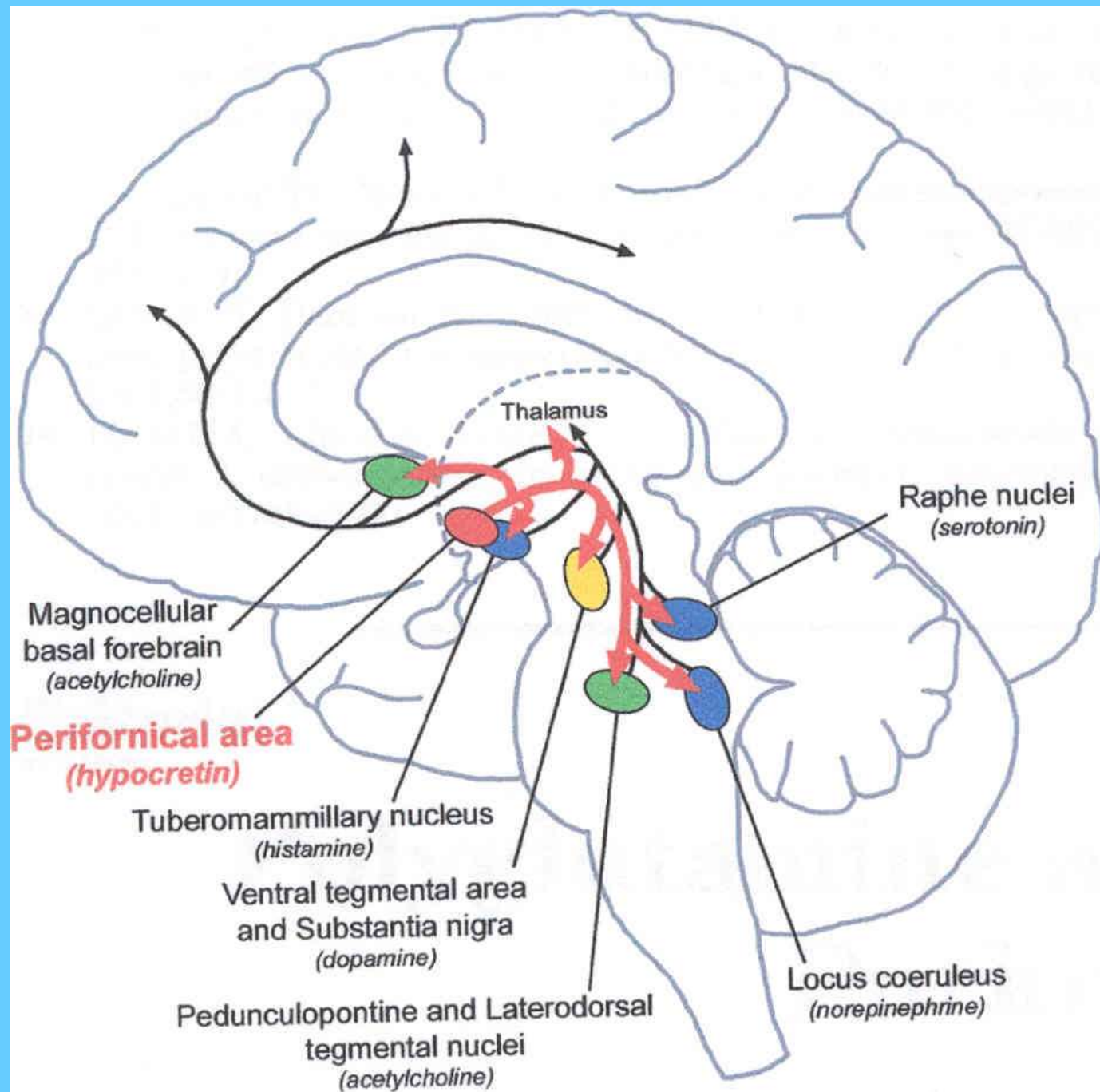


INSONNIA CRONICA: EPIDEMIOLOGIA, FISIOPATOLOGIA E DIAGNOSI

Luigi Ferini Strambi

Università Vita-Salute San Raffaele

Milano



Main brain areas responsible for waking and sleep

WAKING:

Ascending Reticular Activating System (ARAS)

Locus coeruleus: **NA**

Cholinergic neurons in the pontine brainstem: **ACh**

Cholinergic neurons in the basal forebrain: **ACh**

Tuberomammillary nucleus: **histamine**

Tuberal hypothalamus: **orexin**

NON-REM SLEEP:

Ventrolateral preoptic nucleus (VLPO): **GABA -galanine**

REM SLEEP:

Ponto-mesencephalic areas : Laterodorsal tegmental nucleus (LDT): **ACh**

Peduncolopontine tegmental nucleus (PPT): **ACh**

Figure 1
Characteristic electroencephalographic patterns of human sleep stages

Awake: low voltage – random, fast



Drowsy: 8 to 12 cps – alpha waves



Stage 1: 3 to 7 cps – theta waves



Stage 2: 12 to 14 cps – sleep spindles and K complexes



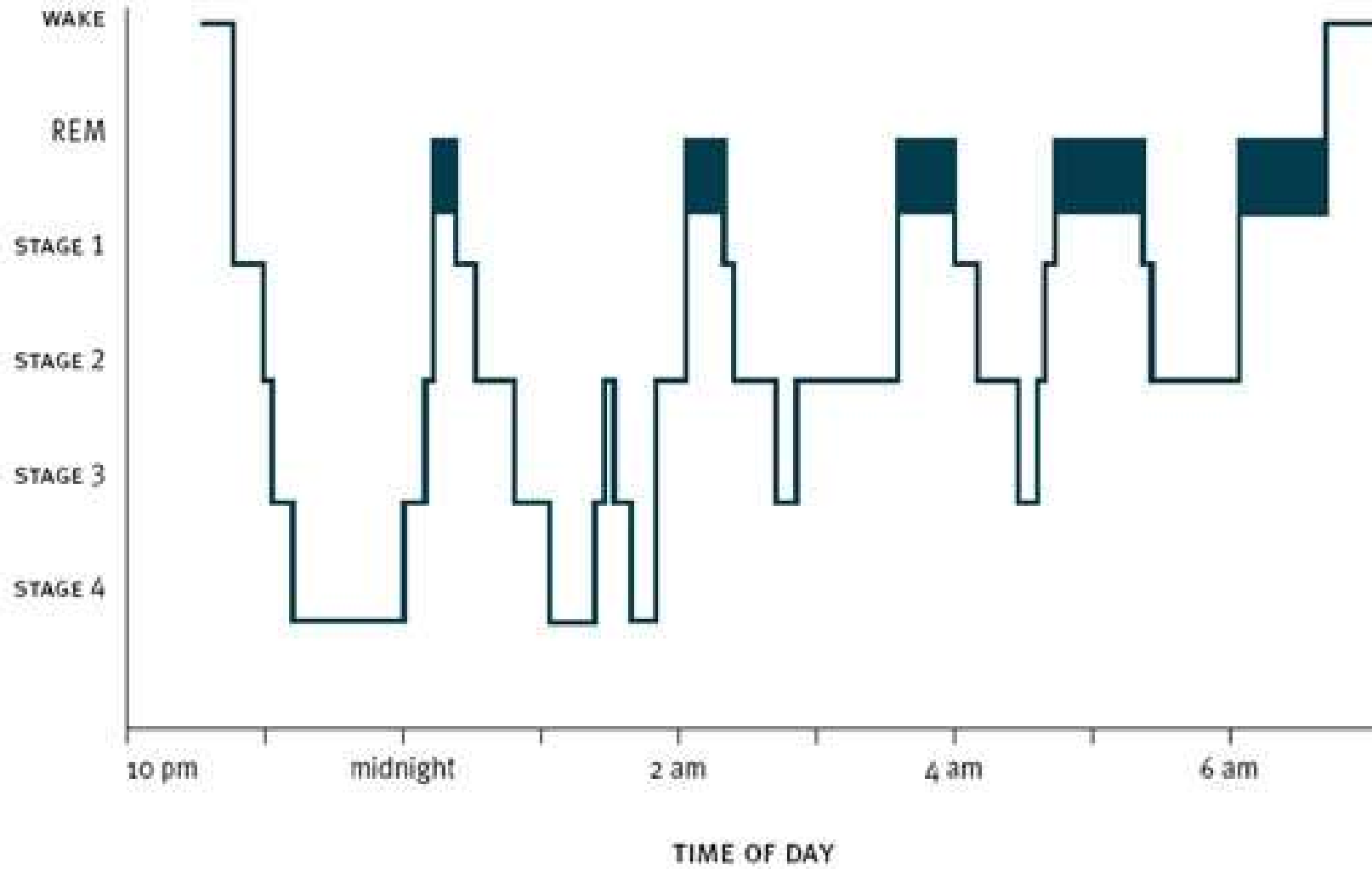
Delta sleep: (stages 3 and 4) 1/2 to 2 cps – delta waves $>75 \mu$ V



REM sleep: low voltage – random, fast with sawtooth waves



Hypnogram (young adult)



Pre - sleep - W



SWS



REM - sleep



Post - sleep - W



ACTIVATION



High DEACTIVATION

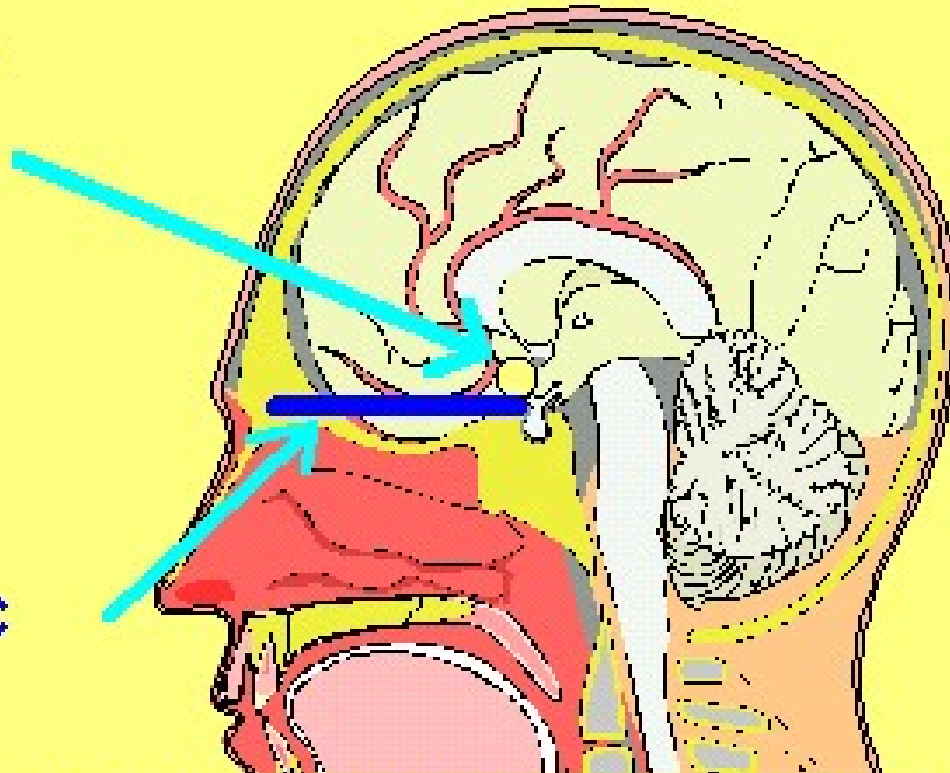


Low DEACTIVATION

Light and the Clock

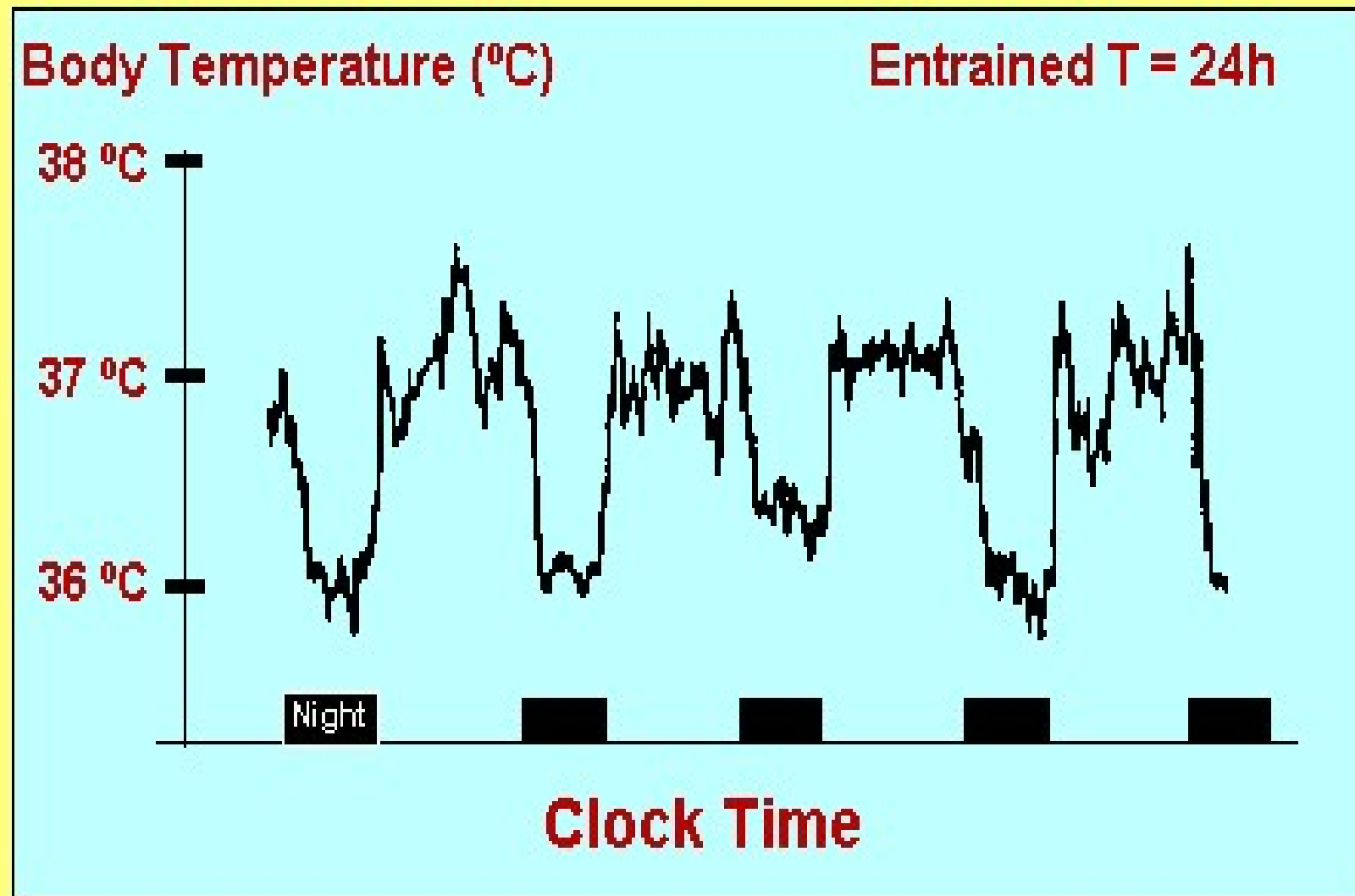
**Suprachiasmatic
nuclei**

**Retino-hypothalamic
tract**



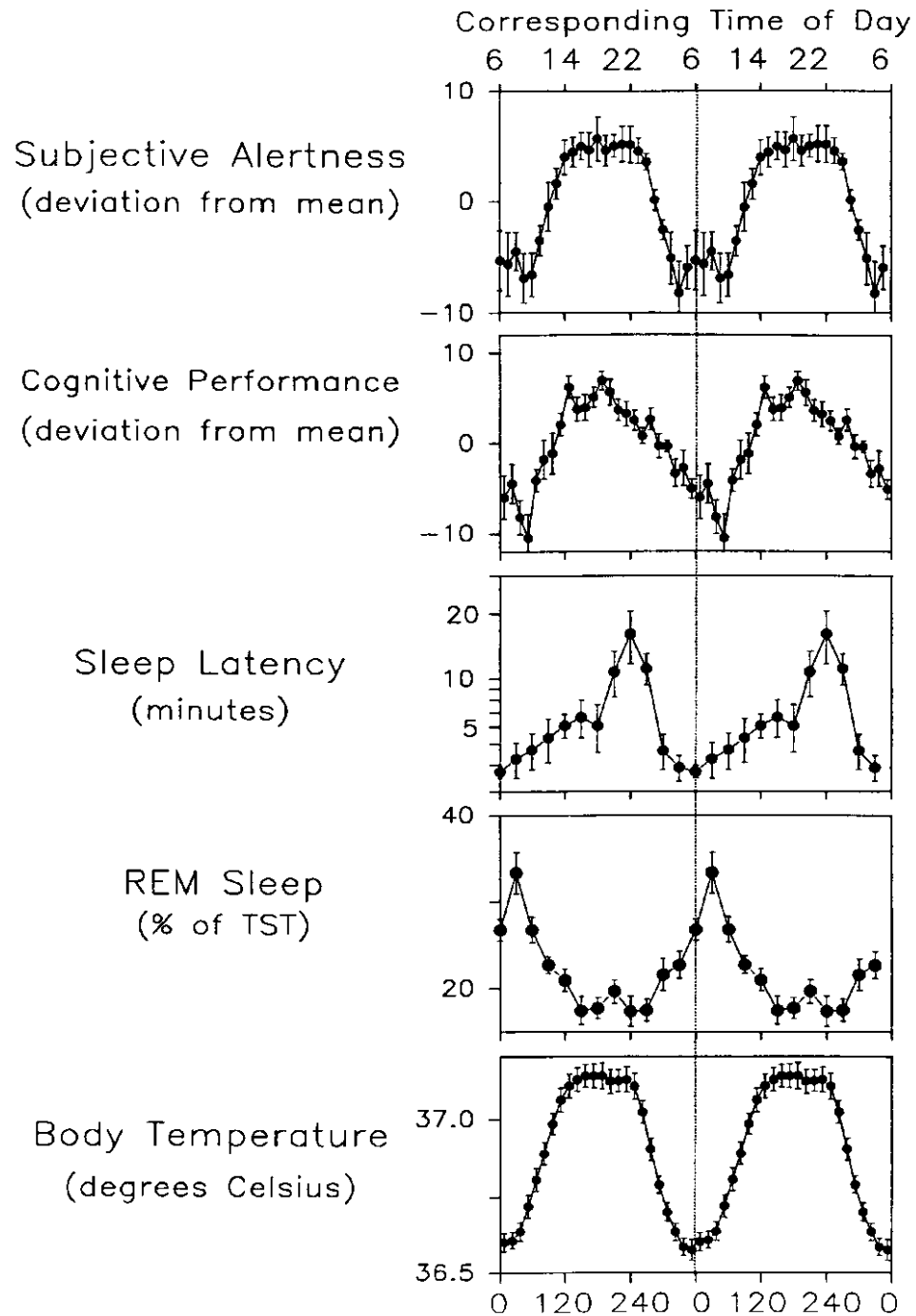
The pacemaker to the circadian rhythm is called the suprachiasmatic nucleus (SCN). It is located near the hypothalamus. The suprachiasmatic nucleus is profoundly affected by light. Light can, in a very lawful manner, cause system changes in the timing of sleep and wake function. The influence of light on the SCN is via the retino-hypothalamic tract.

Body Temperature



The second major determiner is one's circadian rhythm. A variety of different physiological parameters are reflective of this 24-hour rhythm. Core body temperature depicted on this page is the most common measure used to assess one's circadian rhythm.

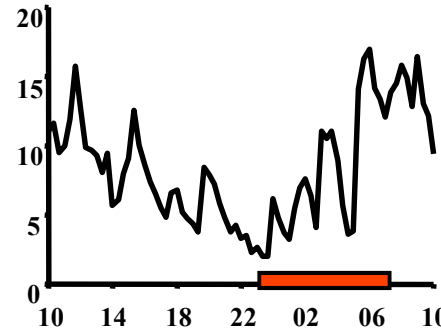
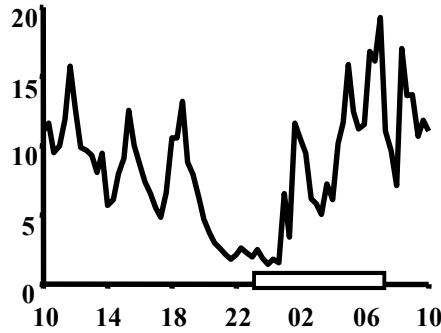
Czeisler et al.1981



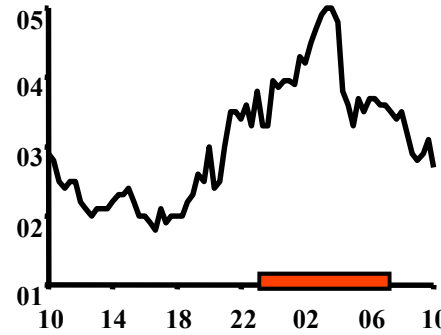
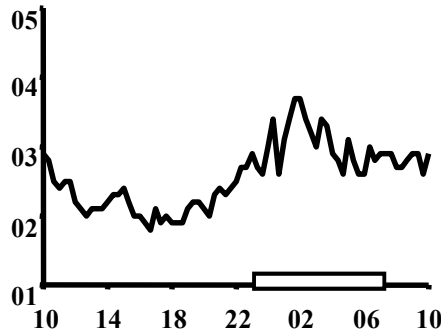
Sleep

No sleep

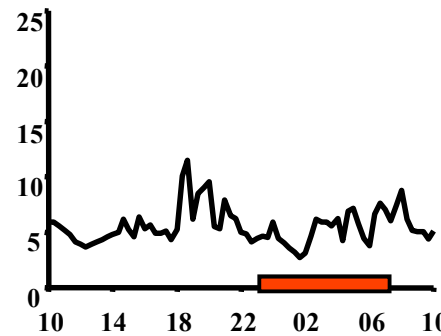
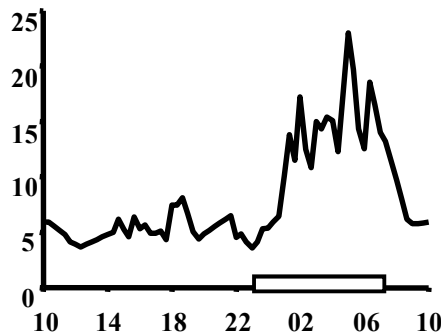
Cortisol
($\mu\text{g}/\text{dl}$)



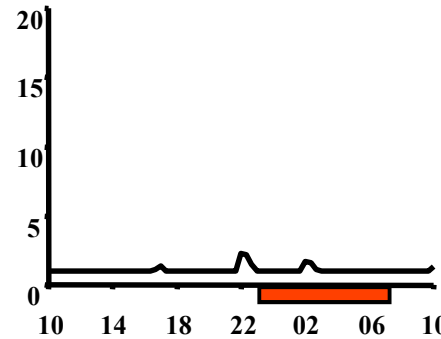
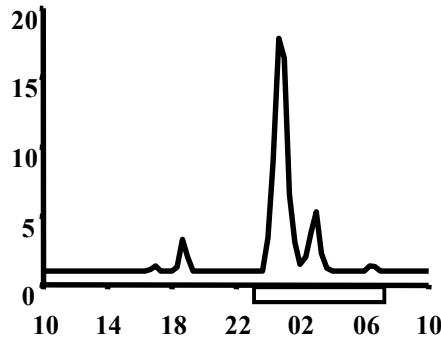
Thyrotropin
($\mu\text{U}/\text{ml}$)



Prolactin
(ng/ml)



Growth Hormone
($\mu\text{g}/\text{L}$)



**acute
sleep
deprivation**

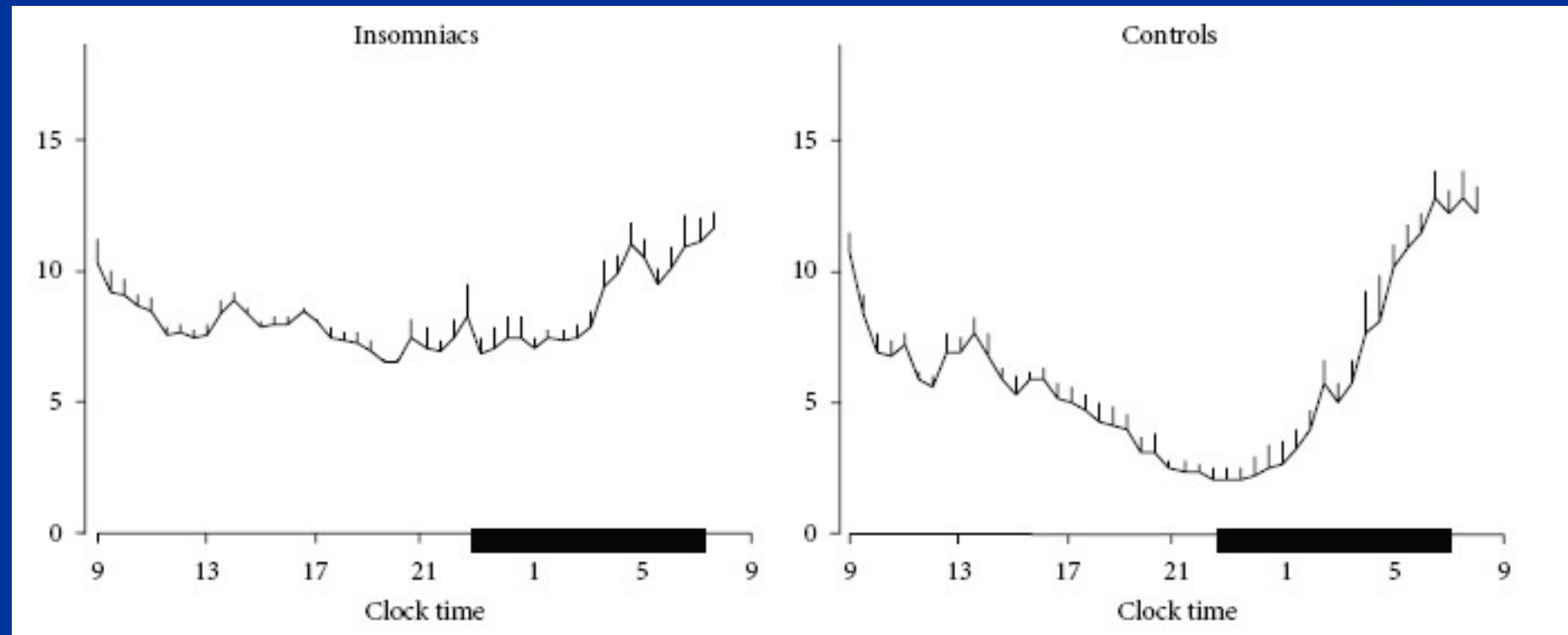
Clock Time

Impact of Sleep and Its Disturbances on Hypothalamo-Pituitary-Adrenal Axis Activity

Marcella Balbo, Rachel Leproult, and Eve Van Cauter

International Journal of Endocrinology
Volume 2010, Article ID 759234, 16 pages

Cortisol rhythm

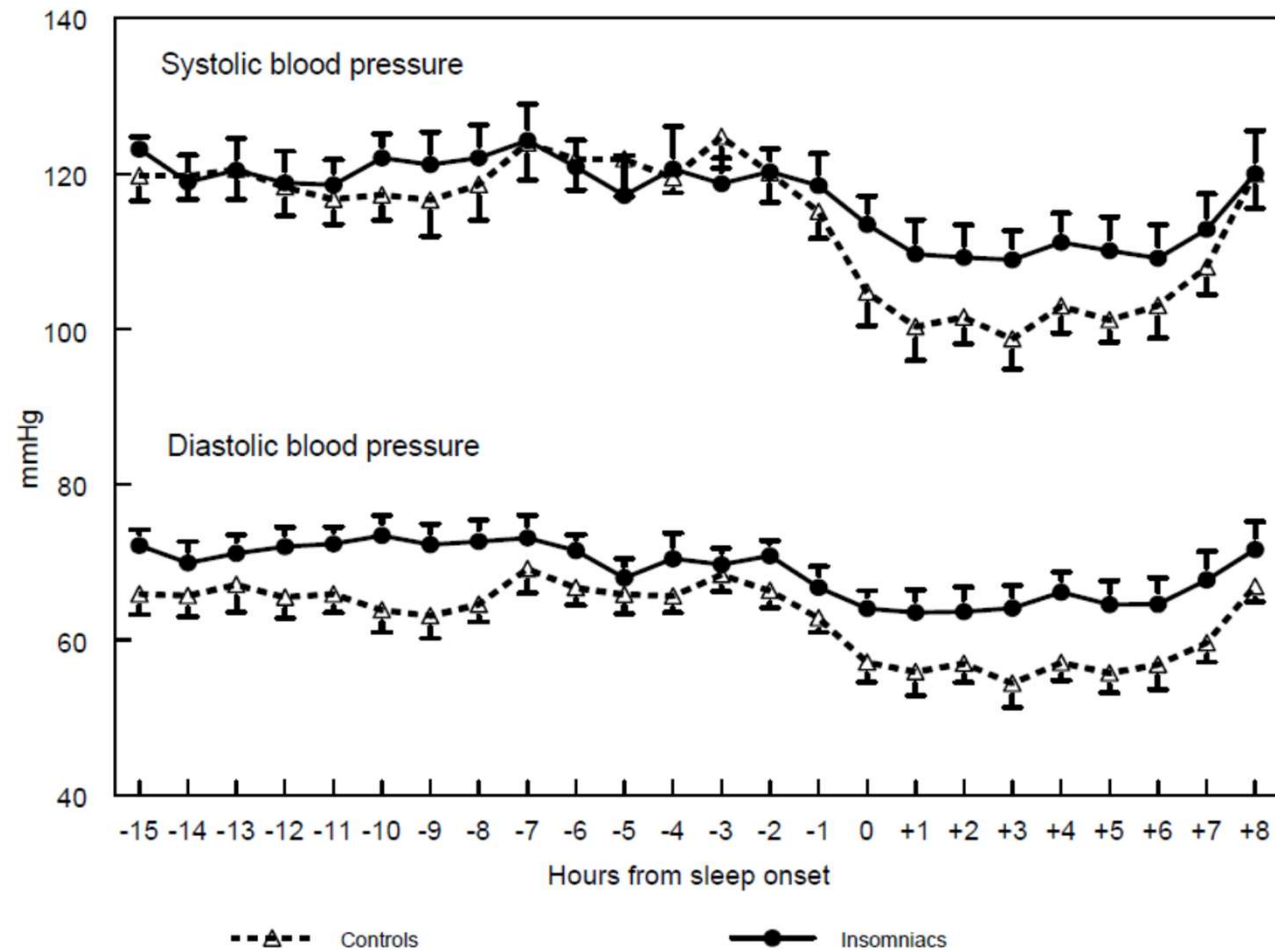


Night time blood pressure in normotensive subjects with chronic insomnia: implications for cardiovascular risk.

Paola A. Lanfranchi,, Marie-Helene Pennestri, Lorraine Fradette, Marie Dumont, Charles M. Morin, Jacques Montplaisir

Sleep, 2009

Figure 2



PRIVAZIONE DI SONNO

- **Diminuisce l'attività delle cellule “natural killers” nell'uomo**

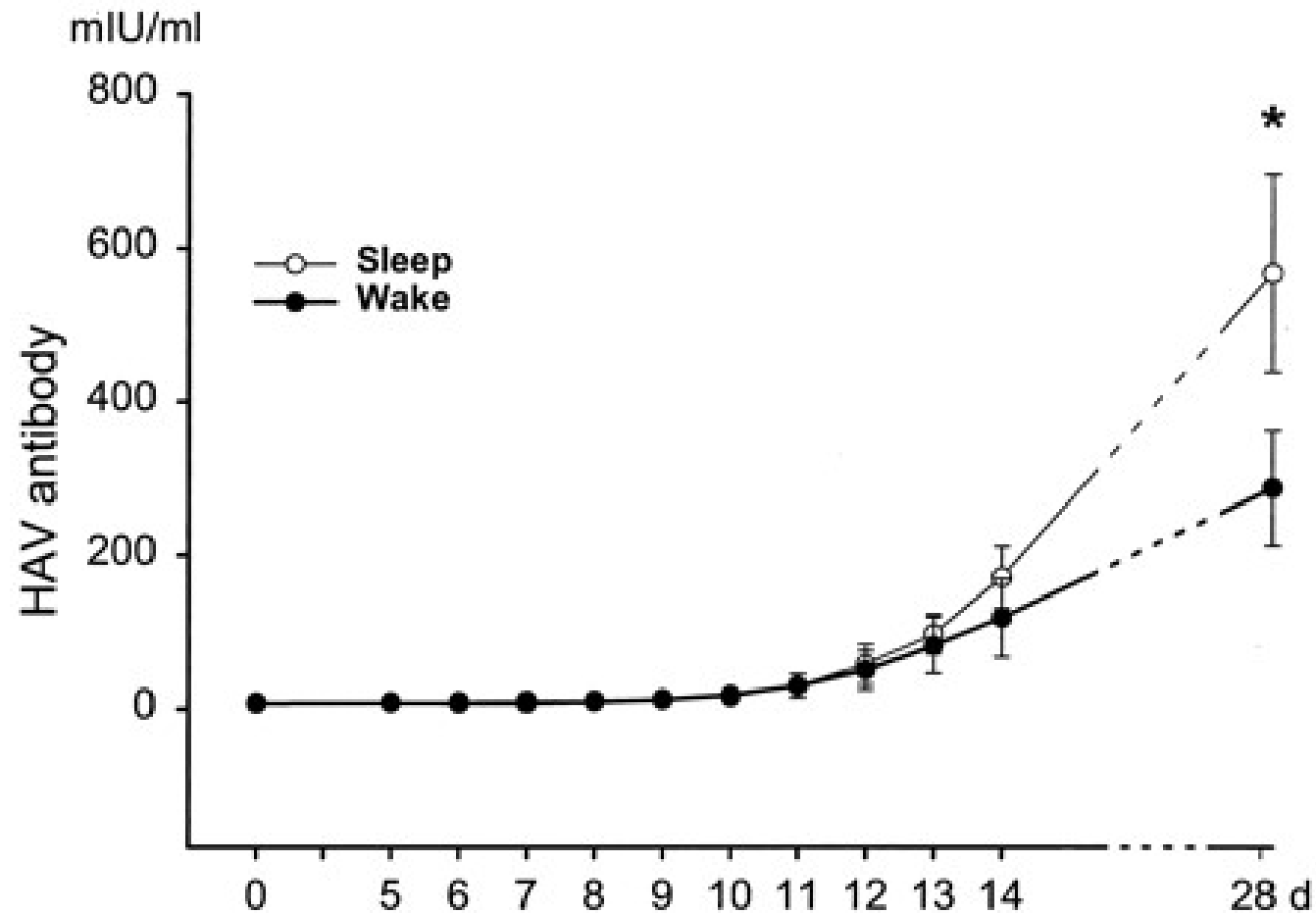
Moldofsky, 1989

PRIVAZIONE DI SONNO

- **Impedisce nel topo messo a contatto con un virus influenzale di sviluppare “memoria immunitaria”**

Brown et al, 1989

sleep loss impairs the human antibody response to hepatitis A vaccination

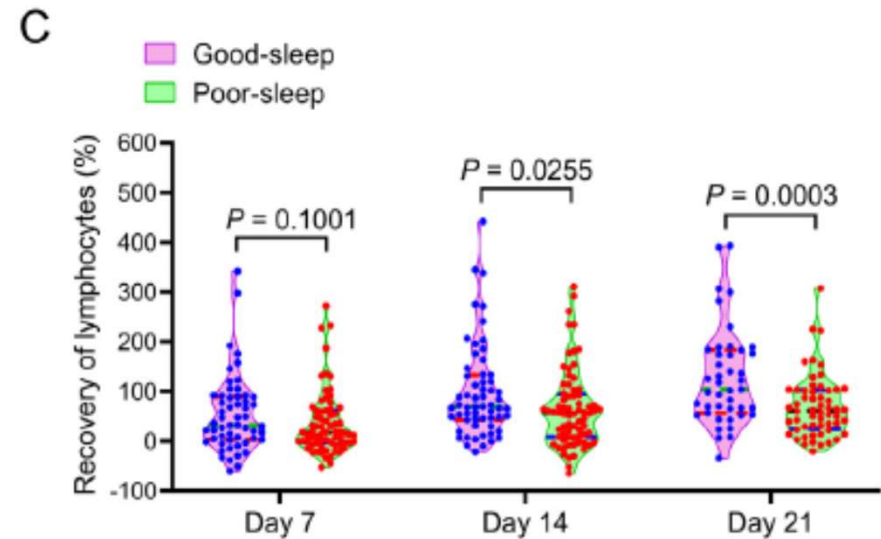
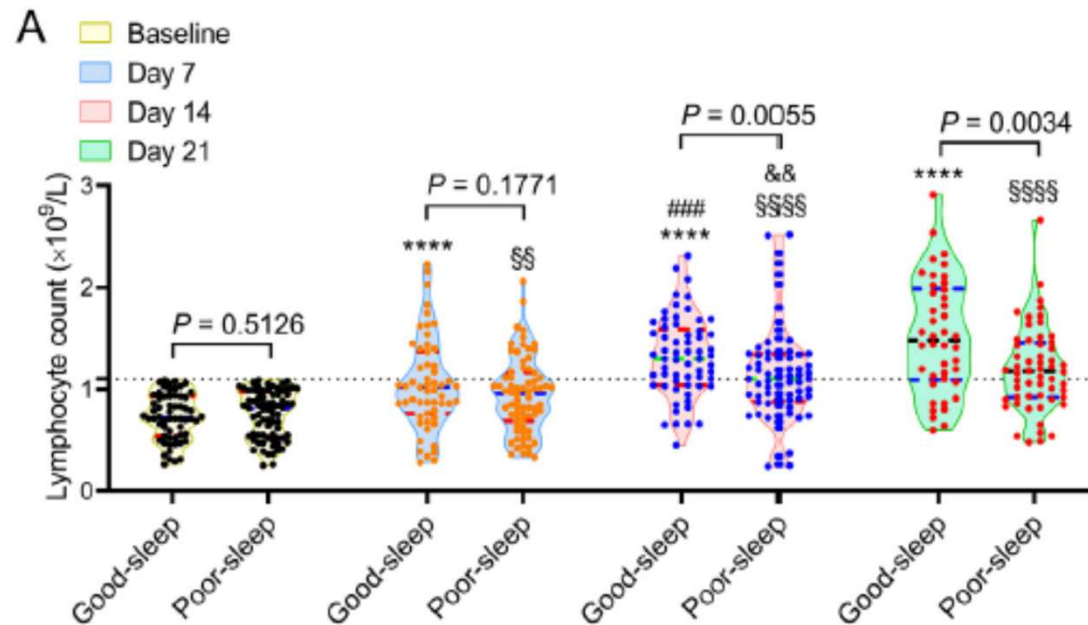


total loss of sleep in the night following vaccination
impairs immune response 28 days later

Poor-sleep is associated with slow recovery from lymphopenia and an increased need for ICU care in hospitalized patients with COVID-19: A retrospective cohort study

Jiancheng Zhang^{a,b,1}, Dan Xu^{a,1}, Bing Xie^{a,1}, Yujing Zhang^{a,1}, Haiyan Huang^{a,1}, Hongmei Liu^{c,1}

Brain, Behavior, and Immunity 88 (2020) 50–58



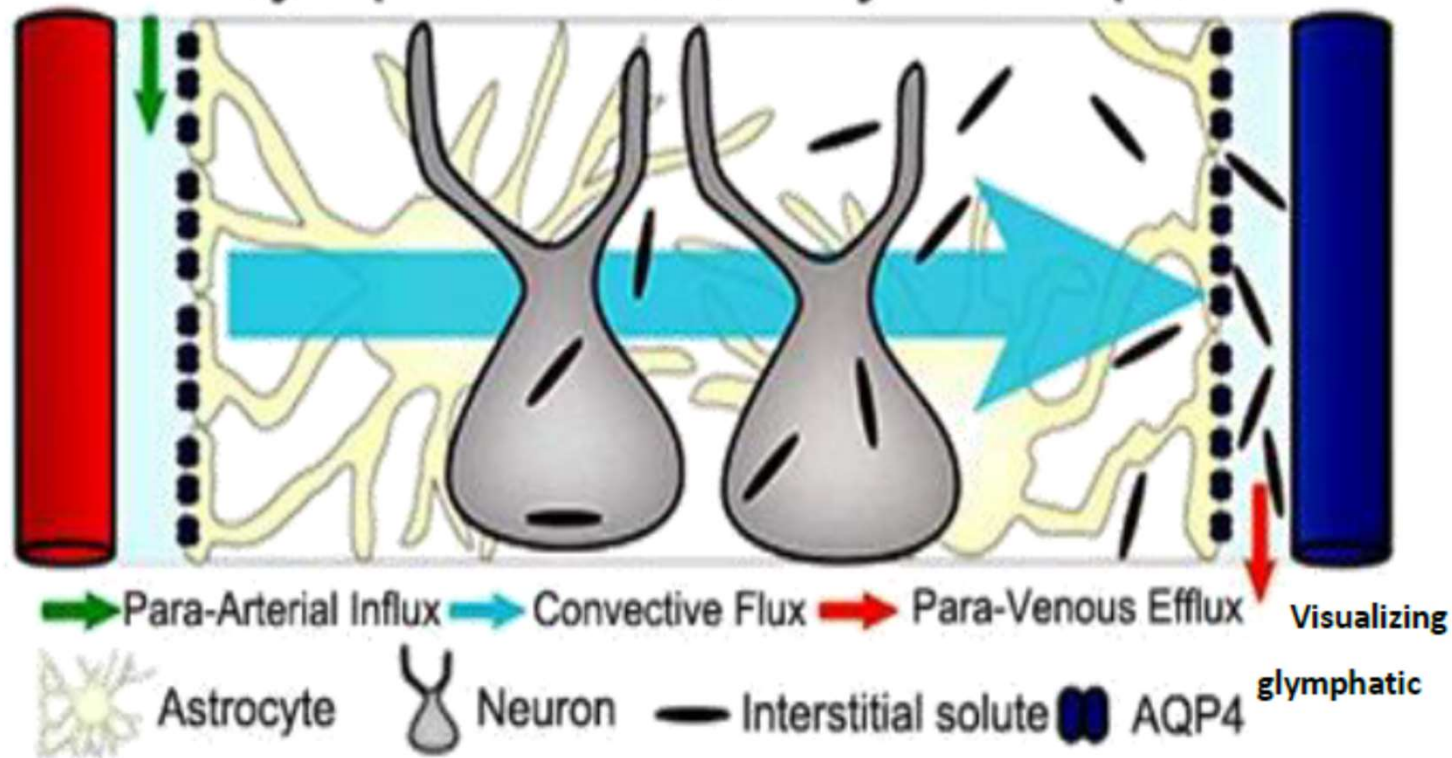
	Normal range	Total (n = 135)	Good-sleep (n = 60)	Poor-sleep (n = 75)	P value
Requiring ICU care	-	9 (6.7)	<u>0 (0)</u>	<u>9 (12.0)</u>	0.0151
Total length of hospital stay, median (IQR), d	-	29.0 (21.0–45.0)	<u>25.0 (20.5–36.5)</u>	<u>33.0 (23.0–47.0)</u>	0.0116

The Brain's Waste-Removal System

By Helene Benveniste, M.D., Ph.D.

Cerebrum August 2018

Glymphatic Pathway Transport



Glymphatic Transport, Waste Clearance, and Sleep

One exciting study concerning the glymphatic pathway reported the enhancing effect of sleep on influx and clearance of waste solutes, including $A\beta$. In this rodent study, glymphatic influx increased by 95 percent and $A\beta$ was cleared twice as fast in the cortex during slow wave sleep (or state of anesthesia with ketamine/xylazine), than during wakefulness.²³

The Relationship between Hippocampal Volume and Cognition in Patients with Chronic Primary Insomnia

Hyun Jin Noh,^a Eun Yeon Joo,^a Sung Tae Kim,^b So Mee Yoon,^c Dae Lim Koo,^a
Daeyoung Kim,^a Geun-Ho Lee,^d Seung Bong Hong^a

J Clin Neurol 2012;8:130-138

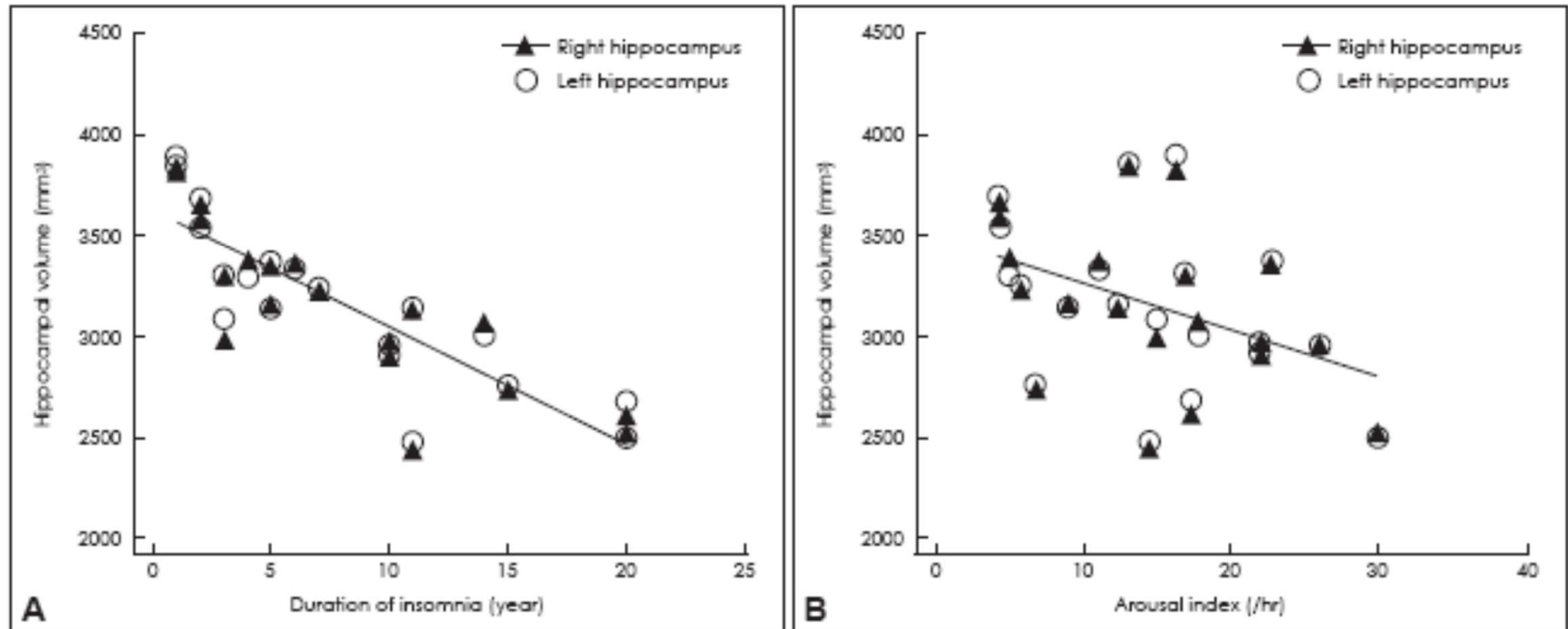


Fig. 1. Scatter plots of left or right hippocampal volume and duration of insomnia and arousal index in patients with chronic insomnia. Higher values on the arousal index correspond to poor sleep quality. Left or right hippocampal volume was negatively correlated with the insomnia duration (left: $r=-0.872$, $p<0.001$; right: $r=-0.868$, $p<0.001$) (A) and with the arousal index in nighttime polysomnography (left: $r=-0.435$, $p=0.045$; right: $r=-0.409$, $p=0.026$) (B).

PRINCIPALI SISTEMI DI CLASSIFICAZIONE DEI DISTURBI DEL SONNO

Una classificazione diagnostica dei disturbi del sonno si è resa assolutamente necessaria al fine di standardizzare le definizioni anche a fini epidemiologici, aumentare le conoscenze in materia, facilitare il riconoscimento dei sintomi e promuovere uno spettro più ampio di diagnosi differenziali.



American Academy of Sleep Medicine

*International Classification of Sleep Disorders:
Diagnostic and Coding Manual, ICSD-3
American Academy of Sleep Medicine 2014.*



*Diagnostic and statistical manual of mental
disorders, 5th ed, Washington, DC: APA 2013.*

CLASSIFICAZIONE INTERNAZIONALE DEI DISTURBI DEL SONNO (ICSD)

Prodotta dall'*American Academy of Sleep Medicine* in associazione con l'*European Sleep Research Society*, la *Japanese Society of Sleep Research* e la *Latin American Sleep Society*, pubblicata per la prima volta nel 1990, è giunta alla sua terza edizione (ICSD-3) nel marzo 2014.

Rispetto all'ICSD -2 che elencava 81 disturbi del sonno distribuiti in otto diverse categorie , **la terza edizione include 60 diagnosi racchiuse all'interno di sette categorie diagnostiche:**

Insomnia

Sleep-related breathing disorders

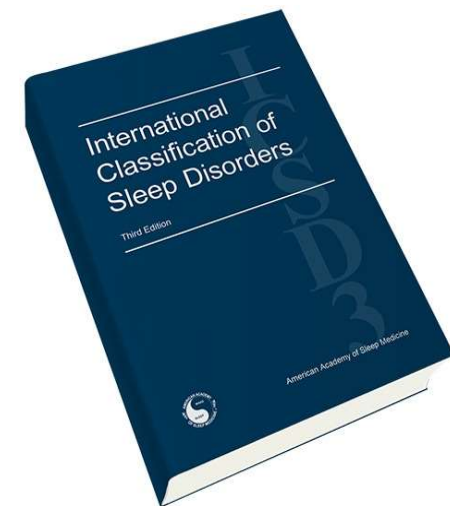
Central disorders of hypersomnolence

Circadian rhythm sleep-wake disorders

Parasomnias

Sleep-related movement disorders

Other sleep disorder



American Academy of Sleep Medicine



Sleep-Wake Disorders



DISTURBI DEL SONNO –VEGLIA nel DSM -V

DISTURBO DA INSONNIA

DISTURBO DA IPERSONNOLENZA

NARCOLESSIA

DISTURBI DEL SONNO CORRELATI ALLA RESPIRAZIONE

DISTURBI CIRCADIANI DEL RITMO-SONNO VEGLIA

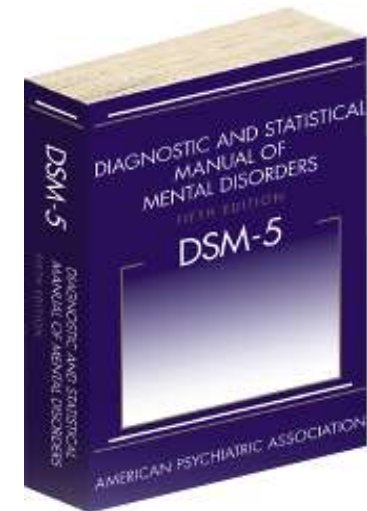
DISTURBI DELL'AROUSAL DEL SONNO NON REM

DISTURBO DA SOGNI TERRIFICI

DISTURBO COMPORTAMENTALE DEL SONNO REM

SINDROME DELLE GAMBE SENZA RIPOSO

DISTURBI DEL SONNO-VEGLIA INDOTTI DA SOSTANZE O FARMACI



Diagnostic Criteria of Chronic Insomnia Disorder

Criteria A-F must be met

A. The patient reports, or the patient's parent or caregiver observes:

1. Difficulty initiating sleep.
2. Difficulty maintaining sleep.
3. Waking up earlier than desired.
4. Resistance to going to bed on appropriate schedule.
5. Difficulty sleeping without parent or caregiver intervention.

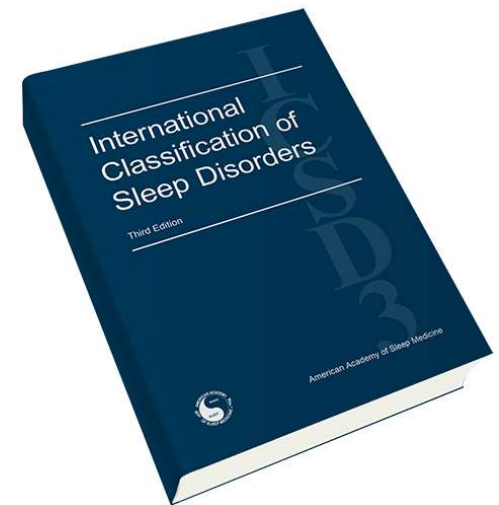
B. The patient reports, or the patient's parent or caregiver observes:
Daytime dysfunction or concerns about or dissatisfaction with sleep.

C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable) for sleep.

D. The sleep disturbance and associated daytime symptoms occur at least three times per week.

E. The sleep disturbance and associated daytime symptoms have been present for at least three months

F. The sleep/wake difficulty is not better explained by another sleep disorder.



ICSD-3

Diagnostic Criteria of Chronic Insomnia Disorder

Criteria A-F must be met

A. The patient reports, or the patient's parent or caregiver observes:

1. Difficulty initiating sleep.
2. Difficulty maintaining sleep.
3. Waking up earlier than desired.
4. Resistance to going to bed on appropriate schedule.
5. Difficulty sleeping without parent or caregiver intervention.

B. The patient reports, or the patient's parent or caregiver observes:

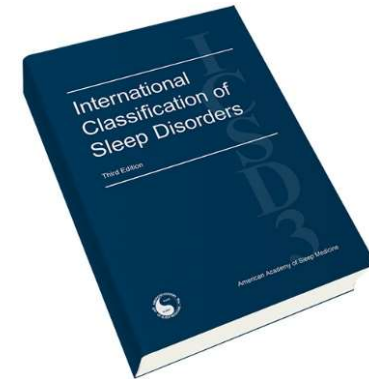
Daytime dysfunction or concerns about or dissatisfaction with sleep.

C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable) for sleep.

D. The sleep disturbance and associated daytime symptoms occur at least three times per week.

E. The sleep disturbance and associated daytime symptoms have been present for at least three months

F. The sleep/wake difficulty is not better explained by another sleep disorder.



ICSD-3

INSOMNIA DISORDER

Diagnostic Criteria

The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty:

1. **Fatigue/malaise.**
2. Attention, concentration, or memory impairment.
3. Impaired social, family, occupational, or academic performance.
4. Mood disturbance/irritability.
5. Daytime sleepiness.
6. Behavioral problems (e.g., hyperactivity, impulsivity, aggression).
7. Reduced motivation/energy/initiative.
8. Proneness for errors/accidents.
9. Concerns about or dissatisfaction with sleep.

The Pathophysiology of Insomnia

Jessica C. Levenson, PhD; Daniel B. Kay, PhD; and Daniel J. Buysse, MD

CHEST 2015; 147(4):1179-1192

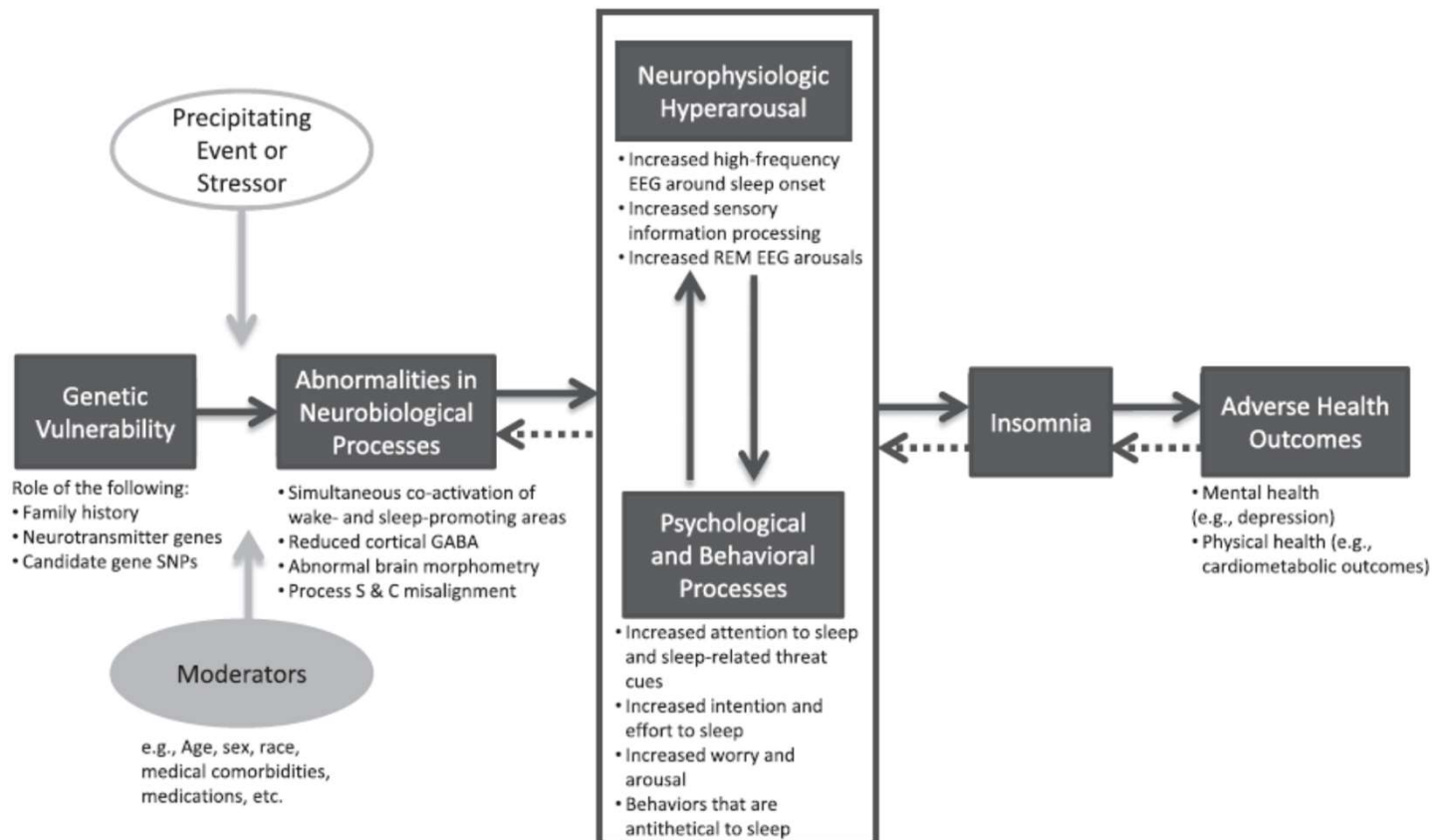
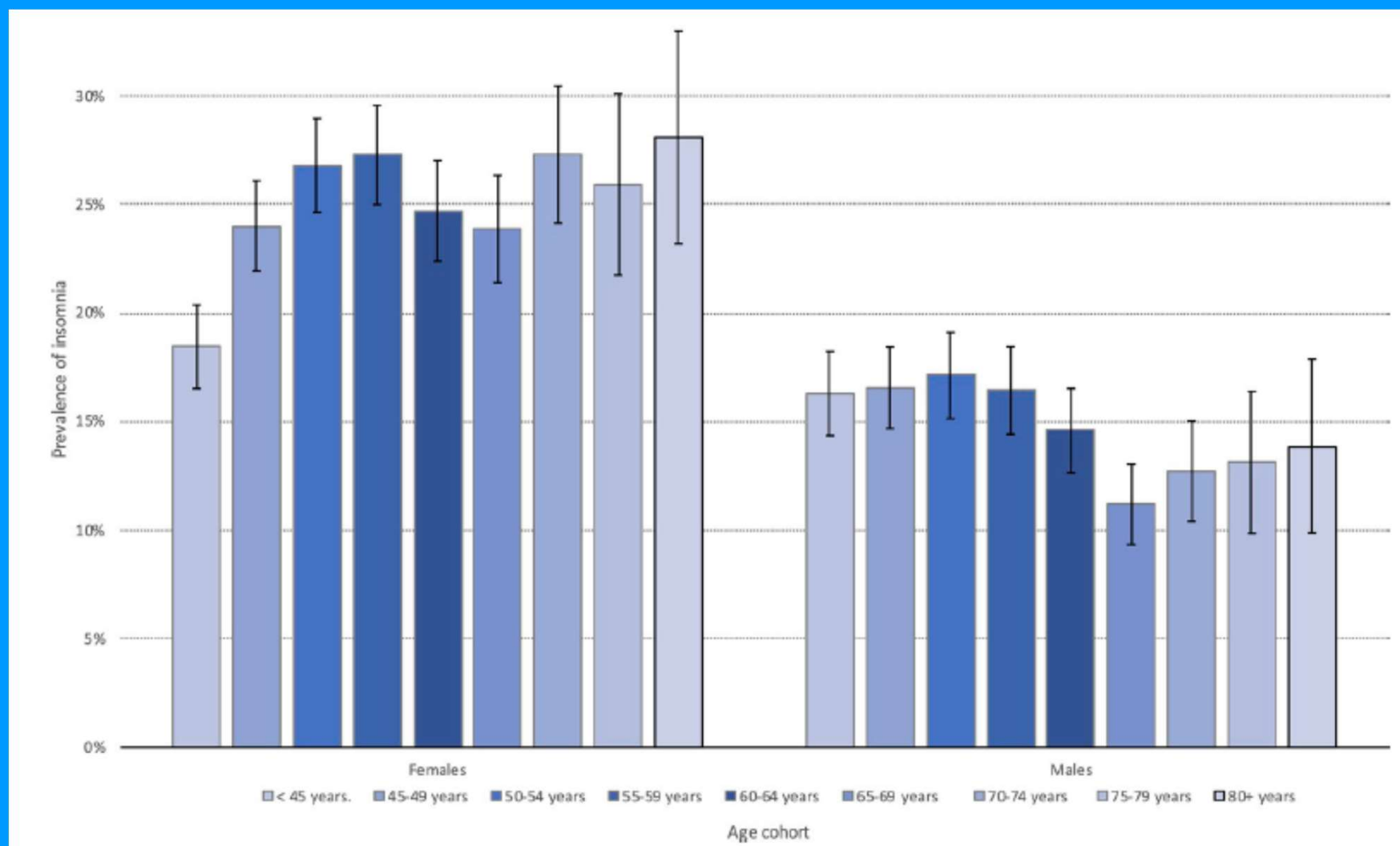


Figure 1 – Model of the pathophysiology of insomnia. GABA = γ -aminobutyric acid; SNP = single-nucleotide polymorphism.

Sleep patterns and insomnia in a large population-based study of middle-aged and older adults: The Tromsø study 2015–2016

Børge Sivertsen^{1,2,3}  | Ståle Pallesen^{4,5}  | Oddgeir Friborg⁶ |

J Sleep Res. 2021;30:e13095.



Prevalence of ICSD-3 insomnia

Insomnia and risk of cardiovascular disease.

Javaheri S, Redline S.

Insomnia, especially when accompanied by short sleep duration, is associated with increased risk for hypertension, coronary heart disease and recurrent acute coronary syndrome.

Purported mechanisms likely relate to dysregulation of the hypothalamic pituitary axis, **increased sympathetic nervous system activity, and increased inflammation.**

Insomnia and the risk of hypertension: A meta-analysis of prospective cohort studies

Liqing Li ^{a, b, 1}, Yong Gan ^{b, 1}, Xiaogang Zhou ^c, Heng Jiang ^{d, e}, Yulan Zhao ^a, Qingfeng Tian ^f,

[Sleep Medicine Reviews 56 \(2021\) 101403](#)

Practice points

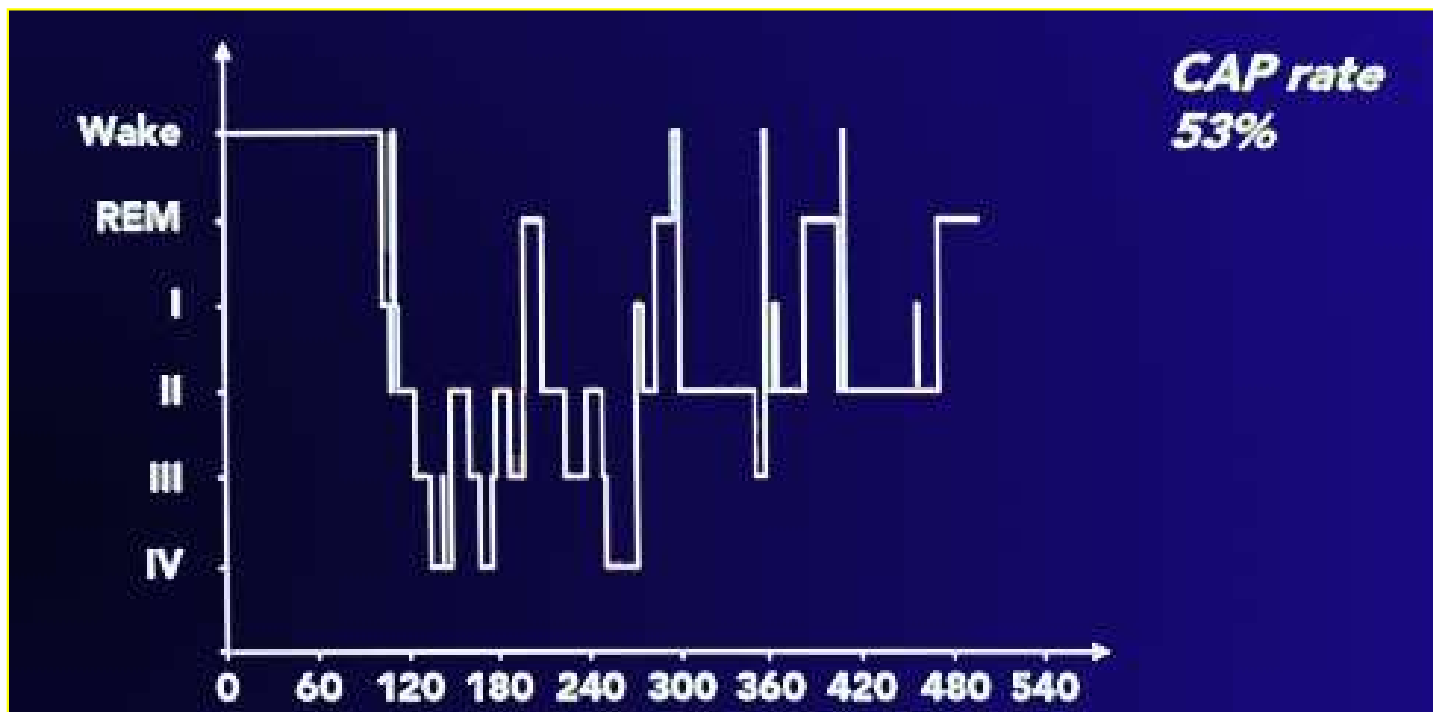
1. Insomnia symptoms were associated with a significantly increased risk of hypertension.
2. An increased risk of hypertension was observed in participants with difficulty maintaining sleep and early morning awakening.
3. Difficulty falling asleep was unassociated with hypertension.



Insonnia:

Differenze cliniche ed
ipotesi diagnostiche

INSONNIA INIZIALE



DIFFICOLTA' DI ADDORMENTAMENTO

- **DISTURBO D'ANSIA**
- **S. DELLE GAMBE SENZA RIPOSO**
- **CATTIVA IGIENE DEL SONNO (poltrona, TV, attività sportiva intensa serale)**
- **RITARDO DI FASE**

Diagnostic criteria for Restless Legs Syndrome (RLS)

Essential features

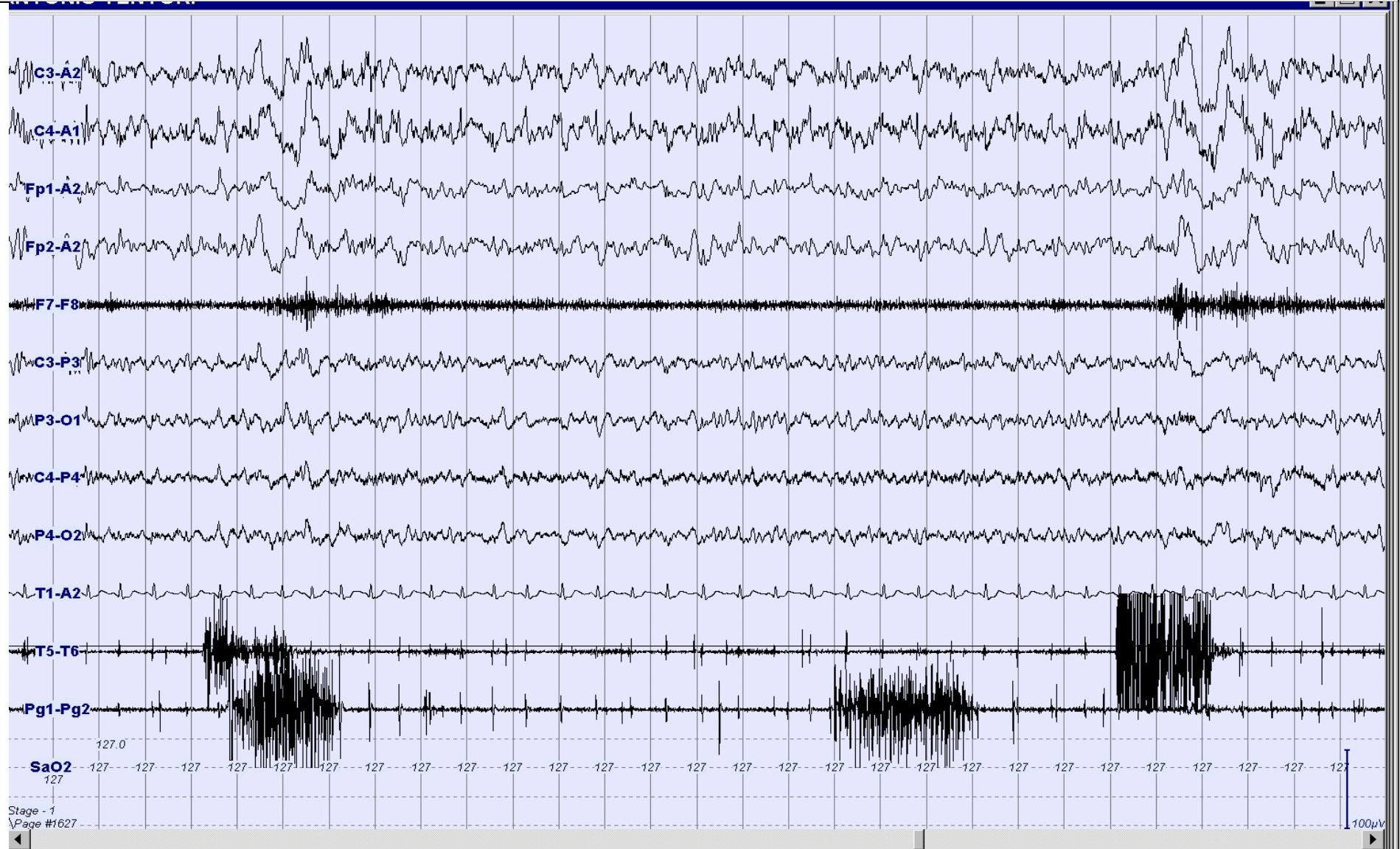
- 1) An urge to move the legs
- 2) that is present at rest
- 3) relieved by movement, and
- 4) demonstrates a circadian pattern with peak symptoms occurring at night or in the evening

Diagnostic criteria for RLS-

Non essential but common features

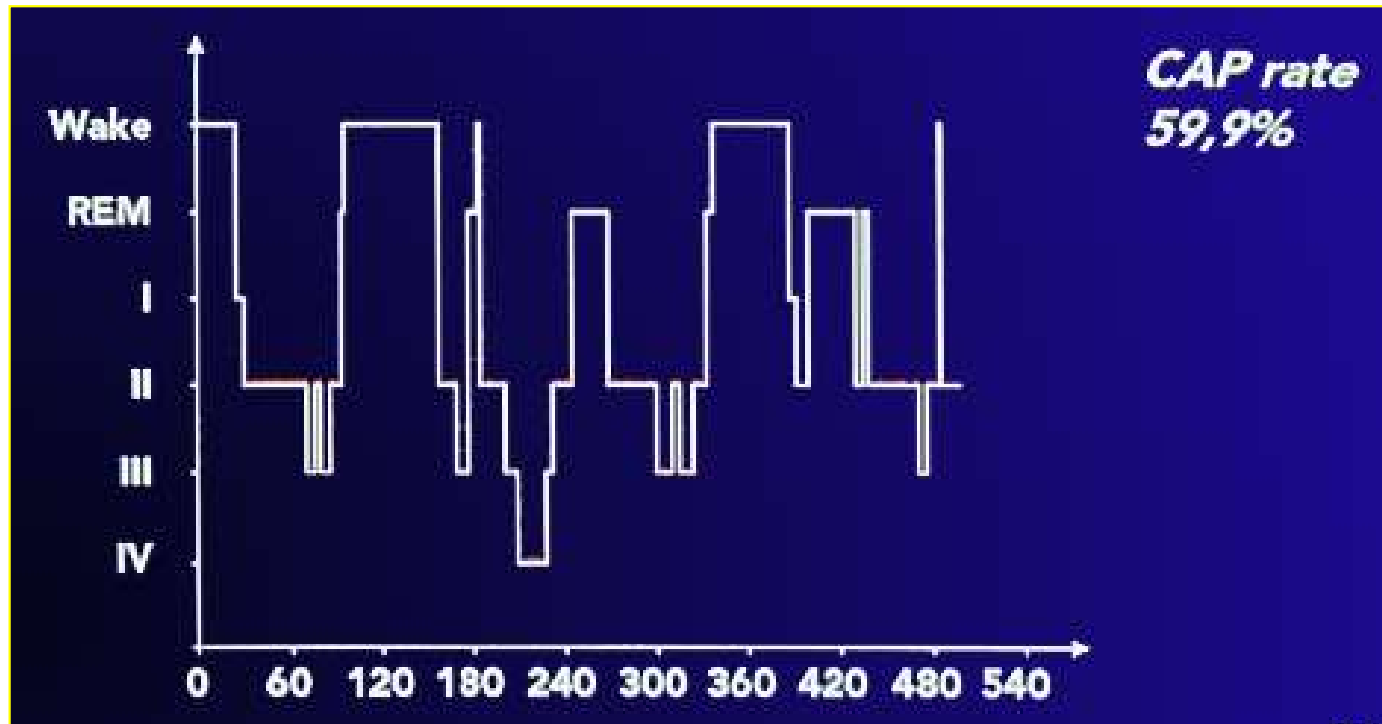
- **Family history**
- **Response to dopaminergic therapy**
- **Experience of PLM during sleep or during wakefulness**
- **Sleep disturbance**

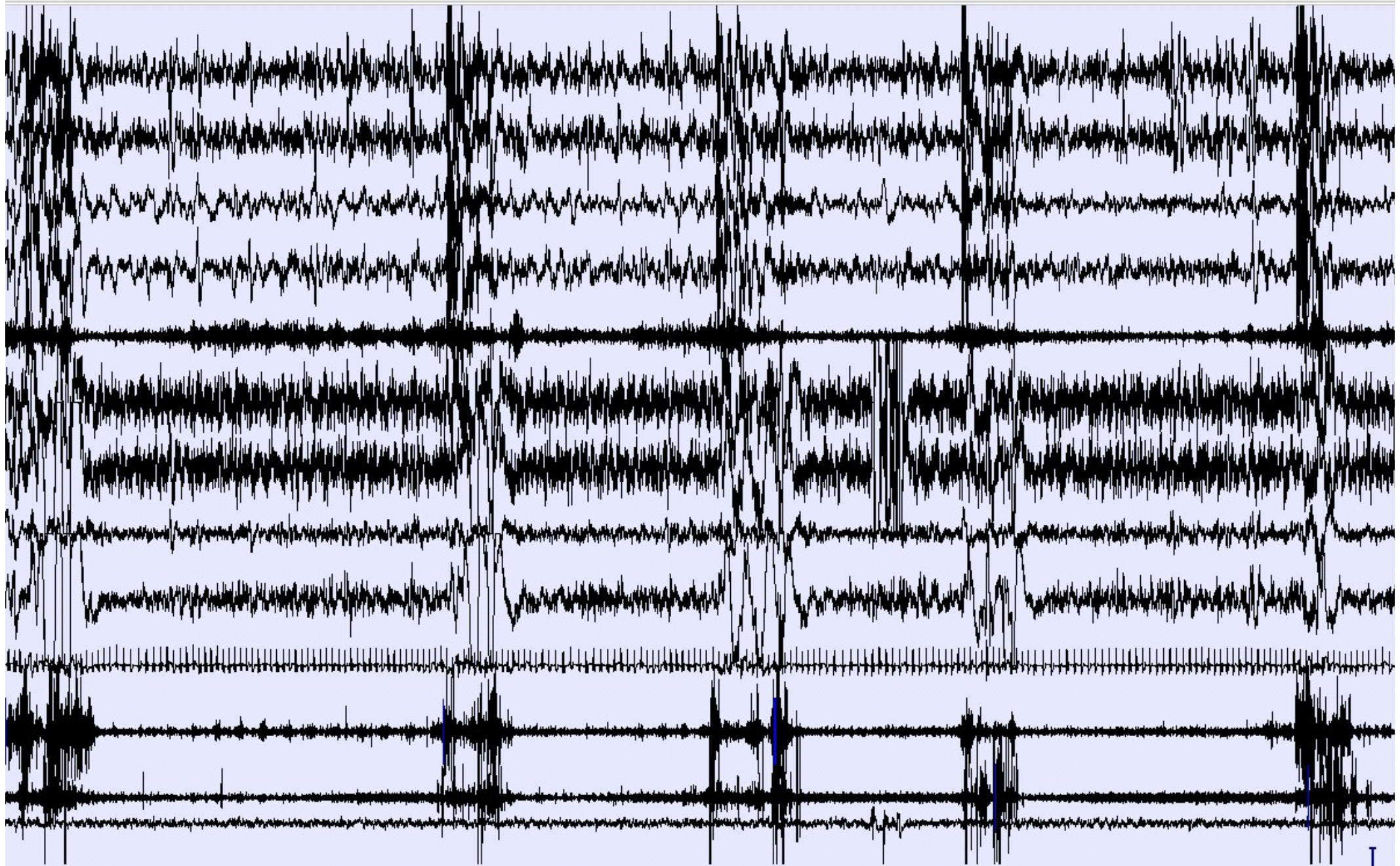
PERIODIC LEG MOVEMENTS



Stage - 1
Page #1627

INSONNIA INTERMEDIA (RISVEGLI NOTTURNI PROLUNGATI)





Stage - 1

Stage - 2

Stage - 2

Stage - 1

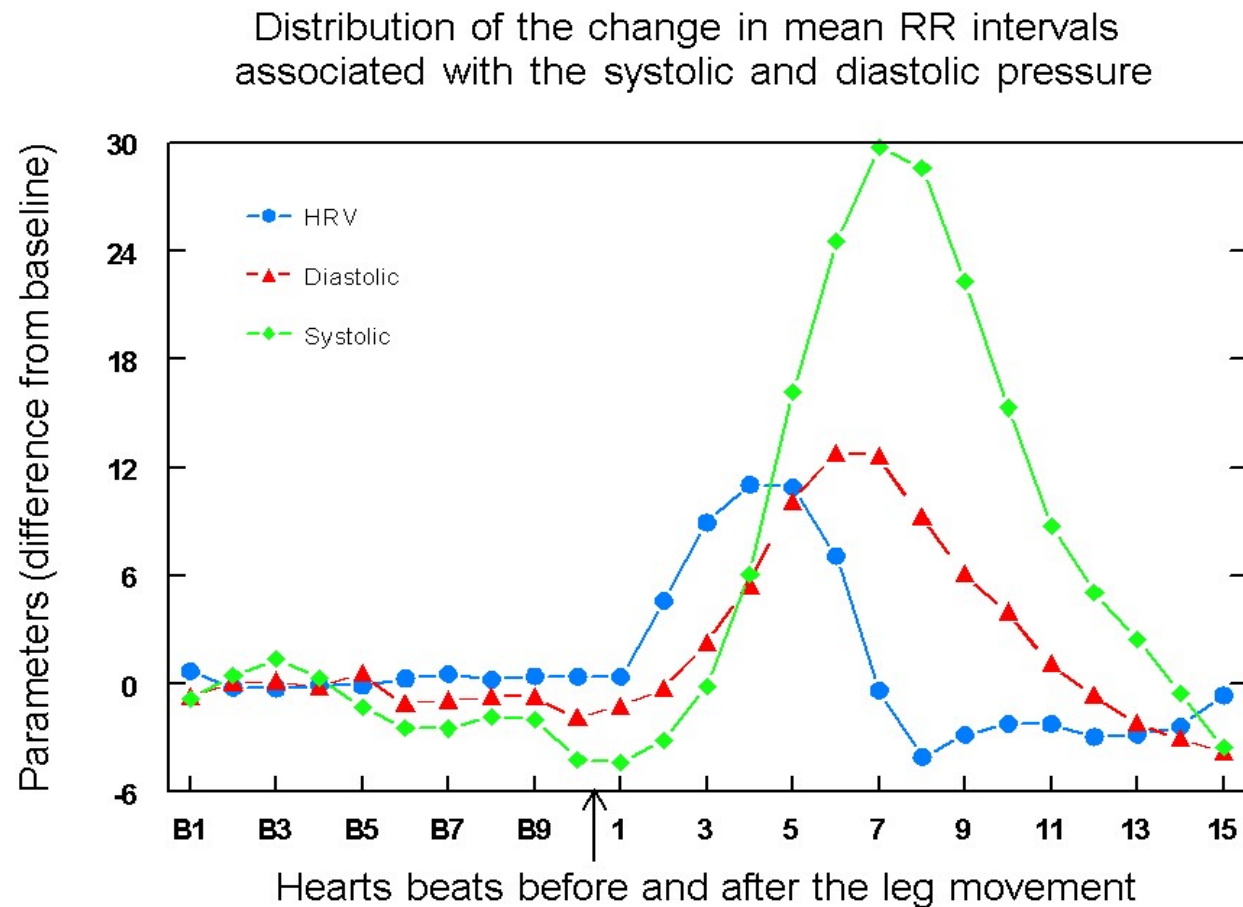
Stage - 1

Stage - 2

St.
10

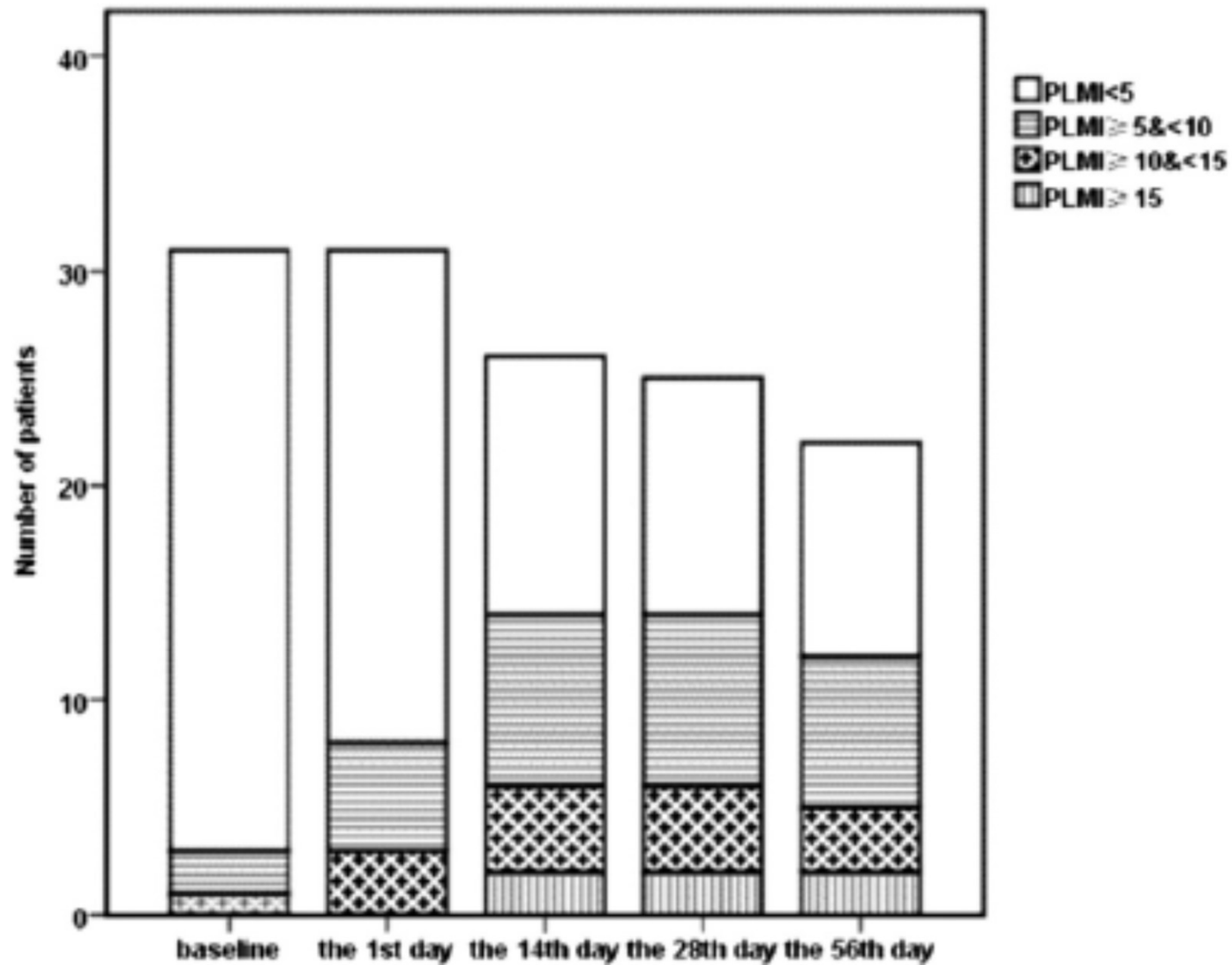
RLS and periodic limb movements

In RLS, PLMs induce a repetitive rise in blood pressure and heart rate



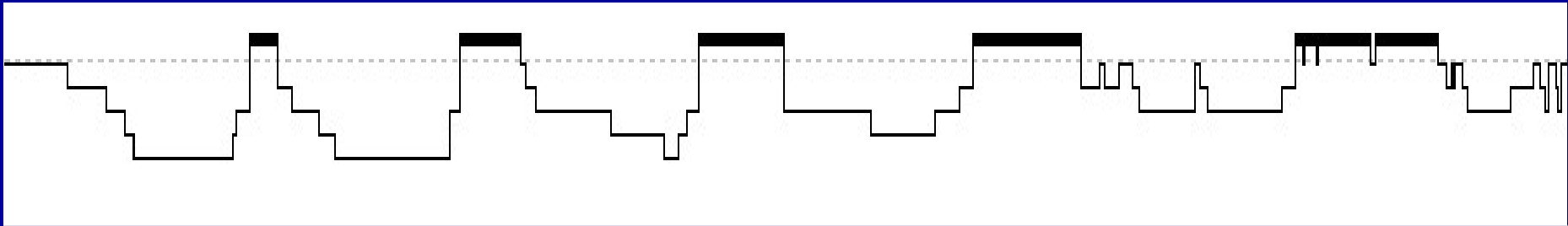
Sertraline and periodic limb movements during sleep: an 8-week open-label study in depressed patients with insomnia

B. Zhang et al./Sleep Medicine 14 (2013) 1405–1412



CONSEGUENZE FUNZIONALI DELLE APNEE IN SONNO IPNOGRAMMA

REM
W
1
2
3
4



REM
W
1
2
3
4



OSA = IPERSONNIA ?



Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: A systematic review and meta-analysis

Ye Zhang ^a, Rong Ren ^a, Fei Lei ^a, Junying Zhou ^a, Jihui Zhang ^b, Yun-Kwok Wing ^b, Larry D. Sanford ^{c, **}, Xiangdong Tang ^{a, *}

Sleep Medicine Reviews 45 (2019) 1–17

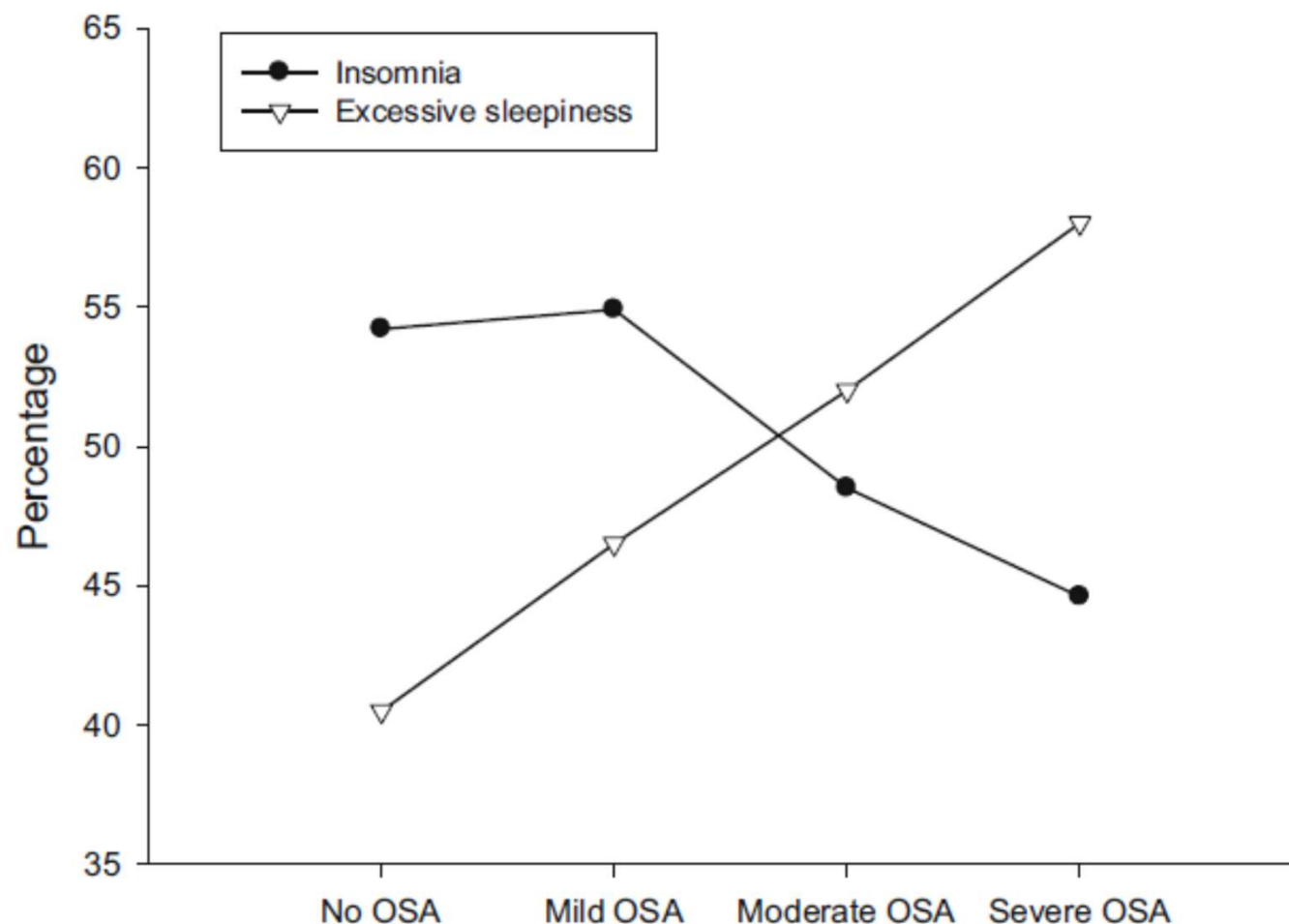
Prevalence rates of insomnia:

- difficulty falling asleep = 18 %
- difficulty maintaining sleep = 42%
- early morning awakening = 21%

Prevalence of excessive sleepiness is higher whereas insomnia is lower with greater severity of obstructive sleep apnea

Bjørn Bjorvatn • Sverre Lehmann • Shashi Gulati • Harald Aurlen • Ståle Pallesen • Ingvild W. Saxvig

Sleep Breath (2015) 19:1387–1393



obstructive sleep apnea (OSA) severity. No OSA, AHI <5; mild OSA, AHI 5–14.9; moderate OSA, AHI 15–29.9; severe OSA, AHI 30 or higher



BMI= 21,8

AHI= 59,6



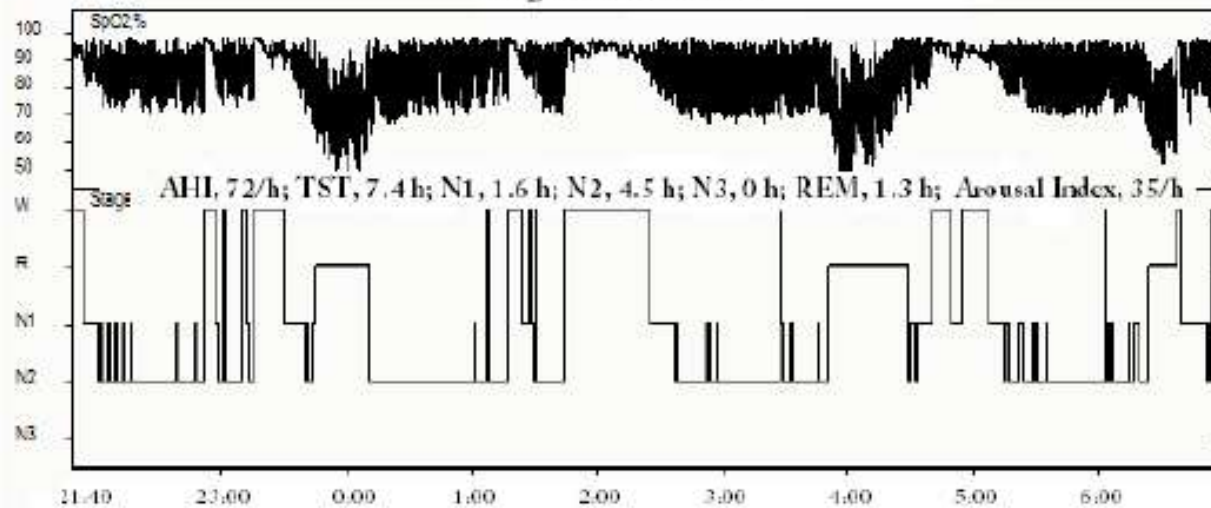
BMI= 49,3

Persistent Insomnia Despite Long-Term Nightly Use of Sleeping Pills

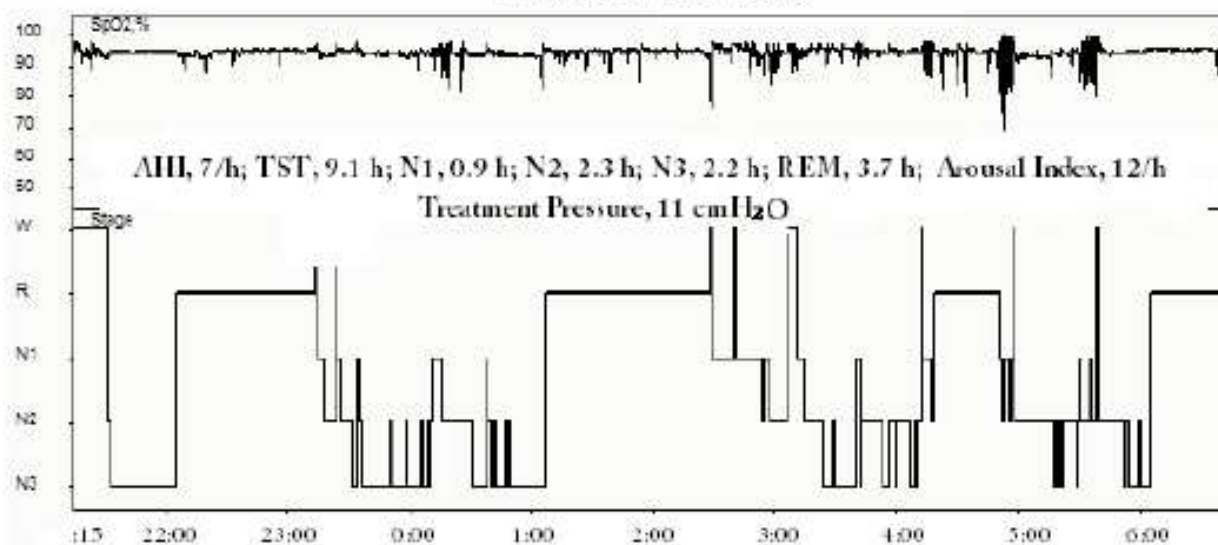
Yun Li, M.D.; Zhe Li, M.D.; Fei Lei, M.D.; Lina Du, M.D.; Xiangdong Tang, M.D., Ph.D.

Journal of Clinical Sleep Medicine, Vol. 9, No. 8, 2013

Diagnosis (March 1, 2012)



First CPAP (March 10, 2012)



Can drugs induce or aggravate sleep apneas? A case–noncase study in VigiBase[®], the WHO pharmacovigilance database

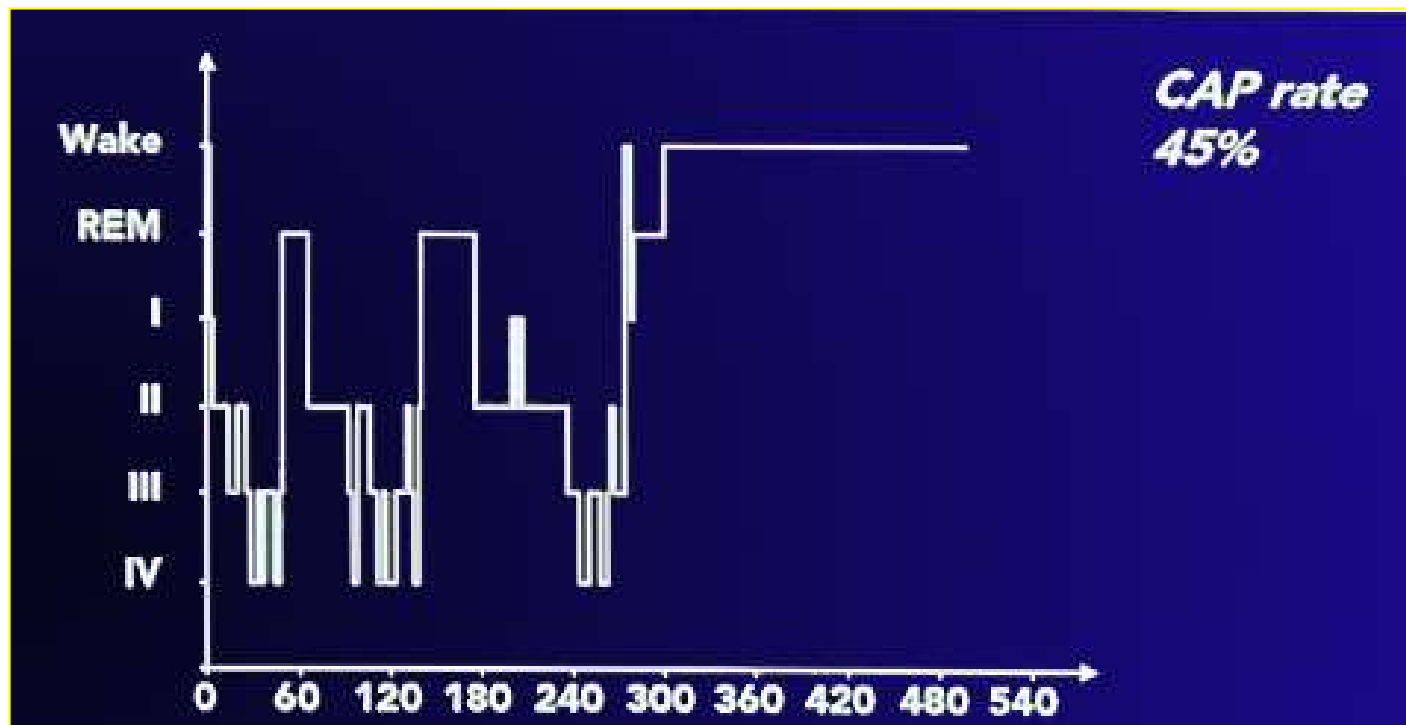
M. Linselle *et al.*

Fundamental & Clinical Pharmacology 31 (2017) 359–366

Table IV ROR values for 'suspected' drugs and pharmacological classes (ATC level 5) (>2%).

Exposure to	Cases (N = 5022)	Noncases (N = 10 678 529)	ROR	95% CI	P-value
Sodium oxybate	168	5749	64.3	55.0–75.1	<0.0001
Rofecoxib	663	65 391	24.7	22.4–26.8	<0.0001
Alendronic acid	273	40 183	15.2	13.5–17.2	<0.0001
Digoxin	104	25 685	8.8	7.2–10.7	<0.0001
Quetiapine	192	57 216	7.4	6.4–8.5	<0.0001
Esomeprazole	103	43 205	5.2	4.2–6.3	<0.0001
Clozapine	104	93 708	2.4	2.0–2.9	<0.0001
Coxibs	702	139 836	12.2	11.3–13.3	<0.0001
Bisphosphonates	376	103 924	8.2	7.4–9.1	<0.0001
Digitalis glycosides	104	28 214	8.0	6.6–9.7	<0.0001
Antipsychotics 'diazepines, oxazepines, thiazepines, and oxepines'	381	198 437	4.3	3.9–4.8	<0.0001
Benzodiazepine derivatives	119	100 195	2.6	2.1–3.1	<0.0001
Interferons	212	199 665	2.3	2.0–2.7	<0.0001

INSONNIA TERMINALE



RISVEGLIO PRECOCE

- **DEPRESSIONE**
- **CATTIVA IGIENE DEL SONNO**
- **ALCOOL**
- **ANTICIPO DI FASE**

A systematic review on sleep alterations anticipating the onset of bipolar disorder

C. Pancheri^{a,b}, N. Verdolini^{b,c}, I. Pacchiarotti^b, L. Samalin^d, R. Delle Chiaie^a, M. Biondi^a, A.F. Carvalho^{e,f}, M. Valdes^g, P. Ritter^h, E. Vieta^{b,*}, A. Murru^b

European Psychiatry 58 (2019) 45–53

ALTHOUGH LESS FREQUENT, HYPERSOMNIA SEEMS MORE SPECIFIC OF A DEPRESSIVE BD ONSET.

HYPERSOMNIA PRECEDE THE ONSET OF THE DISEASE OF 6-8 MONTHS, ITS FREQUENCY RANGING FROM 14 TO 33 PERCENT.

HYPERSOMNIA **MAY DIFFERENTIATE BIPOLAR DEPRESSION , IN BD TYPE II PATIENTS, FROM UNIPOLAR DEPRESSION, WITH A POSITIVE PREDICTIVE VALUE OF AROUND **70 PERCENT**.**

Insomnia as a predictor of mental disorders: A systematic review and meta-analysis

E. Hertenstein et al. / Sleep Medicine Reviews 43 (2019) 96–105

Insomnia is a significant predictor for the onset of:

- **Depression** (10 studies, OR 2.83)
- **Anxiety** (6 studies, OR 3.23)
- **Alcohol** abuse (2 studies, OR 1.35)



**Grazie per
l'attenzione**