture
Day structuring	Avoid daytime sleep
Physical activity during the day	Physical exhaustion
Social activity during the day	Cognitive stimulation, avoiding daytime sleep
Avoiding extensive daytime sleep	Increase in night-time sleep pressure
Late bedtime	Increase in night-time sleep pressure
Light (sunlight >light therapy device, light therapy device e.g., 10,000 lux for 30 min) regulation of melatonin production and breakdown	Regulation of melatonin production and breakdown

ESRS Sleep Medicine Textbook 2022

Brighter nights and darker days predict higher mortality risk: A prospective analysis of personal light exposure in > 88.000 individuals

(UK BIO-Bank): light and dark at the right moments



Windred et al. 2024 PNAS.

Night noise : a *'silent killer'*

- Nighttime noise exposure leads to significant disease burden
- WHO guidelines on limiting environmental noise limitation for health reasons
- Difference between continuous background noise, for which habituation, and incidental noise, for which no habituation, with persistent arousal and disruption of the autonomic nervous system
- Reflects vigilance as survival and defence mechanism given unsafe and vulnerable sleep state (being able to flee in case of danger)
- Advocacy for ensuring nocturnal periods of silence

3 – Factor model of Insomnia by Spielman

(Spielman, Nunes and Glovinsky. Neurol. Clin. 1996)

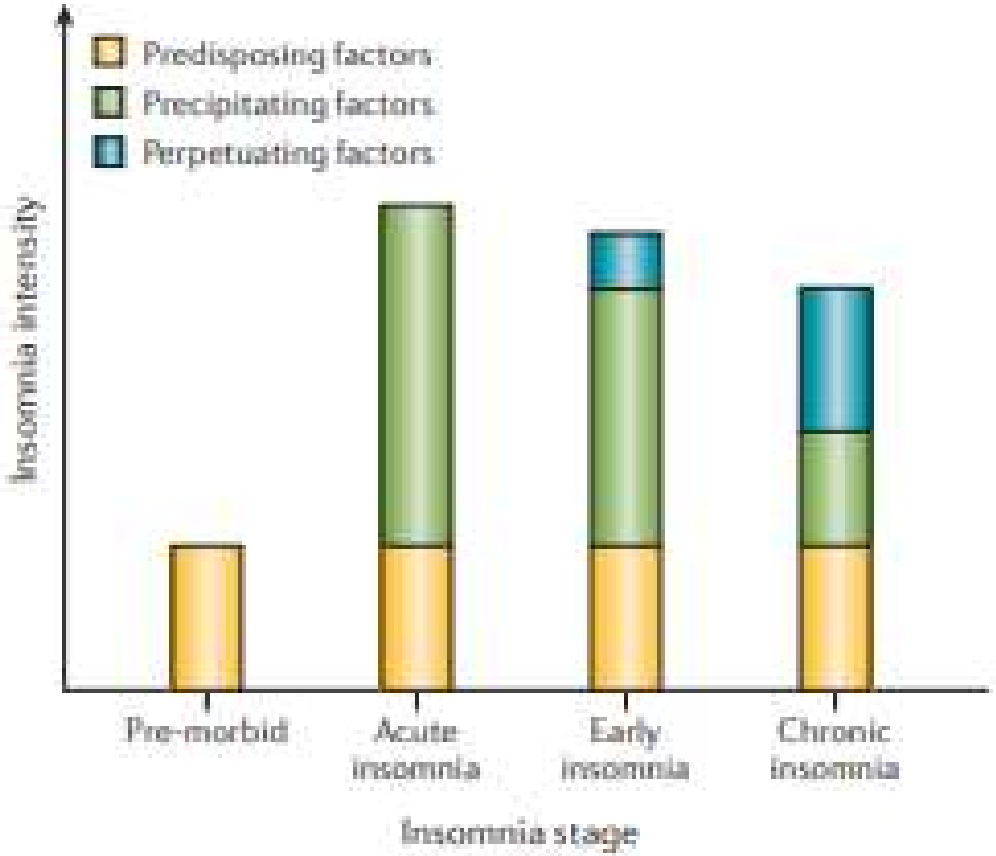


Figure 1 | **The relative importance of three types of factors in the course of insomnia.** The various stages of insomnia are influenced, to different degrees, by predisposing, precipitating and perpetuating factors. Adapted with permission from REF 198, Springer.

Morin et al. Nature Reviews/Disease Primers 2015

Insomnia model by Charles Morin, 1993

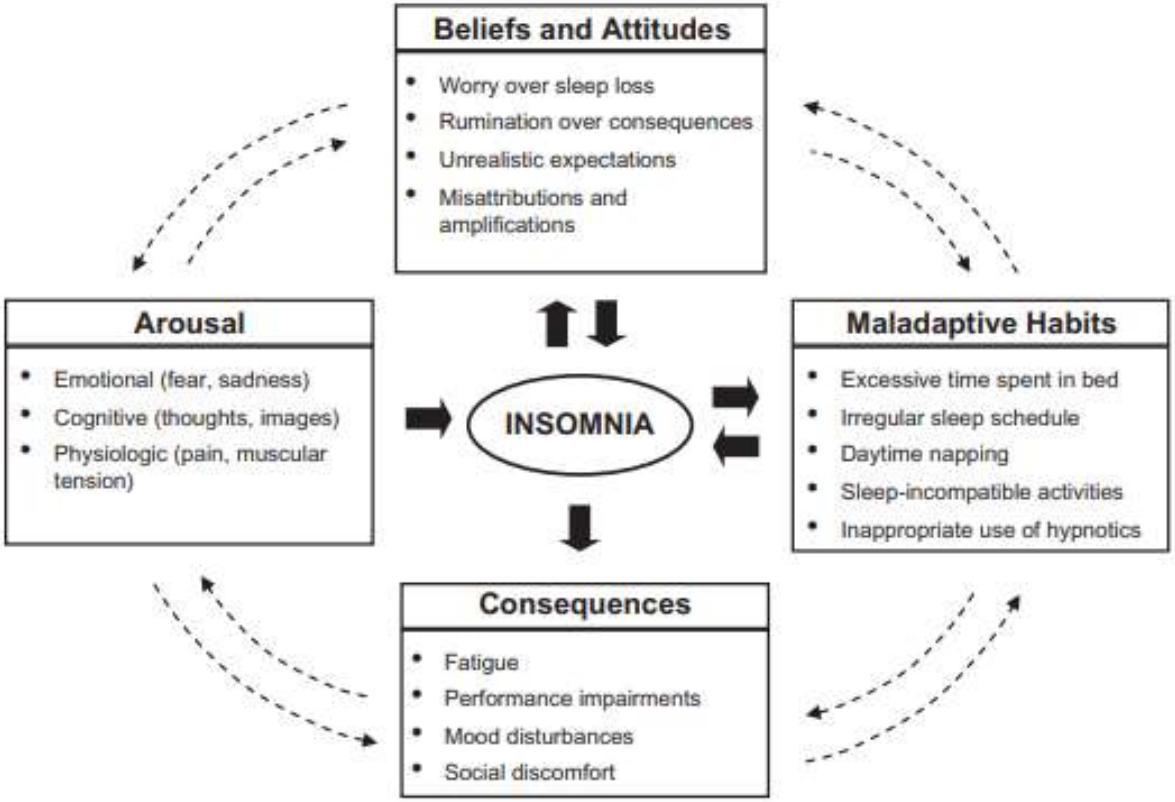


FIGURE 11.1 A conceptual model of insomnia maintenance. A microanalytic model of chronic insomnia showing how maladaptive beliefs and sleep habits can contribute to perpetuate insomnia. Reproduced with permission from Morin (1993).

Morin C. and Bélanger L. Book: Behavioral treatments for sleep disorders. Chapter 11 Cognitive Therapy for Dysfunctional Beliefs about sleep and Insomnia. ISBN 978-0-12-381522-4. DOI: 107 10.1016/B978-0-12-381522-4.00011

TABLE 2 CBT-I ingredients (from Baglioni et al., 2020)

CBT-I strategy	Description
Sleep restriction	*Behavioural strategy*: A method that aims at strengthening homeostatic sleep pressure and stabilizing circadian control of sleep and wakefulness, by decreasing the opportunity to sleep over successive nights. Patients are instructed to restrict their time in bed to match their average (self-report in sleep diaries) total sleep duration. The time in bed is then gradually increased until reaching patients' optimal sleep need. An alternative method, called *sleep compression*, consists in gradual constriction of time in bed until reaching the optimal sleep need.
Stimulus control	*Behavioural strategy*: Several instructions aiming at strengthening the bed as a cue for sleep, weakening it as a cue for activities that might interfere with sleep, and helping the insomniac acquire a consistent sleep rhythm, based on operant conditioning model: (1) lie down to go to sleep only when you are sleepy; (2) do not use your bed for anything except your sleep and sexual activity; (3) if you find yourself unable to fall asleep, get up and go to another room. Stay up as long as you wish, and come back to bed when you feel sleepy; (4) If you still cannot fall asleep, repeat step (3). Do this as often as is necessary throughout the night; (5) Set your alarm and get up at the same time every morning irrespective of how much sleep you got during the night; (6) no napping during daytime.
Sleep hygiene education	Behavioural and educational strategy: General health instructions about internal and external factors that might influence sleep (e.g. sport, light, temperature, etc.).
Relaxation	Behavioural and cognitive strategy: A set of methods aiming at reducing somatic or cognitive hyperarousal (e.g. progressive muscle relaxation, autogenic training, imagery training, meditation).
Cognitive reappraisal	Cognitive strategy: Strategies directed to reduce dysfunctional beliefs, attitudes, concerns and false beliefs about the cause of insomnia and about the inability to sleep.
Cognitive control/ Worry time	Cognitive strategy: The patient is instructed to sit comfortably in an armchair, and write down a list of worries and list of what to do the next day. The rationale of this strategy is to prevent emotionally loaded intrusive thoughts during the sleep-onset period, as all worries have been "already" processed before going to bed.
Paradoxical intention	Cognitive strategy: Strategy aimed at reducing the anticipatory anxiety at the time of falling asleep. Patients are instructed to remain still in bed with the eyes closed and to try to keep awake as long as they can. This takes away the responsibility to try to fall asleep, which in turn often leads to falling asleep quicker.

Abbreviation: CBT-I, cognitive-behavioural treatment for insomnia.

Outline

- Some basic physiology: sleep homeostasis and circadian rhythm
- Sleep changes with ageing
- Diagnostic assessment
- Sleep disorders in the elderly
  - Insomnia and psychiatric comorbidity
  - Sleep disordered breathing
  - RLS
  - RBD and other parasomnias
- Non-pharmacological interventions
  - Do not forget environmental factors
- **Impact of medication**
  - **Risk for sleep disturbance**
  - **Pharmacological treatment**
- Summary and Recommendations

Pharmacological interventions

TABLE 11 Major drug classes used to treat insomnia in Europe

BZ	Diazepam, flunitrazepam, flurazepam, lormetazepam, nitrazepam, oxazepam, temazepam, triazolam
BZRA	Zaleplone, zolpidem, zopiclone, eszopiclone
Sedating antidepressants	Agomelatine, amitriptyline, doxepin, mianserin, mirtazapine, trazodone, trimipramine
Antipsychotics	Chlorprothixene, levomepromazine, melperone, olanzapine, pipamperone, prothipendyl, quetiapine
Antihistamines	Diphenhydramine, doxylamine, hydroxyzine, promethazine
Phytotherapeutics	Hops, kava-kava, melissa, passiflora, valerian, lavender
Melatonin receptor agonists	Fast-release melatonin, ramelteon, PR melatonin
Orexin receptor antagonists	Daridorexant

Abbreviations: BZ, benzodiazepines; BZRA, benzodiazepine receptor agonists; PR, prolonged-release.

Riemann D. et al. 2023, J Sleep Res. European Insomnia Guideline: An update

Effects of psychotropic drugs: hypnotics: enhancing CNS inhibition

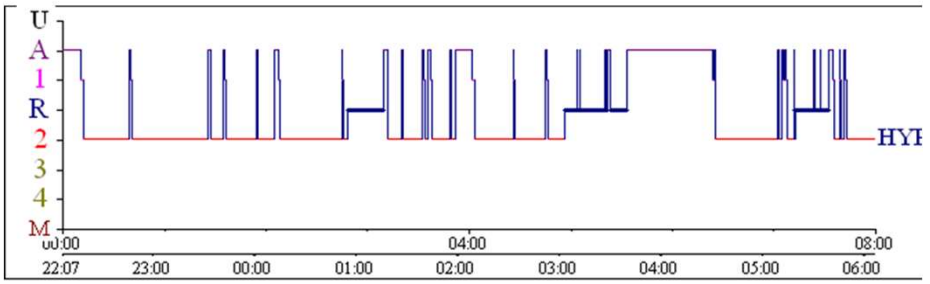
BZD & Z-drugs:

Subjective experiences:

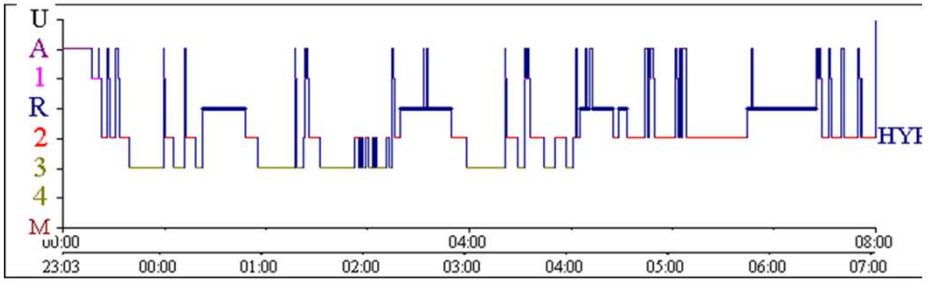
- ↓SL
- ↓WASO
- ↑ TST

PSG findings

- ↓SL
- ↓WASO
- ↑ TST
- ↑sleep spindles
- ↓REM sleep
- ↓↓ SWS (just like alcohol)
- ↑↑ NREM2



HYPNOGRAM ONDER BENZODIAZEPINES (vrouwelijk, °13/08/65) (PSG in 08/2009)



HYPNOGRAM ZONDER BENZODIAZEPINES (vrouwelijk, °14/09/77) (PSG in 02/2009)

Dujardin et al. Sleep Med Clin 2018, Earl et al. Curr Opinion Pneum Med. 2020)

BZ and BZRA

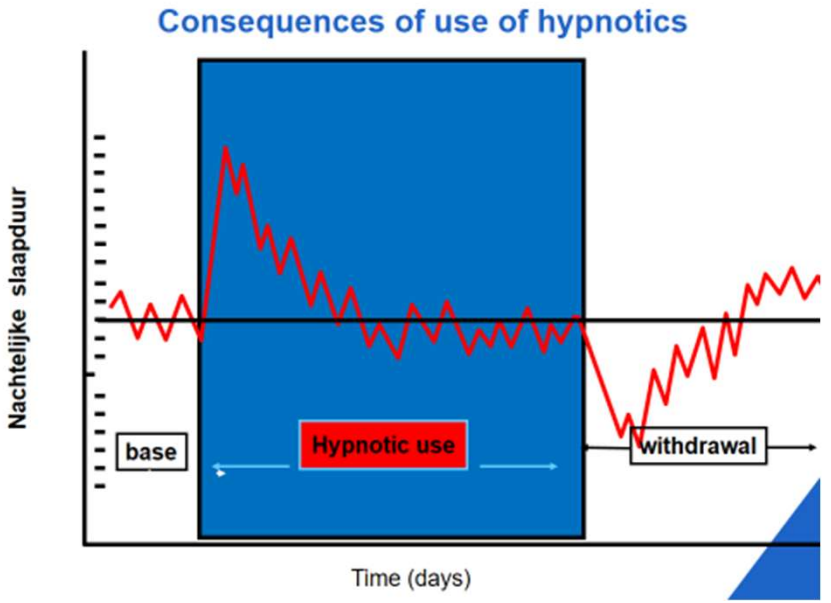
Potential adverse events:

- Hangover/daytime sedation/somnolence
  - Traffic accidents
  - Falls and fractures
- Anterograde amnesia, provoke confusional states
- Negative effects on cognition, memory function
- Emotional blunting, dysphoria
- Respiratory depression (increase of apnea and hypopnea)
- Nocturnal muscle relaxation
- Tolerance
- Risk of physical and psychological dependence as early as 1 or 2 weeks after intake
- Rebound insomnia
- **Warning in 2019** (FDA) possibility of complex sleep behaviour, such as sleep walking, sleep driving, unsafely using a stove, … (Z-drugs)

Dujardin et al. Sleep Med Clin 2018, Earl et al. Curr Opinion Pneum Med. 2020), Etchetto et al., 2020, Riemann et al. 2023 J Sleep Res. European Insomnia Guideline: An update

BZ and BZRA

- **Withdrawal symptoms:**
  - Agitation
  - Mood swings
  - Anxiety
  - Muscle tension and spasms
  - Sensation of needle pricks
  - Increased sensitivity to light and sound
  - Epileptic seizures



- **Practical advise:**
  - Avoid prolonged use in adults (≤ 4 weeks)
    - *(tolerance already after a few days to a week)*
  - Dosage as low as possible
  - Avoid use in 65 years or older
  - Do not stop suddenly: taper off: recommendations range 10-20-25% dose reduction every 2 weeks (BCFI: 10-20% per week or every 2 weeks)

Earl et al. Curr Opinion Pneum Med. 2020)

Riemann et al. J Sleep Research, 2017

- Discuss sleep hygiëne and refer for *Cognitive Behavioral Therapy for Insomnia (CBT-I)*

- **Belgium: government-project:**
  - Supervision by GP and pharmacist, collaboration with psychologist
  - Gradual reduction of 10-20% per month (can be extended twice by 1 month)
  - Discuss sleep hygiëne and refer for *CBT-I*

24/05/23 om 11:54 Bijgewerkt om 12:39

(//www.artsenkrant.com/auteurs/geert-verrijken-106.html) **Geert Verrijken (//www.artsenkrant.com/auteurs/geert-verrijken-106.html)** Directeur Redactie RHC

"Het voorschrijven van benzodiazepines moet sterk verminderen en men dient alternatieve oplossingen te zoeken. Om dat te bereiken lanceren we in het najaar een grote sensibiliseringscampagne gebouwd op de synergie tussen apothekers, klinisch psychologen en huisartsen." Dat zei minister van sociale zaken en volksgezondheid Frank Vandenbroucke (Vooruit) in de Kamercommissie gezondheid en gelijke kansen.

Minister Vandenbroucke lanceert in het najaar een sensibiliseringscampagne specifiek gericht op huisartsen.

Daarmee ging hij in op een vraag van N-VA-parlementslid en apotheker Kathleen Depoorter over het stijgende gebruik van verslavende slaap- en kalmeermiddelen bij de bevolking, vooral dan bij jongeren.

Pharmacological interventions

- **Trazodone** *(100-150 mg)*
  - may be helpful for the treatment of insomnia in patients with dementia *(McCleery, Cohen, & Sharpley, 2016)*
  - Normalization of ISWRD in pts with Alzheimer's dementia + ISWRD *(Grippe et al., 2015)*
- **Mirtazapine** *(7.5-15 mg)*
  - Improve sleep continuity in non-demented pts *(Rothschild-Fuentes et al., 2013)*
  - No improvement of night-time sleep in RCT in Alzheimer's dementia (Scoralick et al., 2017)
  - However, effective for pts with comorbid depression
  - Possible side effect : restless legs
- **TCA**
  - should not be used, can lead to confusions due to anticholinergic properties

Pharmacological interventions

Quetiapine

- Probably best pharmacological treatment of most elderly with/ without cognitive impairment with insomnia, particularly if associated with restlessness psychotic and affective symptoms
- Monitoring:
  - liver enzymes
  - electrocardiography (QTc duration)
  - BP (hypotension) *(Schwerthoffer, Fatke, & Forstl, 2020)*
- Lowest necessary dosage *(12,5 to 25mg)* and shortest possible of time
- Frequently used in much higher dosages than necessary
- Modest scientific evidence *(Bauer, McIntyre, Szamosi, & Eriksson, 2013; Karsten, Hagenauw, Kamphuis, Lancel, & Karsten, 2017; Kim, Lee, Lee, & Cho, 2014; Rock, Goodwin, Wulff, McTavish, & Harmer, 2016; Thompson et al., 2016, Boldingh-Debernard, Frost, & Roland, 2019)*

Pharmacological interventions

- **Risperidone**
  - In low dosages *(0,5-1,5mg)* approved for treatment of dementia-related behavioural problems including nocturnal sleep and restlessness
  - Several studies: efficacy in treating ISWRD in dementia
  - Not better or safer than very low dosages haloperidol
  - Possible side effects: serious extrapyramidal side effects (Lewy body dementia)

Prolonged neuroleptic treatment in elderly patients is associated with increased mortality

Pharmacological interventions

- **Alcohol**: never use for treatment of insomnia
- **Diphenhydramine and other antihistamines** to be avoided in elderly, particularly those with cognitive impairment:
  - May induce excessive antihistaminergic (e.g., excessive sedation, and delirium) and anticholinergic (e.g., deterioration of cognition, urinary retention, and delirium) effects
- **Dual orexin antagonists** (DORA; suvorexant, lemborexant, daridorexant, filorexant), and orexin-2-receptor antagonists (OX2R; seltorexant):
  - Innovative treatment principles inducing specific changes in sleep architecture (e.g., an increase in REM sleep), maintaining a more natural sleep architecture
  - Less side effects regarding drug interactions, memory impairment, and drug dependence than conventional hypnotics *(Hoyer, Allen, & Jacobson, 2020)*
  - more useful for sleep maintenance than sleep onset *(Herring et al., 2017; Rosenberg et al., 2019)*
  - insomnia in patients with mild-to-moderate probable Alzheimer's disease: significant ↑ TST *(Herring et al., 2020)*
  - Trial for ISWRD associated with dementia in Alzheimer's disease and obstructive sleep apnea (Hoyer et al., 2020)

Pharmacological interventions

- **Herbal medicine** may not offer significant pharmacological effects, but valuable psychological efficiency, also in elderly individuals.

- **Melatonin and melatonin agonists** (Ramelteon):
  - may exert a beneficial effect in patients with ISWRD, but more scientific evidence would be appreciated *(Asano, Ishitobi, Tanaka, & Wada, 2013; Cardinali, Furio, & Brusco, 2011; Gehrman et al., 2009)*
  - may be helpful for elderly patients with RBD *(Jung & St. Louis, 2016)*

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Summary and recommendations

- The evolution of sleep with age is a process that affects everyone to variable degrees
- Physiological alteration of sleep with increasing age: shorter and shallower night-time sleep
- In addition, sleep alterations in age may be affected by somatic and psychiatric comorbidities or indicate the development of primary sleep disorders, which may be present even in a subclinical state
- Therefore, sleep complaints in the elderly should not be attributed to the ageing process itself without previously screening for underlying comorbidities or primary sleep disorders

Summary and recommendations

- The specific medical, pharmacological, mental, and social dimensions of sleep disorders in the elderly must be considered in taking a comprehensive history: a biopsychosocial approach
- Neurobiological links between disturbed sleep and neurodegeneration
- The relationship between sleep disorders and dementia is bidirectional
- Certain forms of dementia show characteristic somnological features
- The treatment of insomnia in the elderly includes pharmacological and non-pharmacological interventions with treatment of underlying pathology

Think sleep!